SCIENTIFIC DISCUSSION

1. Introduction

At the end of 2005 it was estimated that approximately 40 million people are living worldwide with an infection with the human immunodeficiency virus (HIV) or AIDS (acquired immunodeficiency syndrome with HIV being the etiologic agent). AIDS continues to be a leading cause of mortality with approximately 3 million deaths per year.

Treatment for HIV infection has evolved rapidly and highly active antiretroviral therapy (HAART) has resulted in a significant decrease in mortality and morbidity so that HIV infection is now managed as a chronic disease. However, HAART is still limited by intolerance of complicated dosing regimens, long-term toxicities and multi-drug resistance.

In particular intra-class resistance has become common and often limits the choice and efficacy of antiretroviral therapies (ARTs) for patients failing their current regimens. In patients infected with multi-drug resistant virus therapy is more successful if an agent from an ART class to which the patient has not been previously exposed is combined with at least one other active ART. Therefore, the development of ARTs with novel mechanisms of action remains very important, especially for those with few remaining treatment options.

ISENTRESS contains raltegravir as active substance. Raltegravir blocks HIV-1 replication by inhibiting the strand transfer activity of the HIV-encoded enzyme integrase and as such is an Integrase Strand Transfer Inhibitor (InSTI). Integration of the viral genome is an essential and characteristic step in the life cycle of all retroviruses including HIV-1. The rationale behind the development of ISENTRESS is that the inhibition of the HIV integrase represents a new therapeutic target for the treatment of HIV-1 infection.

A so-called full application has been submitted for the marketing authorisation. The assessment was made under accelerated timetable based on a request from the applicant. The CHMP did accept this request as it was considered that there is an unmet medical need for a novel antiretroviral agent that can deliver efficacy against multiple drug resistant HIV and that the information provided with the request for accelerated assessment suggested that raltegravir may indeed meet this unmet need. Therefore, it was possible to concur that there could be a potential for raltegravir to constitute a major public health interest based on its potential to benefit HIV-infected patients with few remaining treatment options.

In the initial Marketing Authorisation Application (MAA) the applicant did not apply for a conditional marketing authorisation. During the evaluation however the CHMP considered - after having consulted with the applicant - that the application would meet the criteria for conditional approval according to Article 14(7) of Regulation (EC) 726/2004 in conjunction with Commission Regulation (EC) 507/2006:

- ISENTRESS is proposed to be indicated for treatment of HIV-1 infection, which is a life-threatening disease, and so falls within the scope of the legislative framework on conditional marketing authorisations as defined in Article 2(1) of Regulation (EC) 507/2006.
- In support of the MAA the applicant provided complete 24-week data from two Phase 3 studies. Comprehensive clinical data up to 48 weeks would be needed to further assess important issues including long-term viral suppression, the safety profile and the resistance pattern. Such data will be generated but were not available in the timeframe of the assessment. In addition, it was considered that further monitoring of resistance to raltegravir and the risk for malignancies is required.
- Based on the available data the risk-benefit analysis was considered to be positive. The product fulfils an unmet medical need as it has a novel mechanism of action that results in activity against HIV that is resistant to many other antiretroviral agents. It likely has an acceptable safety profile and a limited potential for drug interactions. On this basis it could be considered that the benefit to public health of allowing ISENTRESS to be marketed without

undue delay may outweigh the risks inherent in the fact that additional data are still required. Therefore, the application fulfilled the requirements for a Conditional Marketing Authorisation as defined in Article 4(1) of Regulation (EC) 507/2006.

ISENTRESS is available in film-coated tablet containing 400 mg of raltegravir (as potassium). The recommended dosage is 400 mg administered twice daily.

The initially claimed indication was "ISENTRESS is indicated in combination with other anti-retroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy."

The approved indication is:

> "ISENTRESS is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in treatment-experienced adult patients with evidence of HIV-1 replication despite ongoing anti-retroviral therapy.
>
> This indication is based on safety and efficacy data from two double-blind, placebo-controlled trials of 24 weeks duration in treatment-experienced patients (see section 5.1)"

2. Quality aspects

Introduction

ISENTRESS is presented as film-coated tablets containing the active substance raltegravir as the potassium salt. The applicant has utilised a design space approach in developing both the drug substance and drug product.

Active Substance

Raltegravir is *N*-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt. It is a white powder, soluble in water, slightly soluble in methanol, very slightly soluble in acetonitrile and ethanol and insoluble in isopropyl alcohol. It has no chiral centres although polymorphism is observed. Concerning lipophilicity of raltegravir in terms of octanol/water partition, the D_{ow} and $LogD_{ow}$ results at pH=7.4 are 2.80 ± 0.08 and 0.45 ± 0.01, respectively.

- Manufacture

Raltegravir is manufactured utilizing a commercial process that is well described and the potentially critical parameters have been investigated and controls applied as appropriate.

The active ingredient has been fully characterised by conventional spectroscopic techniques. Three polymorphic forms have been identified. The synthetic route routinely results in the commercially marketed form, distinguishable by melting point and XRPD.

Based on laboratory runs the optimum synthetic conditions have been defined using a 'design space' concept. Further studies have investigated the main critical variables and there is evidence of a good understanding of the process, which in turn has enabled the design space limits for each step of synthesis to be defined within agreed boundaries.

- Specification

The specification includes relevant tests with justified limits for identification (IR, flame test for K^+), assay (HPLC), residual solvents, and mean particle size.

Potential impurities, including process impurities, degradation products as well as potential contaminants such as, residual solvents have been investigated in detail. Analytical methods are acceptable and generally, appropriate validation data have been provided. The limits proposed for individual impurity limits are acceptable and all specified impurities are either qualified or below the qualification threshold.

- Stability

High stress studies have served to identify potential degradants and the active substance has been studied under ICH storage conditions. Results at 25°C/60% RH, and 40°C/75% RH for three drug substance lots manufactured using the commercial process are provided and the data confirm that there are no significant degradation products observed for the drug substance when stored in the proposed containers. A justified retest period has been defined and agreed.

Medicinal Product

- Pharmaceutical Development

Based on an *in situ* rat intestinal perfusion study, the measured permeability of raltegravir was similar to that of the high permeability reference compound metoprolol. Raltegravir is classified as a BCS class II compound, i.e. high permeability and low solubility at physiological pH.

Bearing this in mind, the aim of the development program has been to develop a robust formulation and manufacturing process using by defining a design space (as for the synthesis of the active substance), and comprehensive studies have been carried out with this approach.

The formulation of the tablet is standard, based on a matrix of microcrystalline cellulose, lactose monohydrate, calcium phosphate dibasic, hypromellose and poloxamer 407. The excipients were selected to provide a tablet that would erode rather than disintegrate with physical and chemical stability and appropriate dissolution characteristics. The tablet cores were film-coated to mask the bitter taste of the active ingredient using a conventional 'OpadryTM' formulation with good adhesion properties.

A number of prototype formulations were investigated *in vivo*. The study results indicated that the plasma concentration profile for the chosen 400 mg formulation showed a flatter profile, with lower C_{max} and longer T_{max}, consistent with formulation design considerations in line with the intended desirable profile. Based on the positive pharmacokinetic data and results from the biocomparison study, this formulation was selected as the candidate for development to a market formulation.

- Manufacture of the Product

Raltegravir Tablets are manufactured utilizing a standard commercial process that is commonly used for film-coated tablets of this type. It is well described and the potentially critical parameters have been investigated and controls applied as appropriate.

- Product Specification

The product specification includes tests with validated limits for identity (NIR/HPLC), assay (HPLC) degradation products (HPLC), dose uniformity, dissolution, microbial contamination etc.

Batch analytical profiles confirm the satisfactory uniformity of the product.

- Stability of the Product

Stability studies have been performed in line with current CHMP/ICH guidelines.

The packaged product was stored at the long term conditions of 25°C/60%RH and 30°C/65%RH and at the accelerated condition of 40°C/75%RH. One of the batches was evaluated for photostability. Results were available for at least 52 weeks for samples stored at 25°C/60%RH and 30°C/65%RH and for at least 6 months for batches stored at 40°C/75%RH. No significant changes were observed after storage under these conditions with no significant photodegradation.

Overall, the accumulated stability data confirm the shelf-life and storage conditions as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

Comprehensive information has been presented to show that the development and manufacture of the active substance and finished product are sound and satisfactory. The applicant has taken the opportunity to define a workable design space for the active substance and product, based on an understanding of relevant processes in both cases. Satisfactory batch control specifications are in place and batch analytical data confirm the satisfactory uniformity of the product, and this in turn indicates that the product should perform consistently in the clinic, from batch to batch. The accumulated stability data have been used to support a validated retest period and shelf-life and storage conditions.

3. Non-clinical aspects

Introduction

A comprehensive set of nonclinical toxicity studies was conducted prior to and in parallel with the clinical programme. These studies included acute and repeated dose oral studies, safety pharmacology studies, a battery of both *in vitro* and *in vivo* genotoxicity studies, and developmental and reproductive toxicity studies. The rat and dog were chosen as the preclinical toxicology species for raltegravir development.

The pivotal non-clinical toxicity studies were conducted in compliance with current international good laboratory practice (GLP) standards. Amongst the toxicokinetic studies the quantification of the glucuronide metabolite of raltegravir in plasma was not GLP-compliant. Also, in the repeat dose toxicity studies in the dog the determination of the concentration of copper in the bile was not conducted under GLP conditions. However, this was not considered to be critical for the assessment.

Pharmacology

The mode of action related to antiviral activity and resistance aspects is also discussed in the section "Clinical aspects, Pharmacodynamics".

- **Primary pharmacodynamics**

Integrase inhibition

The ability of raltegravir to inhibit the enzymatic activity of purified recombinant HIV-1 integrase was evaluated in an *in vitro* assay. Using a pre-assembled complex of HIV-1 integrase with a double-stranded "donor" oligonucleotide mimicking one end of the mature HIV-1 cDNA the assay measured the ability of integrase to catalyse the covalent joining or strand transfer of the donor DNA into a target DNA. Raltegravir inhibited this reaction with an apparent IC_{50} of approximately 10 nM. The results indicated that raltegravir inhibits the third step of the integration process (i.e. strand transfer) and is therefore designated an Integrase Strand Transfer Inhibitor (InSTI).

Activity against laboratory and primary HIV-1 isolates

Antiviral assays were multiple-cycle replication assays in which replication was detected by measuring the accumulation of HIV-1 and -2 gag proteins (p24 and p27) in cell culture supernatant

fluids.

- Raltegravir inhibited replication of the laboratory HIV-1 isolate H9IIIB in MT4 cells with a 95% cell inhibitory concentration (CIC_{95}) of 18.7 ± 14 nM (n=77) in the presence of 10% fetal bovine serum (FBS).
- In the presence of 50% normal human serum the apparent antiviral activity of raltegravir against H9IIIB was reduced with a CIC_{95} of 31 ± 20 nM (n=90).
- The 15 primary HIV-1 isolates tested included six subtypes representing both syncytium-inducing and non-syncytium-inducing isolates. Raltegravir inhibited replication of these isolates in primary human PBMCs in the presence of 20% FBS with CIC_{95} values from 6 to 50 nM.
- Raltegravir inhibited replication of a laboratory HIV-2 isolate in CEMx174 cells and 10% FBS with an average CIC_{95} of 6.3 nM.

Antiviral mechanism of raltegravir in cell culture

Cells from the human T cell line SupT1 were infected with a laboratory HIV-1 isolate with and without 1 μM raltegravir. The progress of infection was evaluated at different times using a series of quantitative PCR assays to measure the abundance of various HIV-1 DNA forms.

Raltegravir at 1 μM did not significantly inhibit the synthesis of HIV-1 DNA, but 1 μM raltegravir reduced detectable integration at 48 hr by approximately 50-fold. In addition, the presence of raltegravir resulted in a 15.8-fold increase in the abundance of 2-LTR circles as consequence of reduced integration activity.

Mutations in HIV-1 integrase that reduce susceptibility to raltegravir

The potential for HIV-1 to develop resistance to raltegravir was evaluated by culturing a laboratory HIV-1 isolate in human T lymphoid H9 cells in increasing concentrations of the agent over a period of months. Viruses able to replicate in higher concentrations of raltegravir emerged at the end of most passages and were characterised in detail by amplifying and molecularly cloning their integrase genes and determining the nucleotide sequences. A series of specific amino acid changes occurred over time during culture in increasing raltegravir concentrations.

The first change observed was Q148K, which arose during growth in 25 to 50 nM i.e. exceeding the IC_{95}. After passage in 1 μM, mutations E138A and G140A were sequentially incorporated. Additional mutations in the integrase gene appeared increasing raltegravir concentrations suggesting correlation of raltegravir with the appearance of mutations in the integrase gene.

The introduction of observed mutations in a wild-type HIV-1 isolate and the testing of resultant viruses in a single-cycle HIV-1 infectivity assay showed that the Q148K, E138A/Q148 and E138A/G140A/Q148K mutations resulted in average fold-shift IC_{50} values of 46-fold, 90-fold and 508-fold, respectively.

Other mutations were observed in the integrase genes of viruses isolated from HIV-1-infected patients who failed ART regimens including raltegravir. These mutations, including the primary mutations N155H, Q148H, and Q148R, each conferred a greater than 10-fold increase in the IC_{50}.

- **Secondary pharmacodynamics**

Raltegravir was evaluated in a series of *in vitro* assays to investigate its potential to act on human targets. The evaluation of specificity of raltegravir in RNA-dependent DNA Polymerase activity assay showed that raltegravir is not an inhibitor of HIV-1 reverse transcriptase polymerase activity at the highest concentration tested (100 μM-IC50 > 50 μM).

In an *in vitro* biochemical assay to test inhibition of RNase H activity of HIV-1 reverse transcriptase, no relevant activity of raltegravir up to 25 μM (the highest concentration tested) was observed. Inhibition of HIV-1 reverse transcription is, therefore, not responsible for the antiviral activity of

raltegravir (IC50 > 25 μM). Raltegravir did not inhibit human DNA polymerases α, β, or γ by more than 50% at the highest concentration tested (i.e., IC50 >50 μM for each of the three polymerases).

Raltegravir was also tested in a series of enzyme activity assays, transporter assays, and receptor-ligand displacement assays. Raltegravir did not significantly inhibit any of the 166 enzymes, transporters and receptors included in the screening panel (IC50 > 10 μM for all assays).

- **Safety pharmacology programme**

Three GLP compliant studies to evaluate effects of raltegravir on the cardiovascular, respiratory and central nervous systems were performed.

- A cardiovascular telemetry study, performed in dogs, after a single 5, 15 or 45 mg/kg dose, resulted in the absence of any change in cardiovascular indices attributable to raltegravir treatment, reaching Cmax of 3.6, 10 and 25 μM, respectively, at 1 hour after dosing.
- Raltegravir potential to affect respiratory or neurobehavioural system was tested following single oral administration of 30, 90 or 120 mg/kg to Sprague Dawley rats. Both studies showed that raltegravir does not induce any treatment related changes. A maximum concentration of approximately 30 μM was reached at the highest dose, as estimated from toxicokinetic data.

Ancillary pharmacology studies were performed to determine the effects of raltegravir in cardiovascular, respiratory, and renal function in dogs, and CNS and gastrointestinal motility in mice. Single or multiple IV or oral doses ranging from 1 to 5 mg/kg of in dogs showed that: (i) raltegravir do not affect mean arterial pressure, heart rate or cardiac intervals (PR, QRS, QTc) in dogs; (ii) the respiratory function, evaluated by respiratory ventilation, mechanics, blood pH, arterial gases, haemostasis or platelet function is not affected by raltegravir; (iii) with respect to the renal function, raltegravir does not induce treatment related changes in renal plasma flow, glomerular filtration, urine excretion, sodium and potassium excretion. The effects of raltegravir on the CNS in CD-1 mice after a single 100 mg/kg dose administration showed that raltegravir did not affect behaviour, locomotion, grip strength in this study.

Gastrointestinal motility was evaluated in CD-1 mice after administration of a single 10 or 30 mg/kg oral dose. No treatment-related effect on gastrointestinal motility at 10 mg/kg was observed, while an increase in gastrointestinal motility resulted at the highest dose. This is of minimal toxicological significance to humans as confirmed by the absence of signs of increased intestinal transit in the completed chronic toxicology studies in rats and dogs and in human clinical trials.

An additional cellular electrophysiological *in vitro* evaluation of a HIV Integrase Inhibitor on HERG was performed, on CHO-K1 cells. Raltegravir had a very small effect on HERG current at concentrations of 30 μM (0.94 ± 0.02 of control, n=8, for both voltage step and voltage ramp) and 100 μM (0.84 ± 0.04 of control, n=6, voltage step; 0.84 ± 0.06 of control, n=6, voltage ramp). Raltegravir inhibited the HERG current by 16% ± 4% at the highest testable concentration of 100 μM when elicited with 2 voltage-clamp protocols, a voltage step or voltage ramp.

- **Pharmacodynamic drug interactions**

To assess the potential for synergy or antagonism, the antiviral activity of raltegravir was evaluated in cell culture in combination with 18 licensed antiviral agents from all 4 classes (protease inhibitors, nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and entry inhibitor). Each antiviral agent, including raltegravir, was tested over a wide range of concentrations spanning its IC_{50} in the replication assay.

The results showed that when both test compounds were present at lower concentrations (below the 95% cell culture inhibitory concentration), the effect of adding raltegravir to other licensed antiretroviral agents was null or additive. At higher compound concentrations, typically in excess of their IC_{50} values, raltegravir displayed synergistic activity with all other antiviral compounds tested.

Pharmacokinetics

The ADME properties of raltegravir have been evaluated in rat and dog studies with additional studies in rabbits and mice, and a number of *in vitro* assays. A majority of the *in vivo* pharmacokinetic studies was conducted in male animals only.

Absorption/Bioavailability

Raltegravir is a low- (dog) to intermediate- (rat) clearance compound, with a short plasma half-life ($\leq$ 1.6 hr) and a volume of distribution ranging from ~0.4 to 2 L/kg. In both rats and dogs, the compound is rapidly absorbed ($T_{max} \leq 0.6$ hrs) and is orally bioavailable (> 60%).

The dose dependence of the oral pharmacokinetics of raltegravir was evaluated after single administration of raltegravir at four dose levels to male rats (40, 80, 120, 240 mg/kg) and male dogs (5, 15, 45, and 135 mg/kg). In rats, the AUC was nearly linear over the dose range of 40 to 120 mg/kg, but there was no further increase in exposure with increased dose. Above the 120 mg/kg dose absorption of raltegravir was saturable as a result of limited aqueous solubility.

In dogs, the plasma AUC and C_{max} increased proportionally with dose over the dose range of 5 to 45 mg/kg; the increase in either parameter was less than dose-proportional when the dose was increased to 135 mg/kg. Absorption of raltegravir was saturable at doses higher than 45 mg/kg.

Distribution

After oral administration of [^{14}C]raltegravir to rats, radioactivity is distributed rapidly and widely throughout the body. In addition to plasma, the highest concentrations of radioactivity are observed in the gastrointestinal tract and organs of excretion (stomach, small intestine, liver, kidney and urinary bladder). A small amount of radioactivity was detected in the brain. The compound crosses the rat and rabbit placenta and is excreted extensively in the milk of lactating rats. Raltegravir binds to the plasma proteins of the mouse (70%), the rat (74%), the dog (70%) and the human (83%).

The partitioning of raltegravir (0.9-18 μM) into blood cells was studied and the blood-to-plasma concentration ratios were determined to be 0.7, 0.9, and 0.6 for rat, dog, and human, respectively.

Raltegravir was evaluated *in vitro* as a potential inhibitor of P-gp Over a concentration range of 1 to 100 μM raltegravir did not affect [^{3}H]-vinblastine (VBL) accumulation in L-MDR1 and KB-V1 cell lines. In contrast, in the presence of a typical P-gp inhibitor, cyclosporin A, cellular accumulation of [^{3}H]-VBL was increased 10- and 12-fold in L-MDR1 and KB-V1 cells, respectively. Though *in vitro* studies indicated that raltegravir is a substrate of P-gp mediated transport, P-gp is unlikely to have a significant effect on the absorption and elimination of raltegravir. Potential drug interactions have been addressed in section 4.5 of the SPC.

Metabolism/Excretion

Metabolism of raltegravir was assessed in a series of *in vitro* and *in vivo* studies in mice, rats, dogs and humans.

In vitro studies

The *in vitro* metabolism of raltegravir was studied in hepatic microsomes and hepatocytes from rats, dogs, and humans. No significant metabolism of raltegravir was observed in NADPH-fortified microsomal incubations from any of the species. In contrast, raltegravir underwent metabolism in hepatocytes, with the major metabolite in all three species being the glucuronide derivative of the parent compound (M2). Small quantities of the glucose derivative (M1) of the parent compound and the acetyl hydrazine derivative (M3) also were detected. In addition, the data indicated that glucuronidation of the parent compound was the major metabolic pathway in all species and that raltegravir is not a substrate, nor an inducer or inhibitor of cytochrome P450 enzymes.

Further studies showed that the glucuronidation of raltegravir is mainly catalyzed by UGT1A1 with a minor contribution from UGT1A9 and 1A3. Raltegravir was found to be an inhibitor of UGT1A1 or UGT2B7 with IC_{50} values of >50 μM for both UGT activities. Raltegravir is unlikely to interfere with metabolism of other compounds because Raltegravir was found to have very low potential to inhibit CYP 1A2, 2C8, 2C9, 2C19, 2D6, 3A4, or 2B6 enzymes, and no potential to induce CYP3A4. Raltegravir is reported to be neither a substrate nor an inhibitor of cytochrome P450 enzymes. It might be subject to drug-drug interactions when co-administered with compounds that are known to be UGT1A1 inducers (e.g. rifampicin) or inhibitors (e.g. atazanavir, an HIV-protease inhibitor).

In vivo studies

The metabolism of [^{14}C]raltegravir was assessed in mice (20 mg/kg PO), rats (3 mg/kg IV), dogs (1.5 mg/kg IV), and humans (200 mg PO). The glucuronide of raltegravir (M2) was identified as the major radioactive entity in bile of mice, and in bile and urine of rats and dogs accounting for 62% and 31% of the administered dose, respectively. The glucose conjugate of the parent compound (M1; rat urine, dog urine and bile) and the acetyl hydrazine derivative (M3, rat urine) were the only other metabolites detected in rats and dogs and each metabolite represented <2% of the dose. The fraction of the dose excreted in urine and bile as unchanged parent compound was 10% in rats and 30% in dogs indicating that metabolism (via glucuronidation) is the major mechanism of clearance of raltegravir in preclinical species. The only metabolite detected in humans was M2 which accounted for 72% of the dose recovered in urine and was the major circulating metabolite in all species (mouse, rat, dog, and human). Although M2 circulates at significant levels in humans the pharmacological activity can be attributed to the parent compound since M2 has no activity against HIV-1.

Metabolism via glucuronidation is also the principal mode of clearance of raltegravir in humans since the majority of the dose recovered in urine was due to M2, and since a significant fraction of the parent compound observed in faeces is likely derived from the hydrolysis of M2 secreted in bile as observed in preclinical species.

Raltegravir is mainly excreted in the faeces (50 to 74%) in all species, with the remainder appearing in urine. The high recovery of the dose in faeces after IV administration indicates that biliary secretion is the primary mode of elimination of raltegravir-related radioactivity consistent with results observed in bile-duct cannulated rats. In rats, the recovery of the dose in urine was independent of the route of administration suggesting that absorption of the compound was complete in this species. In dogs, the lower recovery of dose in urine after P.O. administration relative to the IV route suggests that absorption of raltegravir is incomplete.

Raltegravir is excreted into the milk of lactating rats. The concentrations of the parent compound in maternal plasma and milk on lactational day (LD) 14 following daily oral administration of raltegravir at 300 or 600 mg/kg/day from Gestational Day (GD) 6 to LD 14 were measured. At 2 hours post the last dose LD 14, the milk-to-plasma concentration ratios were ~3 at both doses.

Toxicology

The toxicity of raltegravir was studied in mouse, rat, rabbit and dog models, investigating single- and repeat dose studies, genotoxicity, carcinogenicity (on-going), reproductive toxicity studies and a number of non-pivotal additional toxicity studies

- Single dose toxicity

Five toxicity studies were conducted with raltegravir in mice, rats and dogs to determine its approximate acute toxicity following a single oral dose. Raltegravir was well tolerated in mice and at oral doses up to 2000 mg/kg (LD_{50} >2000 mg/kg).

Intravenous dosing in rats of raltegravir, as a potassium salt in 0.9% (w/v) sodium chloride, caused treatment-related mortality at ≥200 mg/kg. Treatment-related physical signs were observed at 100, 200

and 400 mg/kg/day; No treatment-related body weight effects were noted in the surviving animals at 100 and 200 mg/kg. Based on these results the highest tolerated dose was 100 mg/kg/day. A no-observed-effect-level (NOEL) was not determined.

In oral dosing in dogs, raltegravir was well tolerated up to 250 mg/kg, a dose determined to be within the plateau of exposure to raltegravir following a single administration.

- Repeat dose toxicity (with toxicokinetics)

Repeat dose toxicity and toxicokinetic studies with raltegravir were conducted in mice (doses 50-5000 mg/kg/day), rats (doses 30-1200 mg/kg/day), dogs (doses 5-500 mg/kg/day) and rabbits (one toxicokinetic study). Pivotal GLP toxicity studies after repeat doses were performed over 14 weeks in the mouse, 27 weeks in the rat and 53 weeks in the dog.

Repeat dose studies in mice

In a 14-week oral range-finding study, treatment-related findings at dosages ≥1000 mg/kg/day of raltegravir included mortality, a variety of physical signs (typically distended abdomen, laboured breathing, audible respiratory noises, decreased activity, and eye partially closed), and body weight loss and/or decreases in body weight gain. The histopathological observations were limited to changes in the stomach of animals that died early, suggesting an irritant effect of the compound. The no-effect level for this study is 50 mg/kg/day.

Repeat dose studies in rats

Raltegravir was administered in oral toxicity studies of 5, 14, and 27 weeks duration. In the 5-week oral toxicity study, target organ toxicity was not observed and only minor increases in ALT and evidence of stomach mucosa irritation were found. In the 14 week repeat dose study, the only drug related effect observed up to 120 mg/kg/day was post-dose salivation which was reported to be related to poor palatability of the compound. Raltegravir caused mortality at 600 mg/kg/day in the 27-week study that was associated with body weight loss, urine staining and/or decreased food consumption prior to death. Up to 17% decreases in mean body weight gain were observed in surviving male rats at 600 mg/kg/day. There were no other significant findings in the antemortem parameters of these studies including haematology, serum biochemistry, and urinalysis evaluations. Degeneration of the glandular mucosa of the stomach was observed at 600 mg/kg/day and 120 mg/kg/day upon histopathological evaluation of the tissues. Additional observations were likely due to poor palatability, aspiration and/or irritation of the compound, including stomach inflammation in the 5-week study and postdosing salivation audible respiratory sounds, and inflammation in the nose and nasopharynx in the 27-week study. The NOAEL was considered to be 120 mg/kg/day which provides an exposure margin of 1.6-fold above the expected exposure of the 400 mg/BID dose in patients.

Repeat dose studies in dogs

Oral studies: In dogs, raltegravir was studied in repeat dose oral toxicity studies of 5, 14, 27 and 53 weeks duration. No deaths associated with drug treatment were observed during any of the dog studies. With the exception of emesis with or without body weight loss, and there were no treatment-related changes during the antemortem phase of the studies. Emesis was transient and/or intermittent and the underlining mechanism is unknown. There were no treatment-related changes in the gross or histopathological appearance of tissues examined from these studies in dogs. Therefore, the no-effect level in dogs, with the exception of emesis, following 53 weeks of treatment was ≥360 mg/kg/day.

Intravenous studies: Repeat dose i.v. toxicity studies in dogs revealed changes to liver enzymes and kidney function biochemistry. The 3-Day escalating toxicity *i.v.* study in dogs showed treatment-related changes in serum biochemistry at 100 mg/kg/day including increases in AST, ALT, and alkaline phosphatase. Treatment-related histopathological changes consisted of interstitial inflammation of the renal cortex in the female. The inflammation was considered very slight and was characterized by mixtures of lymphocytes and macrophages in association with tubular dilatation. No

treatment-related histopathological changes in the liver were observed. Based on the mortality observed in this study during intravenous administration of 358 mg/kg, likely due to cardiac arrhythmia secondary to the amount of administered potassium (raltegravir potassium salt) the maximum tolerated dose of raltegravir, when formulated as a monopotassium salt and administered intravenously, is considered to be <358 mg/kg. Treatment-related changes observed in the 7-days *i.v.* toxicity study at both doses (30 or 100 mg/kg/day) included transient postdosing emesis/retching and local changes at the injection sites (swelling and/or induration, and red/purple discoloration). Additional changes at 100 mg/kg/day consisted of persistent swelling and red/purple discoloration of the forelimbs, body weight loss, minimal increases in serum urea nitrogen, increases in alanine aminotransferase activity, alkaline phosphatase activity, and cholesterol, and very slight, multifocal tubular dilatation in the cortex of the kidneys. Based on the physical signs seen at 30 mg/kg/day, the NOEL for treatment-related changes was considered to be <30 mg/kg/day. At the NOEL safety margins were 6.5-fold or 24-fold the AUC and C_{max} of the 400-mg/BID MRD.

Toxicokinetic data

The toxicokinetic programme was performed in the context of the repeat dose toxicity studies. With respect to toxicokinetics the results showed no significant sex-differences in systemic exposure to raltegravir and no accumulation of raltegravir after repeated exposure.

Furthermore, toxicokinetic studies in mice were conducted in parallel with the ongoing main carcinogenicity study:

- Results from a 27-week study in mice indicate that at the high dose, 400 mg/kg/day in females and 250 mg/kg/day in males, systemic exposure is approximately 2-fold greater (females) or equal to (males) the AUC (54 mM•hr) at the 400-mg/BID MRD when adjusted for 30% and 17% unbound drug in mice and humans, respectively.
- Results from a 26-week study in rats indicate that at 300 to 600 mg/kg/day in females and 150 to 300 mg/kg/day in males, systemic exposure is approximately 10.3-fold greater (females) or 1.7-fold greater (males) the AUC (54 mM•hr) at the 400-mg/BID MRD when adjusted for 26% and 17% unbound drug in rats and humans, respectively.

- Genotoxicity

Raltegravir has been tested for genotoxicity in four GLP studies. Raltegravir did not show any mutagenic/genotoxic effects in the (i) *in vitro* bacterial mutation assay (Salmonella typhimurium strains and Escherichia coli strain); (ii) alkaline elution/rat hepatocyte assay (Primary Rat hepatocytes); (iii) chromosome aberration assay (Chinese Hamster Ovary cells); (iv) *in vivo* in the mouse micronucleus assay (Mouse/CRL). All studies were conducted using a range of doses; at the highest dose, there was evidence of cytotoxicity and/or drug insolubility. The results are uniformly negative, indicating the absence of genotoxic potential for raltegravir.

- Carcinogenicity

No short term carcinogenicity studies (e.g. with use of a transgenic model) were conducted.

Long-term studies

Two-year GLP carcinogenicity studies in mice and rats are currently ongoing and scheduled to be completed in 4Q 2007 with a draft report expected in 3Q-4Q 2008. In mice, oral doses of 50, 250, and 400 mg/kg/day in females and 50, 100 and 250 mg/kg/day in males were selected for the carcinogenicity study. In rats, oral doses of 50, 150, and 300 mg/kg/day in males and 50, 300 and 600 mg/kg/day in females were selected for the carcinogenicity study.

1-year interim data has shown high mortality rates: up to 38% in female mice dosed 400 mg/kg/day; up to 26% in female rats dosed 600 mg/kg/day and up to 20% in male rats dosed 300 mg/kg/day. The cause of these deaths was attributed to aspiration of dosing material into the nose/nasopharynx. Effects

of drug irritation to the nose/nasopharynx were seen and include chronic inflammation and epithelial hyperplasia and metaplasia.

The CHMP considered it acceptable that the carcinogenicity studies have not yet been completed. According to the guideline on carcinogenicity evaluation of medicinal products for the treatment of HIV infection (EMEA/CHMP/SWP/194898/2006) the submission of the results of the carcinogenicity studies as a post-approval commitment may be accepted for products intended for the treatment of patients with limited treatment options or of a clearly demonstrable added value. The applicant did commit to provide the final study report within a defined time-frame.

- Reproduction Toxicity

The potential for raltegravir to affect reproductive system was studied in rats and rabbits.

Fertility and early embryonic development

Raltegravir was administered orally to female rats at dose levels of 150, 300, or 600 mg/kg/day for 14 days prior to cohabitation, during cohabitation, and through GD 7. There were no treatment-related findings in the F_0 generation and there were no treatment-related effects on embryonic/fetal survival in the F_1 generation. Based on these data, the no-effect level for effects of raltegravir on fertility in F_0 female rats was ≥600 mg/kg/day.

Male rats were administered raltegravir orally once daily at doses of 100, 300, or 600 mg/kg/day for approximately 8 weeks. There were no treatment-related effects on mortality, physical signs, body weights, food consumption, mating performance, fertility, embryonic/fetal survival, sperm count, or sperm motility. There were no treatment-related gross changes in the thoracic or abdominal cavities. There were no treatment-related alterations in testicular weights nor were there gross or microscopic changes in the testes or epididymides. Based on these findings, the no-effect level for routine antemortem and postmortem parameters in male rats was ≥600 mg/kg/day. The no-effect level for male fertility was ≥600 mg/kg/day.

Embryo-fetal, prenatal and postnatal development including maternal function

In an oral range-finding reproduction study in female rats, raltegravir was administered once daily at doses of 150, 300, 450, or 600 mg/kg/day to pregnant rats from GD 6 through LD 20. There was no evidence of significant treatment-related maternal or developmental toxicity. Based on these results, the recommended high-dose level for the subsequent developmental toxicity study in rats was 600 mg/kg/day.

In an oral developmental and reproduction study in female rats (with post-weaning assessment), raltegravir was administered to female rats once daily at doses of 100, 300, or 600 mg/kg/day from GD 6 through 20 or through LD 20. There were no treatment-related findings in the F_0 generation. In the F_1 generation, the only treatment-related finding was an increase in the incidence of supernumerary ribs in the 600-mg/kg/day group as compared to concurrent control and to historical control. There were no treatment-related findings in the F_2 generation. Based on the results of this study, the no-effect level for maternal toxicity was ≥600 mg/kg/day. Based on the treatment-related increase in supernumerary ribs in the F_1 generation at 600-mg/kg/day group, the no-effect level for developmental toxicity was 300 mg/kg/day.

In an oral range-finding study in pregnant rabbits, raltegravir was administered to pregnant rabbits at doses of 125, 250, 500, or 1000 mg/kg/day from GD 7 though 20. There was no evidence of treatment-related maternal toxicity or developmental toxicity in the raltegravir-treated groups. Based on these results, the recommended high-dose level for the subsequent oral developmental toxicity study of raltegravir in rabbits was 1000 mg/kg/day.

In an oral developmental toxicity study in pregnant rabbits, raltegravir was administered once daily to pregnant rabbits at doses of 100, 500, or 1000 mg/kg/day from GD 7 through 20. There were no

indications of maternal toxicity or developmental toxicity at any dose level. Based on these results, the no-effect level of raltegravir for maternal and developmental toxicity was ≥1000 mg/kg/day.

The safety margin at the NOEL for developmental toxicity is reported to be approximately 3.4-fold the value at the maximum recommended dose (MRD). In rabbits, no developmental toxicity was found at the maximum dose of 1000 mg/kg/day, resulting in a safety margin of about 3.7-fold relative to the AUC in patients at the MRD.

Relevant findings have been appropriately addressed in sections 4.6 and 5.3 of the SPC.

Oral toxicity study in juvenile rats

In an oral range-finding toxicity study in juvenile rats, raltegravir was administered once daily at doses of 150, 300, 450, or 600 mg/kg/day from postnatal day (PND) 5 to postnatal week (PNW) 9. The only indication of toxicity was slightly decreased mean serum glucose values in males of the 450 mg/kg/day and 600 mg/kg/day groups. Based on these results, in a subsequent oral toxicity study in juvenile rats, raltegravir was administered to groups of 43 or 44 juvenile rats per sex at dose levels of 50, 200, or 600 mg/kg/day from PND 5 to PNW 8. A total of 19 deaths were reported during the study, but none of the deaths were considered to be treatment-related.

In the remaining study animals the applicant reported that there was no evidence of toxicity based on ante mortem parameters of mortality, physical signs, body weights, developmental signs, haematology, serum biochemistry, ophthalmologic examination, behavioural assessments, and reproductive performance, including embryonic/fetal survival.

Treatment-related histopathological findings consisted of vacuolation of the nonglandular mucosa at the limiting ridge at ≥200 mg/kg/day as well as inflammation which occurred at ≥200 mg/kg/day in males and at 600 mg/kg/day in females. This difference has been related to the absolute amount of drug deposited directly on the stomach mucosa, which is higher in males due to their body weight. Both vacuolar and inflammatory changes recovered following cessation of treatment for approximately 6 weeks. The mucosal epithelial vacuolation and associated increased inflammation were consistent with raltegravir causing very slight irritation to the limiting ridge of the nonglandular stomach of orally gavaged rats. Based on the histopathological results, the no-effect level for treatment-related changes in juvenile rats was 50 mg/kg/day. These findings in juvenile rats were consistent with the stomach irritation effects seen in adult rats.

- Local tolerance

A total of 7 local tolerance studies were conducted: three *in vitro*, two in mice (topical administration) and two in rabbits (dermal administration). Raltegravir is classified as a mild irritant for the free base and as a severe irritant as the potassium salt in the bovine corneal opacity (BCOP) *in vitro* assay. However, when applied to the skin of rabbits, no evidence of irritation was found. The results of the local lymph node assay (LLNA) in mice and of dermal irritation study in rabbits, showed that raltegravir, as either free base or potassium salt, is not a dermal sensitizer. The same conclusion has been drawn after studying the dermal irritation potential of raltegravir (potassium salt) in an *in vitro* human epidermal skin culture system.

- Other toxicity studies

No specific nonclinical toxicity studies were conducted to assess antigenicity or immunotoxicity. However, raltegravir was assessed in multiple-dose studies in rats and dogs. Animals were monitored for clinical signs, by evaluation of haematological (including differential white blood cell counting) and serum biochemical parameters, and by gross and histopathological examination of lymphoid tissues (lymph nodes, spleen, and thymus). There was no evidence of antigenicity or immunotoxicity resulting from these studies.

No nonclinical dependence studies were conducted to support an antiviral indication. Tissue distribution studies indicate that raltegravir is poorly brain penetrating, yielding the lowest detectable concentrations of all tissues tested (0.00971 µg/g of a 6 mg radiolabelled oral dose of raltegravir).

Specific nonclinical studies to evaluate the toxicity of specific metabolites were not conducted. The principal metabolite of raltegravir observed in humans and in rats and dogs is a glucuronide. In the rat and dog toxicity studies exposure to the glucuronide was 3.3-fold and 3.6-fold, respectively, above the projected exposure in patients receiving 400 mg/BID raltegravir.

The toxicological assessment of impurities is covered by an oral gavage study in rats over approximately 5 weeks. The results of this study support the proposed specification limits.

- Other studies

After a single dose administration of raltegravir (1000, 1500, or 2000 mg/kg) by oral gavage to female mice, the phototoxicity potential was determined exposing animals to UVB light (280 to 320 nm, 5 minutes), UVA light (300 to 400 nm-4hrs) and visible light (400 to 900 nm-4hrs). Additional groups of mice were placed in the dark during the 4-hour exposure period as negative controls. No treatment-related mortality, body weight effects, or phototoxic effects were noted in any dose group. Based on these findings, raltegravir is considered non-phototoxic at doses up to 2000 mg/kg.

An assessment of the potential for raltegravir to cause *in vitro* haemolysis of human, dog, or rat erythrocytes was conducted prior to initiation of the toxicity studies. The *in vitro* haemolysis assay produced negative results for raltegravir.

Ecotoxicity/environmental risk assessment

An environmental risk assessment conducted according to the guidance EMEA/CHMP/SWP/4447/00 was provided.
In the phase I, a worst-case PEC in surface water was higher than the action limit of 0.01 µg/L stated in the guidance hence a phase II environmental fate and effect analysis was performed. The conclusions from these phase II studies were that raltegravir is unlikely to represent a risk to the aquatic environment or to microorganisms. The results indicate that raltegravir is unlikely to bioaccumulate.

4. Clinical aspects

Introduction

The main clinical programme to support the marketing authorisation application for ISENTRESS consisted of:

- two identical phase III double-blind, randomised, placebo-controlled trials investigating the safety, tolerability, and efficacy of raltegravir 400 mg b.i.d. in combination with optimised background therapy (OBT) in treatment-experienced patients who failed antiretroviral therapies with triple-class resistant virus (Protocols 018 and 019);
- one phase II study for dose-finding in combination therapy in treatment-experienced patients (Protocol 005);
- one phase II study for proof of concept in monotherapy (part 1) and thereafter dose-finding in combination therapy (part 2), both in treatment-naïve patients (Protocol 004).

Details of these studies are summarised in Table 1. Furthermore, a phase I program was conducted investigating amongst others the pharmacokinetics profile including different pharmaceutical formulations as well as drug-drug interactions.

The clinical development program of raltegravir was consistent with the CHMP guidance, and specifically in accordance with the applicable EU guideline for the clinical development of medicinal products for the treatment of HIV infection (CPMP/EWP/633/02). The overall development strategy for raltegravir including the clinical programme was subject to CHMP Scientific Advice.

A paediatric development programme has not been initiated at time of application for marketing authorisation.

The approved indication for ISENTRESS is the treatment of human immunodeficiency virus (HIV-1) infection in treatment-experienced adult patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy, in combination with other antiretroviral medicinal products. The difference to the initially claimed indication is the restriction to the use in adult patients. The recommended dose is 400 mg twice daily.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

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

Table 1 Summary of main clinical studies

Protocol	Design /Duration	Treatment	N	Population	Study objectives	Primary Endpoint
004 (phase IIa) Part 1	Multi-center, double-blind, randomized, dose ranging, controlled study /10 days	100 mg BID 200 mg BID 400 mg BID 600 mg BID Comparator: placebo	7 7 6 8 7	Treatment-naive patients with plasma HIV RNA ≥5000 copies/ml and CD4 cell counts ≥100 cells/mm3; at least 18 years of age	Part 1: Dose finding and proof of concept (monotherapy)	Change from baseline in plasma HIV RNA on day 10
004 (phase IIa) Part 2	Multi-center, double-blind, randomized, dose ranging, controlled study /48 wks with extension to 144 wks	100 mg BID 200 mg BID 400 mg BID 600 mg BID Comparator: EFV	39 40 41 40 38		Part 2: Dose finding (combination therapy: TDF+3TC)	Proportion of patients with HIV RNA <400 copies/ml at Week 24
005 (phase IIb)	Multi-center, double-blind, randomized, dose ranging, placebo controlled study /48 wks with extension to 144 wks	200 mg BID 400 mg BID 600 mg BID Placebo	43 45 45 45	Treatment-experienced patients with plasma HIV RNA >5000 copies/ml and CD4 cell counts >50 cells/mm3 and documented resistant to at least one ART in each of the three classes; at least 18 years of age	Dose finding (combination therapy: OBT)	Change from baseline in HIV RNA at Week 24
P018 (phase III)	Multi-center, double-blind, randomized, placebo controlled study /48 wks with extension to 152 wks	400 mg BID Placebo	232 118	Treatment-experienced with plasma HIV RNA ≥1000 copies/ml and documented resistance to 3 ART classes; at least 16 years of age	Demonstration of efficacy (combination therapy: OBT)	Proportion of patients with HIV RNA <400 copies/ml at Week 16

019 (phase III)	Multi-center, double-blind, randomized, placebo controlled study /48 wks with extension to 152 wks	400 mg BID Placebo	230 119	Treatment-experienced with plasma HIV RNA ≥1000 copies/ml and documented resistance to 3 ART classes; at least 16 years of age	Demonstration of efficacy (combination therapy: OBT)	Proportion of patients with HIV RNA <400 copies/ml at Week 16

Pharmacokinetics

The programme investigating the clinical pharmacokinetics of raltegravir comprised several phase I studies in healthy subjects and in special populations (patients with hepatic insufficiency, patients with renal insufficiency) as well as an additional study studying the effect of UGT1A1 polymorphism.

Concentrations of raltegravir in human biological fluids (plasma and urine) were determined using validated liquid chromatography-tandem mass spectrometric detection (LC-MS/MS) methods. The lower limit of quantitation (LLOQ) for the plasma assay was 4.5nM (2ng/ml) and the linear calibration range was 4.5-2250 nM (2-1000 ng/ml). The LLOQ for urine assay was 563 nM (250 ng/ml) and the linear calibration range was 563-56300 nM (250-25000 ng/ml). All the methods were properly validated and met usual acceptance criteria.

- Absorption

The absolute bioavailability of raltegravir from clinically used formulations has not been determined. In a mass balance study in which a single dose of 200 mg [^{14}C]-raltegravir (185.92 µCi) formulated in a capsule was administered to eight male subjects in the fasted state urinary recovery suggested that the minimum bioavailability in this study was 32%.

Bioequivalence

The clinical development was performed with three different pharmaceutical formulations. First a rapidly disintegrating tablet was developed (Phase I lactose formulation) followed by a tablet presenting improved pharmacokinetic properties (Phase I poloxamer formulation). The Phase II/III/FMI poloxamer formulation was developed for use in later clinical studies and is intended for marketing.

An open-label, single-dose, 4-period, partially randomised, crossover bioequivalence study was conducted in fifteen young, healthy, male subjects investigating different formulations of raltegravir in a fasted state (study 007). This study included the comparison between the Phase I lactose formulation tablet and the Phase I poloxamer formulation tablet. Raltegravir was more bioavailable from the Phase 1 lactose tablet than from the Phase 1 poloxamer formulation ($AUC_{0-\infty}$: 25.69 µM•hr versus 16.07 µM•hr; geometric Mean (90% CI for GMR) for Treatment Ratio: 0.63 (0.51, 0.77)).

A bioequivalence study was not performed between these phase I formulations and the phase II/III/FMI formulation. As shown in Table 2 a comparison between monotherapy in ART-naïve patients in study 004 and multiple dosing of healthy volunteers in the fasted state showed that mean raltegravir PK parameters on dosing with the Phase I poloxamer formulation were generally similar to those observed with the Phase II/III/FMI poloxamer formulation. There was also no evidence of any formulation-related alterations in clearance and so the results of the three drug interaction studies performed with the Phase I poloxamer formulation were considered to be applicable to the Phase II/III/FMI poloxamer formulation.

Table 2 Geometric Mean PK values in studies with multiple 400 mg doses in the fasted state

Protocol	Formulation	N	$AUC_{0\text{-}12\ hr}$ (µM•hr)†	C_{max} (µM)†	$C_{12\ hr}$ (nM)†	T_{max} (hr)‡
001	Phase I Lactose	6	28.68	11.18	200.6	1
004	Phase II/III/FMI Poloxamer	6	14.3	4.5	141.7	-
008	Phase I Poloxamer	9	10.29	2.87	142.2	1.5
010	Phase I Poloxamer	10	19.25	5.95	124.6	2.0
017	Phase II/III/FMI Poloxamer	15	9.97	2.85	129	4.0

Effect of food

In a cross over study in 20 subjects, a single dose of 400 mg as the Phase II/III/FMI poloxamer formulation was administered either with a standard high fat meal or in the fasting state (study 028). The extent of raltegravir absorption ($AUC_{0\text{-}\infty}$) was slightly higher in the fed state but food slowed the rate and extended the duration of absorption with a 34% decrease in C_{max}, an 8.5-fold increase in $C_{12\ h}$ and a 7.3 h delay in T_{max}.

A second study investigated the food effect in a 4-period crossover design in 20 subjects who all received 400 mg raltegravir q12h for 10 days (study 035). On Days 4, 6, 8 and 10 subjects were randomised to receive the morning dose after one of the following: Treatment A (low-fat meal), Treatment B (moderate-fat meal), Treatment C (high-fat meal) and Treatment D (fasted). Blood samples were collected after the morning doses on Days 4, 6, 8 and 10 (last dose in the morning). The results are presented in Table 3.

Table 3 Raltegravir Steady-State PK - Specified Meal or Fasted

Parameter	Food Regimen GM				Food Regimen GMR			90% CIs for GM Ratio Fed to Fasted		
(units)	N	High	Mod.	Low	Fasted	High	Mod.	Low	High	Mod.	Low
C_{12hr} (nM)	19	453	182	93.9	110	4.13	1.66	0.86	(2.60, 6.57)	(1.04, 2.64)	(0.54, 1.36)
$AUC_{0\text{-}12h}$ (µM*hr)	19	21.2	11.3	5.38	10.0	2.11	1.13	0.54	(1.60, 2.80)	(0.85, 1.49)	(0.41, 0.71)
C_{max} (µM)	19	5.32	2.85	1.31	2.71	1.96	1.05	0.48	(1.41, 2.73)	(0.75, 1.46)	(0.35, 0.67)
T_{max} (hours)[a]	19	4.00	4.00	3.00	3.00				(1.05, 12.00)	(1.00, 10.00)	(0.50, 12.00)

High = high-fat meal; Mod. = moderate-fat meal; Low = low-fat meal.
[a] Median (min, max) values presented for T_{max}.

The results suggest that a low fat meal resulted in plasma levels lower than seen in the fasted state while a high fat meal increased C_{max}, AUC and C_{12h} and a moderate fat meal increased C_{12h} but had only a small effect on C_{max} and AUC. It is proposed that the differences between low, moderate and high-fat meals may be attributable to differences in gastric or biliary secretions secondary to meal fat content or change in gastric pH. However, considerable inter-individual variability was seen particularly with respect to C_{12hr} for which the coefficients of variation were 201%, 123% and 221% percent for low, moderate and high-fat meals, respectively, compared to 47% for the fasted state.

Raltegravir was taken with or without food in clinical studies in patients. Therefore, although the true effect of food on the absorption of raltegravir remains uncertain, the SPC recommends that it may be taken with or without food.

- Distribution

Raltegravir is 83% bound to human plasma proteins; binding is independent of concentration (2-10 µM). Directional transport studies in LLC-PK1 cells expressing human (L-MDR1) P-gp

indicated that raltegravir is a substrate of P-gp in humans. However, there was no effect on [^{3}H]-vinblastine (VBL) accumulation in L-MDR1 and KB-V1 cell lines, indicating that raltegravir is not a P-gp inhibitor. Based on the estimated apparent volume of distribution (Vss/F) of 287 L raltegravir seems to distribute extensively beyond the extracellular space. Raltegravir crossed the placenta in rats and rabbits and there was substantial excretion into rat milk.

- Elimination

In the mass balance study 51.1% of the radioactivity was recovered in faeces and 31.8% in urine over a 10-day period post-dose and mostly within 72 hours (study 011). Approximately 8 to 11% of the oral dose was excreted unchanged in urine during a steady-state dosing interval, with renal clearance values of approximately 54 to 65 ml/min. The apparent terminal elimination half-lives after multiple doses were 1 h (α) and 10 to 12 h (β) with an inflection point at around 12 h for most subjects. After administration of 400 mg doses in studies 025 and 028 $AUC_{0\text{-}12hr}$ accounted for approximately 88% of $AUC_{0\text{-}\infty}$ and thus $AUC_{12hr\text{-}\infty}$ accounted for approximately 12% of $AUC_{0\text{-}\infty}$.

Based on *in vitro* studies and a clinical interaction study with oral midazolam raltegravir is not expected to be a substrate, inhibitor or inducer of cytochrome P450 at clinically recommended doses. Studies of *in vitro* metabolism indicated that glucuronidation of the parent compound was the major metabolic pathway in humans, mainly catalysed by UGT1A1 with a minor contribution from UGT1A9 and 1A3. The glucuronidated metabolite (M2) does not exhibit potentially useful antiviral activity. Raltegravir is not a potent inhibitor of UGT1A1 or UGT2B7.

Polymorphisms in UGT1A1 are common and the applicant conducted a study to compare the pharmacokinetics of raltegravir in subjects homozygous for the $(TA)_6$ allele (UGT1A1*1/*1 genotype) or homozygous for the $(TA)_7$ allele (UGT1A1*28/*28 genotype; expected maximal impairment of UGT1A1 activity) (study (013)). Subjects in the two groups were matched for race, gender, age and BMI. Each subject received a 400 mg single oral dose of raltegravir (Phase II/III/FMI poloxamer formulation) in the fasted state.

The study enrolled 30 subjects in the UGT1A1 *28/*28 group and 27 in the UGT1A1*1/*1 group. All subjects were included in the PK and statistical analyses. On comparing former with the latter genotype the GMR for $AUC_{0\text{-}\infty}$ was 1.41 (90% confidence interval 0.96, 2.09) while the GMR for C_{max} was 1.40 (90% confidence interval 0.86, 2.28). In addition, there was an increase of 91% in the observed C_{12hr} for raltegravir in subjects with UGT1A1*28/*28 compared to subjects with UGT1A1*1/*1.

Raltegravir pharmacokinetics in subjects deficient in UGT1A1 were consistent with those observed on co-administration with atazanavir (a UGT1A1 inhibitor). Since plasma levels of raltegravir would be higher in those with UGT1A1*28/*28 there is no efficacy concern arising from these data. Taking into account particularly the comparative safety data from the two groups in study 005 (i.e. with and without co-administered atazanavir) no dose adjustment is advised with respect to UGT1A1 activity.

- Dose proportionality and time dependencies

Dose proportionality of raltegravir has been assessed in healthy adult subjects for the Phase I lactose formulation (Protocol 001) and for the Phase II/II/FMI formulation (study 025).

Single and multiple doses across a wide range were employed in healthy subjects (study 001); administration was in the fasting state except that single doses of 100 mg and 200 mg were also taken with a high fat meal. Steady state was achieved within two days of dosing at all dose levels examined with average accumulation ratios for AUC0-12hr and Cmax of 0.7 to 1.2 and for C12 hr of 1.2 to 1.6. After administration of multiple doses the AUC0-12hr and Cmax did not show dose proportionality beyond 600 mg twice daily.

However, in a definitive assessment of dose proportionality with single doses in study 025 the $AUC_{0-\infty}$ and C_{max} were dose proportional over 100 to 1600 mg and there was approximate dose proportionality for C_{12} h over 100 to 800 mg.

Raltegravir does not appear to display time-dependent pharmacokinetics.

- Inter- and intra-subject variability

Data from healthy subjects and from patients (mainly from sparse sampling) demonstrated that there was variability in T_{max} within and between subjects that was associated with variability in C_{max} and C_{12hr} so that a later T_{max} resulted in a lower C_{max} and higher C_{12hr} compared to an earlier T_{max}. It was noted that the same subject could have very different T_{max} values on different sampling days, indicating that the variability in T_{max} cannot be fully explained by a constant descriptor such as gender or UGT1A1 genotype.

Table 4 presents pharmacokinetic data obtained after administration of the Phase II/III/FIM poloxamer formulation in healthy subjects (study 025) and HIV-infected patients (studies 018 and 019), respectively.

Table 4 Intersubject and Intrasubject Variability for Raltegravir Pharmacokinetic Parameters

Pharmacokinetic Parameter	Study Number	W-S Variance (log scale) Point Estimate (% CV)[†]	B-S Variance (log scale) Point Estimate (% CV)[†]
Phase I			
C_{12hr} (nM)	025	0.1405 (38.8 %)	0.187 (45.2%)
$AUC_{0-\infty}$ (μM•hr)	025	0.1759 (43.9%)	0.439 (74.2%)
Phase III			
Geometric Mean Observed C_{12hr} (nM)	018, 019	0.907 (122%)	1.705 (212%)

Food, gastric pH and concomitant medications (e.g. that affect UGT1A1 activity or increase intra-gastric pH) are also likely to affect exposure. The impact of some of these factors on raltegravir pharmacokinetics can be seen in an examination of mean observed raltegravir C_{12h} values during dosing with 400 mg twice daily in HIV positive patients under various dosing conditions in the Phase II and III studies (Table 5).

Table 5 Raltegravir Geometric Mean Observed C_{12hr} Values Obtained under Various Dosing Conditions

Treatment (all 400 mg BID)	N	GM (90% CI) for GM Obs C_{12hr}	Dosing Conditions
P004 monotherapy (full profile)	6	142 (88, 229)	monotherapy, fasted
P004 +3TC, TDF (full profile)	6	239 (150, 381)	+3TC, TDF, fasted
P004 +3TC, TDF	29	329 (230, 471)	+3TC, TDF, food[†]
P005, 018, 019 combined	285	269 (240, 301)	+OBT, food[†]
P018, 019 combined	260	272 (241, 306)	+OBT food[†]
P018, 019 TPV in OBT	59	155 (120, 202)	+OBT with TPV, food[†]
P018, 019 no TPV in OBT	201	320 (281, 364)	+OBT no TPV, food[†]
P005, ATV in OBT	8	363 (209, 628)	+OBT with ATV, food[†]
P005, no ATV in OBT	17	203 (133, 310)	+OBT no ATV, food[†]

[†]"food" in Dosing Conditions column indicates dosing was conducted without regard to food intake, and so may have been either fasted or fed
GM Obs C_{12hr} = geometric mean of observed C_{12hr} values from sparse PK sampling
N = number of patients in the treatment group.
OBT = Optimized Background Therapy; 3TC = Lamivudine; TDF = tenofovir; ATV = Atazanavir; TPV = tipranavir/ritonavir

The pharmacokinetic data collected during studies in treatment experienced patients were too few and collected under too variable conditions to allow for reliable conclusions to be drawn from population PK analyses.

As a result, it was not possible to determine from available evidence whether the extremes of plasma concentrations of raltegravir that have been documented have a clinically important effect on safety and efficacy. The applicant's proposals for pharmacokinetic criteria that might indicate no important effects for safety (AUC increase) and efficacy (C_{12h}) were considered to be unreliable. The SPC describes the inter- and intra-individual variability observed and mentions possible contributing factors. The CHMP requested that the applicant provides post-approval a detailed plan to further explore the implications for safety and efficacy of the inter- and intra-individual variability in the pharmacokinetics of raltegravir.

- Special populations

Renal impairment

Due to the projected minor component of renal elimination for raltegravir the applicant compared the pharmacokinetics only between subjects with severe renal insufficiency and controls with normal renal function. Of the ten subjects with severe renal insufficiency three had notably lower plasma exposures (AUC 3.6 to 7.4 μM•h) compared to the other seven (AUC ≥ 10 μM•h and up to 43 μM•h) whereas the ten controls all had AUCs in the range 10.8 – 31.7 μM•h. There was no apparent relationship between raltegravir AUC0-∞, Cmax or C12 h and the pre-study creatinine clearance value. No dose adjustment is considered to be necessary when creatinine clearance falls below 30 ml/min.

Hepatic impairment

Raltegravir pharmacokinetics were compared between eight subjects with moderate hepatic insufficiency (Child-Pugh scores 7-8) and eight matched controls per group. Among the eight with moderate hepatic insufficiency the actual range of AUC and Cmax values was wide (e.g. from 3.05 μM•h to 50.08 μM•h) whereas the eight controls all had AUCs in the range 13.24 – 36.42 μM•h. However, this spread of values was similar to that seen in other studies in healthy subjects. On comparing mean values between healthy subjects and those with moderate hepatic insufficiency there was no clinically important effect of moderate hepatic insufficiency on raltegravir pharmacokinetics, which was thought likely because glucuronidation is spared in hepatic insufficiency. For this reason no study in severe hepatic insufficiency was performed.

Other populations

There did not appear to be significant effect of gender, age race or weight on raltegravir pharmaco-kinetics. However, it needs to be considered that the results from the population PK analysis must be interpreted with caution as the model provided a poor prediction of the absorption phase in the fed state, which is of relevance due to the very large effect on food on the PK profile of raltegravir and the unknown food status of the patients during the data collection in the phase II and III studies.

There are no data in children (age < 16 years).

- Pharmacokinetic interaction studies

Table 6 summarises the data from the drug-drug interaction studies. Single or multiple doses of 400 mg raltegravir were co-administered (except study 006). The formulations used varied but 6 out of 9 studies used one of the two poloxamer formulations and exposure to raltegravir would have been potentially higher in the three that used the Phase I lactose tablets.

Table 6 Results from drug-drug interaction studies

Co-administered Drug	Study	C_{12hr} GMR† (90% CI)†	AUC GMR† (90% CI)†	C_{max} GMR† (90% CI)†
Atazanavir	006	1.95 (1.30, 2.92)	1.72 (1.47, 2.02)	1.53 (1.11, 2.12)
Atazanavir and Ritonavir*	360	1.41 (0.90, 2.20)	1.29 (1.02, 1.64)	NA
Atazanavir and Ritonavir	010	1.77 (1.39, 2.25)	1.41 (1.12, 1.78)	1.24 (0.87, 1.77)
Ritonavir	002	0.99 (0.70, 1.40)	0.84 (0.70, 1.01)	0.76 (0.55, 1.04)
Efavirenz	003	0.79 (0.49, 1.28)	0.64 (0.52, 0.80)	0.64 (0.41, 0.98)
Rifampicin	009	0.39 (0.30, 0.51)	0.60 (0.39, 0.91)	0.62 (0.37, 1.04)
Tipranavir and Ritonavir	017	0.45 (0.31, 0.66)	0.76 (0.49, 1.19)	0.82 (0.46, 1.46)
Tipranavir and Ritonavir*	375	0.49 (0.37, 0.64)	0.65 (0.58, 0.73)	NA
TMC125	026	0.66 (0.34, 1.26)	0.90 (0.68, 1.18)	0.89 (0.68, 1.15)
Tenofovir	008	1.03 (0.73, 1.45)	1.49 (1.15, 1.94)	1.64 (1.16, 2.32)
Tenofovir	004/005#	1.42 (0.89, 2.28)	1.41 (1.11, 1.79)	1.33 (0.96, 1.85)

† Geometric Mean Ratio (co-administration/administration alone) for single-dose $AUC_{0-\infty}$ (002, 003, 006, 009) or multiple-dose $AUC_{0-\tau}$ (studies 004, 005, 008, 010, 017, 026) and $C_{12\ hr}$ on the day of co-administration

* Population PK estimates

\# Data derived from patient sampling during phase 2 studies

In addition, an interaction study with midazolam was conducted (study 016). The study confirms that raltegravir does not alter the pharmacokinetics of a CYP3A4 substrate (GMR (90% CI): AUC 0.92 ng•h/ml (0.82, 1.03); C_{max} 1.03 µg/ml (0.87, 1.22)).

Overall, raltegravir probably has a low propensity to affect or to be affected by the majority of co-administered medicinal products. Nevertheless, the following issues were particularly discussed during the assessment:

- During the 10-day monotherapy phase in ART naïve patients in 004 the PK findings were similar to those observed in healthy subjects when administered the same dose and formulation. However, during combination therapy with tenofovir and lamivudine the AUC0-12 h (41%), Cmax and C12 h (42%) raltegravir were higher compared to the monotherapy phase. Also, exposure to lamivudine was higher when it was given with raltegravir compared to administration with efavirenz (each in combination with tenofovir).
- Administration of omeprazole prior to administration of raltegravir in healthy subjects resulted in an approximately 3.1-fold increase in raltegravir $AUC_{0-\infty}$, 4.1-fold increase in C_{max}, and 46% increase in C_{12hr}. A likely mechanism to explain these results is increased bioavailability due to improved solubility of raltegravir at higher pH. It has been reported that AIDS patients have gastropathy with hypochlorhydria. The applicant proposed that this may explain in part why the population PK data suggested that raltegravir PK parameters were not significantly altered in treatment experienced patients taking a pH-altering agent. However, the data in patients are considered to be unreliable and there is a particular need to further assess the effects of medicinal products that increase intra-gastric pH in patients rather than in healthy subjects.
- Co-administration with rifampicin produces a profound decrease in raltegravir plasma concentrations. The data suggest that an increase in raltegravir dose is needed during co-administration.

The SPC in section 4.5 provides an adequate description of the currently known interaction profile of raltegravir. The CHMP requested further data to be generated post-approval by studying the

interaction between raltegravir and rifabutin, as well as the interaction between raltegravir and one PPI and one H2 blocker.

Pharmacodynamics

The pharmacodynamic properties of raltegravir were investigated in isolates obtained from HIV patients enrolled into the phase II and III studies (see Table 1). The following presents these data together with a brief summary of virological data. In addition, information from the QTc study in healthy subjects and the integrated PK/PD analyses is described.

Details on nonclinical pharmacodynamic studies are presented in section "Nonclinical Aspects".

- Mechanism of action

Raltegravir inhibits the HIV-1 integrase enzyme, which is an enzyme encoded by the HIV-1 responsible for covalent insertion of the HIV-1 proviral DNA into the genomic DNA of the host cell. The process of integration occurs in four steps (assembly, 3' processing, strand transfer, and reparation) of which the first three are realised by the integrase; raltegravir inhibits the third step of the integration process (Integrase Strand Transfer Inhibitor, InSTI).

- Primary and Secondary pharmacology

Raltegravir inhibited the enzymatic activity of purified recombinant HIV-1 integrase with an apparent IC_{50} of approximately 10 nM. In comparison, raltegravir did not inhibit the DNA polymerase or RNaseH activities of HIV-1 reverse transcriptase at concentrations of 25 μM or higher. There was >1,000-fold selectively for integrase with respect to human DNA polymerases α, β and γ, with IC_{50} > 50 μM for each of these polymerases.

In vitro resistance

The potential for HIV-1 to develop resistance to raltegravir was evaluated by culturing a laboratory HIV-1 isolate in human T lymphoid H9 cells in increasing concentrations of the agent over a period of months. The first change observed was Q148K, which arose during growth in 25 to 50 nM i.e. exceeding the CIC_{95}. The Q148K mutation persisted during growth in increasing concentrations up to 500nM. After passage in 1 μM, mutations E138A and G140A were sequentially incorporated. Growth in still higher concentrations resulted in the appearance of additional mutations in the integrase gene. Thus, the ability of HIV variants to replicate in higher concentrations of raltegravir was correlated with the appearance of mutations in the integrase gene.

To further evaluate effects of mutations on susceptibility some of those that had been observed were introduced into a wild-type HIV-1 isolate and the resultant viruses were tested in a single-cycle HIV-1 infectivity assay. The Q148K, E138A/Q148 and E138A/G140A/Q148K mutations resulted in average fold-shift IC_{50} values of 46-fold, 90-fold and 508-fold, respectively.

Viruses containing other integrase mutations were also evaluated for their effects on susceptibility to raltegravir. Some of these mutations were observed during cell culture resistance selection experiments with integrase inhibitors other than raltegravir. In general, these mutations conferred less than 10-fold differences in susceptibility to raltegravir although the N155S mutation resulted in ~19-fold increase in IC_{50}. Other mutations were observed in the integrase genes of viruses isolated from HIV-1-infected patients who failed ART regimens including raltegravir. These mutations, including the primary mutations N155H, Q148H, and Q148R, each conferred a greater than 10-fold increase in the IC_{50}.

In vivo resistance

In raltegravir-treated patients who had viral rebound or non-response in the clinical studies, the emergence of resistant viruses was monitored by isolating plasma viral RNA, determining the amino

acid sequences encoded by the integrase gene and comparing the sequence at virological failure with the sequence at baseline for the same patient. The first resistance mutations were observed at Week 4. The following observations were made:

- Virological failure was generally associated with mutation at either amino acid 148 (Q changed to H, K, or R) or amino acid 155 (N changed to H). When introduced into HIV-1 by site-directed mutagenesis, primary mutations at position 155 or 148 conferred decreased susceptibility to raltegravir and were associated with decreased viral replication capacity in cell culture.
- The majority of viruses isolated at virological failure contained two or more resistance-associated mutations in integrase. In viruses from a small number of virological failures there were two or more secondary mutations without a mutation at amino acid 148 or 155. Individually, secondary mutations at amino acid residues L74, E92, T97, F121, E138 and G140 had a minimal effect on susceptibility to raltegravir but combinations of mutations resulted in decreased susceptibility. Secondary mutations at other positions (e.g. Y143, G163, S230 and D232) have not yet been examined in detail. The addition of secondary mutations to primary mutations sometimes, but not always, resulted in increased viral replication capacity, though replication capacities of these mutants were lower compared to wild-type virus.
- Factors that decreased the likelihood of developing mutation at either amino acid 148 or 155 (i.e. with a Hazard Ratio <1) included lower viral load, the use of darunavir in OBT, PSS >0 and GSS>0. A factor that increased the likelihood of developing a mutation at either amino acid 148 or 155 was lower CD4 count (≤ 50 *vs* > 200).

By Week 24, 84 raltegravir-treated patients in studies 018 and 019 had met the definition of virological failure and integrase genotype data were available for 60 patients. Among the viruses from these 60 patients 42 (70%) showed genotypic evidence of raltegravir resistance when tested at a point near or corresponding to the time of rebound.

Table 7 shows the number and percent of patients displaying signature integrase mutations in the N155 pathway, the Q148 pathway, the Y143 pathway or other pathways. A subgroup analysis is also reported for patients who had baseline GSS of 0, 1 or ≥ 2 (defined as before with respect to counting of enfuvirtide and darunavir).

Table 7 Patients from studies 018 and 019 with virological failure by Week 24 and genotypic data available

Resistance Mutations Observed in Integrase Gene	Integrase Genotypes Available‡ (N = 60) n (%)	Baseline GSS = 0†† (N = 31) n (%)	Baseline GSS = 1†† (N = 15) n (%)	Baseline GSS ≥ 2†† (N = 14) n (%)
N155 pathway	21 (35)	11 (35.5)	5 (33.3)	5 (35.7)
Q148 pathway	9 (15)	5 (16.1)	3 (20)	1 (7.1)
Y143 pathway	5 (8.3)	1 (3.2)	4 (26.7)	0 (0)
Multiple pathways‡‡	4 (6.7)	4 (12.9)	0 (0)	0 (0)
Other pathways	3 (5)	2 (6.5)	0 (0)	1 (7.1)
Without mutations known to confer R	18 (30)	8 (25.8)	3 (20)	7 (50)

Thus available data continue to indicate that the 148 and 155 pathways constitute the major raltegravir resistance pathways but there have been a small number of patients failing raltegravir who have developed integrase mutations that do not include a substitution at either 148 or 155. Substitutions at Y143 (Y143C or Y143R) occurred in some patients and one patient had a substitution at F121 (F121N). Phenotypic testing of site-directed mutants in a single-cycle infectivity assay shows that these substitutions can contribute to raltegravir resistance.

Effect on the OTc interval

The effect of raltegravir on the QTc interval has been investigated in a double-blind, randomised, placebo-controlled, double-dummy, 3-period, balanced cross over study in healthy volunteers using moxifloxacin as the positive control. Mean exposure to raltegravir (in a subset of 12 subjects) after a 1600 mg dose was considerably higher than seen for 400 mg doses. While the actual range of values after 1600 mg was from 2.9 to 56.9 μM for Cmax, 15 to 181 μM.h for AUC 0-12h and 143 to 391 nM for C12h there was no relationship detected between plasma exposure and QTcf. Raltegravir appeared not to have a clinically important effect on the QTc interval and there were no notable effects on heart rate, PR intervals and QRS duration.

Pharmacokinetic/pharmacodynamic (PK/PD) relationship

Two integrated PK/PD reports were produced by the applicant: 360 – PK/PD from 004 and 005 (Phase II dose-finding studies), and 375 – PK/PD from 005, 018 and 019 (pooled 400 mg b.i.d. in treatment-experienced patients plus OBT).

Due to the limited PK sampling in treatment-experienced patients and the degree of inter- and intra-individual variability observed, the CHMP considered that the findings reported from these analyses must be viewed with some considerable caution. Therefore the following conclusions are not considered to be well-founded at present and there is a need for further evaluation of the importance of intermittent or persistent exposure to low or high raltegravir plasma concentrations post-approval:

- In ART-experienced patients in study 005 no PK/PD association was detected for any efficacy response at week 16 compared to the observed C12 h parameters.
- The data from 018 and 019 suggested an association between efficacy and the model-predicted AUC0-12 h. The applicant considered that the range of raltegravir concentrations obtained over 200 to 600 mg doses falls near the top of the concentration-response curve, where treatment response may be only modestly concentration-dependent.
- Based on the monotherapy period of 004 in ART naïve patients the applicant considered that C_{trough} ($C_{12\ hr}$) is likely the most sensitive PK parameter to predict viral response. The lower limit of clinical experience (i.e. with 100 mg b.i.d.) was ~0.4-fold (60% decrease) that seen with the recommended dose regimen of 400 mg b.i.d. Since the applicant considered that 100 mg b.i.d. was an efficacious dose a decrease in plasma exposure of up to 0.4-fold was considered unlikely to affect efficacy.
- Since the applicant considered that AEs did not seem to correlate with C_{max} it was considered that AUC was the most appropriate PK parameter for judging the clinical significance of increases in raltegravir plasma concentrations in terms of safety. In Phase II, 51 patients received 600 mg raltegravir twice daily in combination with tenofovir and/or atazanavir. The applicant states that with this dose a ~50% increase in AUC over that seen with 400 mg would be expected plus an increase by an extra 30 to 70% due to the additional medicinal products. Thus the applicant considered that AUCs approximately 2-fold the typical value observed with 400 mg twice daily dosing were likely achieved without a clear association with AEs.

The applicant did commit to provide CHMP with a detailed plan to further explore the implications for safety and efficacy of the inter- and intra-individual variability in the pharmacokinetics of raltegravir.

Clinical efficacy

The application contained efficacy data from the four studies presented in Table 1. For the assessment of the marketing authorisation application, the following data was available:

- Study 004: week 48 double-blind data for all doses; available data beyond week 48 reported
- Study 005: week 24 double-blind data for all doses; available data beyond week 48 reported

- Study 018: week 16 and week 24 double-blind data (final data for all patients)
- Study 019: week 16 and week 24 double-blind data (final data for all patients)

In addition, the applicant provided limited and preliminary results of week 48 from studies 018 and 019 during the procedure based on data available in-house as of 03.08.2007 and 31.07.2007, respectively. The final week 48 efficacy and safety data was however considered necessary by the CHMP for the assessment; the applicant did commit to provide these data post-approval.

All these studies have been performed with the formulation intended for marketing (Phase II/III/FMI poloxamer formulation).

- Dose response studies

Two studies were conducted to establish the dose for raltegravir in combination antiretroviral therapy, one in ART naïve patients (004) and one in treatment experienced patients (005). The range of doses chosen for study was based on the results of the Phase I pharmacokinetic studies using the Phase I lactose formulation and the noted relationship between mean $C_{12\,hr}$ and the IC_{95} in 50% human serum for antiretroviral activity.

Study 004

Study 004 was a multi-centre, double-blind randomised dose-ranging, controlled study in ART naïve patients, which was conducted in two parts:

- Part I compared raltegravir monotherapy (100 mg, 200 mg, 400 mg and 600 mg, all b.i.d.) with placebo over 10 days (N=35). This was followed by a planned interim analysis before initiation of Part II that necessitated a time gap between Parts I and II.
- Part II compared raltegravir (100 mg, 200 mg, 400 mg and 600 mg, all b.i.d.) with efavirenz 600 mg once daily each administered in combination with tenofovir and lamivudine. By amendment the study will continue to Week 144 (N=198).

In part I the mean ages per group were in the range 35-45 years, log10 HIV RNA was from 4.5 to 5.0 and the CD4 counts were from 256 to 568 mm^{-3}; in part II the mean ages per group were in the range 33-36 years, log10 HIV RNA was from 4.7 to 4.9 and the CD4 counts were from 225 to 277 mm^{-3}.

In part I each active groups showed a change from baseline in HIV RNA that was superior to placebo at Day 10. Over half per active group had <400 copies/ml at Day 10 and one or two per group had <50 copies/ml (Table 8).

Table 8 Percent of patients with HIV RNA <400 copies/ml and <50 copies/ml at Day 10 in study 004, part I

Treatment	N	Percent of patients with HIV RNA <400 copies/ml		Percent of patients with HIV RNA <50 copies/ml	
		n	% (95% CI)	n	% (95% CI)
Raltegravir 100 mg b.i.d.	7	4	57.1 (18.4, 90.1)	1	14.3 (0.4, 57.9)
Raltegravir 200 mg b.i.d.	7	4	57.1 (18.4, 90.1)	2	28.6 (3.7, 71.0)
Raltegravir 400 mg b.i.d.	6	3	50.0 (11.8, 88.2)	2	33.3 (4.3, 77.7)
Raltegravir 600 mg b.i.d.	8	4	50.0 (15.7, 84.3)	1	12.5 (0.3, 52.7)
Placebo	7	0	0.0 (0.0, 41.0)	0	0.0 (0.0, 41.0)

In part II, based on the primary analysis of 171 patients, all raltegravir dose groups showed changes in HIV RNA at Week 24 and at Week 48 that were similar to those in the efavirenz control group (Table 9).

Table 9 Percent of patients with HIV RNA <400 copies/ml over time at Week 48 in study 004, part II

Treatment	Percent of patients with HIV RNA <400 copies/ml		Raltegravir minus Efavirenz
	n	% (95% CI)	Difference (95% CI)
Raltegravir 100 mg b.i.d.	32/33	97.0 (84.2, 99.0)	11.7 (-2.7, 27.8)
Raltegravir 200 mg b.i.d.	27/33	81.8 (64.5, 93.0)	-3.5 (-22.3, 15.1)
Raltegravir 400 mg b.i.d.	35/35	100.0 (90.0, 100.0)	14.7 (4.0, 30.3)
Raltegravir 600 mg b.i.d.	30/34	88.2 (72.5, 96.7)	2.9 (-14.5, 20.5)
Efavirenz 600 mg q.d.	29/34	85.3 (68.9, 95.0)	

Non-completer = Failures

For patients with >100,000 copies/ml at baseline, 77, 75, 83 and 100 % in the four ascending raltegravir dose groups had <50 copies/ml at Week 24 compared with 86% in the efavirenz group. A similar analysis of Week 48 data showed that 85, 67, 67 and 88% raltegravir patients with >100,000 copies/ml at baseline had <50 copies/ml compared with 71% in the efavirenz group.

At Week 24, the average increase in CD4 cell count ranged from 122 to 184 cells/ml for raltegravir groups compared to 101 cells/ml for efavirenz. Corresponding values at Week 48 were 140 to 216 cells/ml compared to 156 cells/ml.

Study 005

Study 005 was a multi-centre, double-blind, randomised, dose-ranging, placebo-controlled study in treatment-experienced patients. Patients had HIV RNA >5,000 copies/ml and CD4 cell counts >50 cells/ml despite current stable (> 3 months) therapy, plus documented resistance to at least one compound in each of the three classes of oral antiretroviral therapies (NRTI, NNRTI and PI). Patients with hepatitis B or C co-infection were excluded.

Raltegravir (200, 400 and 600 mg b.i.d.) was compared with placebo, each administered in combination with an investigator-selected optimised background therapy (OBT). The use of tipranavir or darunavir was not allowed. The duration of the double-blind, dose-ranging portion was at least 24 weeks.

A total of 179 patients were enrolled with one patient never treated. Based on increase of exposure due to atazanavir (almost all subjects received atazanavir boosted with ritonavir) two sub-studies were performed:

A – Patients who did not receive atazanavir in their OBT (N=127);
B – Patients who did receive atazanavir in their OBT (N=52).

Patients were also stratified within each sub-study) by: (1) enfuvirtide use in OBT (yes or no); and (2) degree of resistance to protease inhibitors (PIs) at study entry (resistant to 1 PI or >1 PI).

Patients who discontinued due to lack of efficacy or virological failure after completing at least 16 weeks of double-blind therapy were allowed to enter an open-label post virological failure (OLPVF) phase in which they received raltegravir in addition to current or revised OBT (initially 600 mg b.i.d. but reduced to 400 mg b.i.d. when Phase III data were available). Also, later during the study conduct all patients who had completed at least 24 weeks could continue to receive 400 mg b.i.d. without OBT changes.

Patient disposition shows the dramatic loss of patients from the placebo group into the OLPVF phase with 37 out of 45 patients (82.2%) in the placebo group entering the OLPVF phase.

The median age was 43 years. A diagnosis of AIDS applied to 82%. The median number of prior ARTs was 12 with a median duration of any ART of 10 years. At baseline about half of patients had HIV RNA > 50,000 copies/ml. Excluding enfuvirtide, there was no active antiretroviral compound

(GSS=0) in the OBT for 72% of patients based upon genotypic test results and for 48.3% of patients based upon phenotypic test results.

In sub-study A (no atazanavir that might augment plasma levels of raltegravir) the mean changes from baseline in log10 HIV RNA (OF approach) were -1.83, -1.76, -1.74 and -0.26 for the three ascending raltegravir groups and placebo, respectively. The changes in the three raltegravir groups were each statistically significantly superior to placebo based upon Mann-Whitney-Wilcoxon rank test ($p<0.001$) and adjustment for multiple comparisons. However there was no significant difference between the raltegravir dose groups.

The applicant concluded that the benefit of raltegravir over placebo was not significantly different between the sub-studies A and B. However, the data from sub- study B showed some possible numerical advantages for proportions with < 400 and < 50 copies/ml and for change in CD4 count when raltegravir was co-administered with atazanavir and when 600 mg was used compared to 400 mg (Table 10).

Table 10 Treatment outcome at Week 24 in sub-studies A and B of study 005

Treatment	Sub-study			
	A (no atazanavir use in OBT)		B (atazanavir use in OBT)	
	N	Mean (95% CI)	N	Mean (95% CI)
Percent of patients with HIV RNA <400 copies/ml at Week 24				
Raltegravir 200 mg b.i.d.	30	70.00 (50.60, 85.27)	13	69.23 (38.57, 90.91)
Raltegravir 400 mg b.i.d.	31	64.52 (45.37, 80.77)	14	85.71 (57.19, 98.22)
Raltegravir 600 mg b.i.d.	32	62.50 (43.69, 78.90)	13	92.31 (63.97, 99.81)
Placebo	33	12.12 (3.40, 28.20)	12	25.00 (5.49, 57.19)
Percent of patients with HIV RNA <50 copies/ml at Week 24				
Raltegravir 200 mg b.i.d.	30	63.33 (43.86, 80.07)	13	69.23 (38.57, 90.91)
Raltegravir 400 mg b.i.d.	31	48.39 (30.15, 66.94)	14	71.43 (41.90, 91.61)
Raltegravir 600 mg b.i.d.	32	56.25 (37.66, 73.64)	13	92.31 (63.97, 99.81)
Placebo	33	12.12 (3.40, 28.20)	12	16.67 (2.09, 48.41)
Change from baseline CD4 cell count (cells/ml) at Week 24				
Raltegravir 200 mg b.i.d.	29	60.52 (12.89, 108.14)	12	68.50 (23.80, 113.20)
Raltegravir 400 mg b.i.d.	30	102.30 (59.04, 145.56)	13	137.15 (57.01, 217.30)
Raltegravir 600 mg b.i.d.	30	93.77 (48.93, 138.61)	12	94.83 (44.48, 145.18)
Placebo	32	8.38 (-9.41, 26.16)	11	-3.27 (-38.51, 31.97)

On pooling the data from sub-studies A and B the results for the three raltegravir groups at Week 24 (using the Observed Failure approach for mean change from baseline in viral load and CD4 count) were generally similar although a lower proportion in the 400 mg b.i.d. group achieved <50 copies/ml and there was a higher rate of rebound (Table 11). Nevertheless, for the virological and cellular endpoints all raltegravir groups were superior to placebo.

Table 11 Treatment outcome at Week 24 of all randomised patients in sub-studies A and B of study 005 (pooled data, double-blind phase)

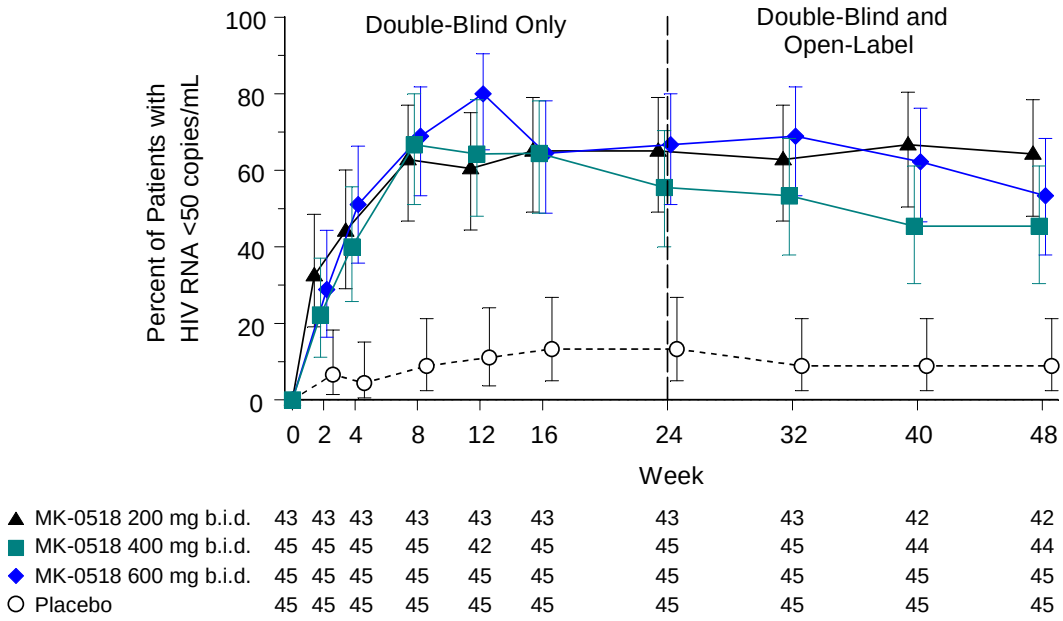
Outcome	Raltegravir			Placebo
	200 mg b.i.d. (N=43) n(%)	400 mg b.i.d. (N=45) n(%)	600 mg b.i.d. (N=45) n(%)	(N=45) n(%)
Patients with HIV RNA <400 copies/ml	30 (69.8)	32 (71.1)	32 (71.1)	7 (15.6)
Patients with HIV RNA <50 copies/ml	28 (65.1)	25 (55.6)	30 (66.7)	6 (13.3)
Patients with >1 log10 drop in HIV RNA or HIV RNA <400 copies/ml	33 (76.74)	36 (80.0)	36 (80.0)	8 (17.8)
Mean HIV RNA change from baseline (log10 copies/ml)	-1.80	-1.87	-1.84	-0.35
Mean CD4 cell count change from baseline (cells/mm3)	62.9	112.8	94.1	5.4
Virologic failure (confirmed)	12 (27.9)	14 (31.1)	12 (26.7)	35 (77.8)
Non responder	1 (2.3)	0 (0.0)	1 (2.2)	25 (55.6)
Rebound	11 (25.6)	14 (31.1)	11 (24.4)	10 (22.2)
Discontinuation due to clinical adverse events	1 (2.3)	0 (0.0)	1 (2.2)	1 (2.2)
Discontinuation due to laboratory adverse events	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation due to other reasons	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

The virological and CD4 responses to raltegravir were of rapid onset with early (2-4 weeks) divergence from the placebo group.

Enfuvirtide use in OBT (Yes vs. No), baseline HIV RNA (<50,000 copies/ml vs. >50,000 copies/ml) and baseline phenotypic sensitivity score (>0 vs. 0) appeared to be strongly associated with time to virological failure while baseline genotypic sensitivity score was less strongly associated with this endpoint.

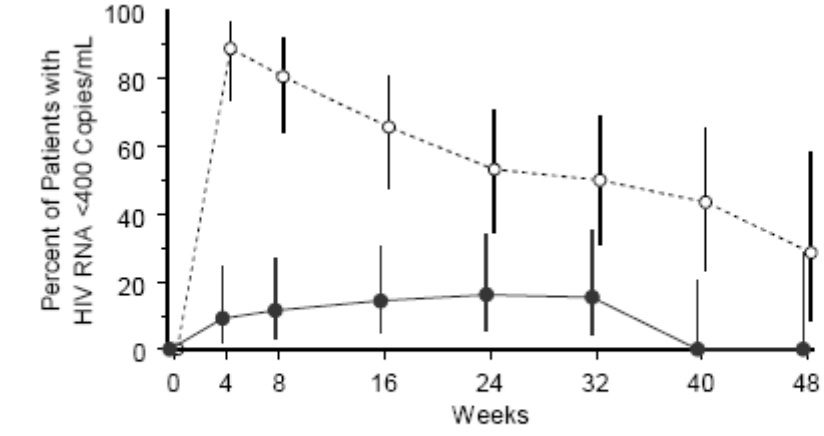
Data available up to week 72 demonstrated a sustained efficacy response to at least Week 48. An example is provided in Figure 1. Time to loss of virological response (TLOVR) has been assessed for raltegravir patients using any data available to week 72. Failures beyond Week 24 were uncommon.

Figure 1 Percent (95% CI) with <50 copies/ml by originally randomised treatment group (Sub-studies A and B combined; Non-completer = Failure approach)



Among patients who had failed during the study and entered the OLPVF phase nearly 90% (32/36) from the original placebo group showed an initial response to raltegravir and achieved <400 copies/ml at Week 4 (Figure 2). Similarly 17/36 achieved <50 copies/ml at Week 4. However, responses tended to drop over time, especially among those who did not achieve <50 copies/ml soon after the initiation of raltegravir.

Figure 2 Percent of patients with HIV RNA <400 copies/ml over time by originally randomised treatment group (raltegravir vs. placebo) – Observed Failure approach (Sub-studies A and B combined; Open-label post virological failure phase)



Week is defined as the time from the patient entering Open-Label Post Virologic Failure Phase (OLPVF)

- Main studies

The two double-blind phase 3 studies with identical protocols have been initiated and are ongoing at time of this assessment. Both were multicentre, double-blind, randomized, placebo-controlled studies to evaluate the safety and antiretroviral activity of raltegravir (400 mg b.i.d) in combination with an optimized background therapy (OBT), versus OBT:

- Protocol 018 (BENCHMRK 1) - conducted at 65 sites in Europe, Asia/Pacific, and South America (n=352);
- Protocol 019 (BENCHMRK 2) - conducted at 53 sites in North and South America (n=351).

METHODS (FOR BOTH STUDIES)

Study Participants

Male and female patients at least 16 years of age were enrolled. Patients were to have a screening plasma HIV RNA >1000 copies/ml on stable ART for ≥2 months and were to be infected with HIV that showed reduced susceptibility to at least one compound in each of NNRTI, NRTI and PI classes based on a genotypic/phenotypic resistance report from the central laboratory.

Blood samples for viral resistance assays were collected at screening to confirm viral resistance as required by the inclusion criteria and to aid selection of OBT by commercial assays. If resistance evaluation with this assay failed, a prior resistance report, which showed reduced susceptibility to one or more ART agents and listed specific mutations indicative of resistance to the specific ART classes, was accepted as documentation for study entry.

Treatments

Raltegravir 400 mg b.i.d. or matching placebo was to be taken without regard to food.

Based on screening resistance testing results and prior treatment and resistance history, ARTs were re-evaluated to optimize the background therapy (OBT). OBT could include investigational medicinal products, which were under review for licensure provided the following protocol specified conditions were met: (1) The agent was available under an expanded access program; (2) The agent had been submitted for regulatory approval; and (3) Potential drug-drug interactions with raltegravir had been evaluated. Darunavir, in combination with ritonavir, became available during the conduct of the studies. The impact of this agent on the efficacy of raltegravir was evaluated and presented as part of the efficacy analyses.

During the double-blind portion of the study the OBT could be changed only for toxicity management (only in-class substitutions were permitted) or after confirmed virological failure, when OBT could be changed upon entry into the open-label post virological failure phase (OLPVF) of the study.

Objectives

The primary efficacy objective was to evaluate the antiretroviral activity of raltegravir 400 mg b.i.d. compared to placebo, both in combination with OBT, as measured by proportions with <400 copies/ml at Week 16.

Other efficacy objectives were

- to evaluate the antiretroviral activity of raltegravir compared to placebo based on:
    a. Proportion of patients with virological response at Week 16
    b. Change from baseline in HIV RNA (log10 copies/ml)
    c. Change from baseline in CD4 cell count
- to evaluate the antiretroviral activity of raltegravir in combination with OBT at Week 48.

An evaluation of the safety and tolerability of raltegravir 400 mg b.i.d. compared to placebo, both in combination with OBT, was performed by review of the accumulated safety data.

Outcomes/endpoints

The primary measurement for efficacy in the study was the percentage with < 400 copies/ml and the primary time point for evaluation of efficacy was Week 16.

Sample size

With 230 patients in the raltegravir group and 115 in the placebo group, each study had 90% power to demonstrate superiority of raltegravir over placebo when the true response rate at Week 16 is 70% for raltegravir and 50% for placebo assuming a discontinuation rate of 10%.

Randomisation

Patients who met the eligibility requirements were randomised to treatment (2 raltegravir: 1 placebo). Patients were stratified by enfuvirtide use in OBT (yes or no) and degree of resistance to protease inhibitors (resistant to 1 PI or >1 PI).

Blinding (masking)

These were double-blind studies in which the patients enrolled, the investigator(s) and study site personnel and applicant's personnel were blinded to the study therapy received until all patients had completed the study to Week 16, the data had been screened for completeness and accuracy and protocol violators were identified.

Statistical methods

The primary analysis population used to assess efficacy was the modified intention to treat (MITT), all treated regardless of any protocol deviations. The MITT was constituted by the population of all randomised patients excluding the ones that did not receive any study medication (see Table 12).

For primary and secondary binary endpoints, a logistic regression model adjusted for following covariates was used: baseline plasma HIV RNA, enfuvirtide use in OBT in enfuvirtide-naïve patients (Yes/No), active PI in OBT determined by phenotypic resistance test (Yes/No), darunavir use in the OBT in darunavir-naïve patients (Yes/No) and treatment group.

The following approaches were used to handle missing values for patients who prematurely discontinued:

- **Observed Failure (OF):** Patients who prematurely discontinued assigned treatment due to lack of efficacy were considered as failures thereafter. The OF approach considers a virological failure endpoint, which is focused on the antiretroviral effect of the treatment
- **Treatment-Related Discontinuation = Failure (TRD=F):** Patients who prematurely discontinued assigned treatment due to lack of efficacy or adverse experiences were considered as failures thereafter. The TRD=F approach considers a treatment failure endpoint, which also takes tolerability into consideration
- **Non-Completer = Failure (NC=F):** Patients who prematurely discontinued assigned treatment regardless of reasons were considered as failures thereafter. The NC=F approach considers a study failure endpoint, which depends on the conduct of the study. In a well-conducted trial, the non-treatment-related discontinuation rate is low and TRD=F is similar to NC=F.

Patients with virological failures starting at Week 16 or beyond were allowed to receive open-label raltegravir (OLPVF).

RESULTS

Participant flow

Table 12 Patient flow in studies 018 and 019 (up to Week 16)

Overall Disposition of Non-Randomized Patients		
	Protocol 018	**Protocol 019**
Non-randomized Patients (N)	148	161
Patient excluded due to:		
Clinical adverse experience	1	3
Ineligible (Inclusion criteria not met / Exclusion criteria met)	132	142
Lost to follow-up	0	2
Patient withdrew consent	8	12
Protocol deviation (screening window exceeded)	5	2
Site terminated	2	0

Overall Disposition of randomised patients						
	Protocol 018			**Protocol 019**		
	Raltegravir 400 mg b.i.d n (%)	Placebo n (%)	Total n (%)	Raltegravir 400 mg b.i.d n (%)	Placebo n (%)	Total n (%)
Double-blind phase						
Total Entered	234 (100)	118 (100)	352 (100)	232 (100)	119 (100)	351 (100)
Never Treated	2 (0.9)	0 (0.0)	2 (0.6)	2 (0.9)	0 (0.0)	2 (0.6)
Treated	232 (99.1)	118 (100)	350 (99.4)	230 (99.1)	119 (100)	349 (99.4)
Continuing in DB	212 (90.6)	68 (57.6)	280 (79.5)	201 (86.6)	77 (64.7)	278 (79.2)
Discontinued study before completing Wk 16	4 (3.4)	4 (3.4)	8 (2.3)	6 (2.6)	3 (2.5)	9 (2.6)
Lack of Efficacy	0	0	0	0 (0.0)	1 (0.8)	1 (0.3)
Clinical AE	0	0	0	3 (1.3)	1 (0.8)	4 (1.1)
Laboratory AE	3 (1.3)	4 (3.4)	7 (2.0)	1 (0.4)	0 (0.0)	1 (0.3)
Consent withdrawn	1 (0.4)	0 (0.0)	1 (0.3)	2 (0.9)	0 (0.0)	2 (0.6)
Loss to follow-up	0	0	0	0 (0.0)	1 (0.8)	1 (0.3)
Discontinued study after completing Wk 16	1 (0.4)	0 (0.0)	1 (0.3)	4 (1.7	0 (0.0)	4 (1.1)
Clinical AE	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.4)	0 (0.0)	1 (0.3)
Consent withdrawn	0	0	0	3 (1.3)	0 (0.0)	3 (0.9)
Virologic failure, entering OLPVF	15 (6.4)	46 (39.0)	61 (17.3)	19 (8.2)	39 (32.8)	58 (16.5)
OLPVF phase						
Total treated	15 (6.4)	46 (39.0)	61 (17.3)	19 (8.2)	39 (32.8)	58 (16.5)
Discontinued from OLPVF	0	0	0	1 (0.4)	0 (0.0)	1 (0.3)
Continuing in OLPVF	15 (6.4)	46 (39.0)	61 (17.3)	18 (7.8)	39 (32.8)	57 (16.2)

Note: MK-0518 and Placebo were administered with Optimized Background Therapy (OBT)
n (%) = Number (percent) of patients in each sub-category
DB = Double-blind; OLPVF = Open label post virologic failure

Conduct of the study

The first protocol amendment (about 6 months after commencement of enrolment) changed the timing of the primary and secondary analyses from Week 24 to Week 16 and extended the study from 48 weeks to 156 weeks. All patients in the double blind and OLPVF phases are eligible for the extension.

Baseline data

Table 13 Patient baseline characteristics by treatment group in studies 018 and 019

	Protocol 018			Protocol 019		
	Raltegravir 400 mg b.i.d. (N = 232)	Placebo (N=118)	Total (N=350)	Raltegravir 400 mg b.i.d. (N = 230)	Placebo (N=119)	Total (N=349)
Gender n (%)						
Male	195 (84.1)	103 (87.3)	298 (85.1)	210 (91.3)	107 (89.9)	317 (90.8)
Female	37 (15.9)	15 (12.7)	52 (14.9)	20 (8.7)	12 (10.1)	32 (9.2)
Race n (%)						
White	175 (75.4)	96 (81.4)	271 (77.4)	126 (54.8)	77 (64.7)	203 (58.2)
Black	18 (7.8)	5 (4.2)	23 (6.6)	48 (20.9)	21 (17.6)	69 (19.8)
Asian	14 (6.0)	5 (4.2)	19 (5.4)	2 (0.9)	1 (0.8)	3 (0.9)
Hispanic	6 (2.6)	1 (0.8)	7 (2.0)	47 (20.4)	18 (15.1)	65 (18.6)
Native American	0	0	0	1 (0.4)	0 (0.0)	1 (0.3)
Others	19 (8.2)	11 (9.3)	30 (8.6)	6 (2.6)	2 (1.7)	8 (2.3)
Region n (%)						
North America	0	0	0	192 (83.5)	99 (83.2)	291 (83.4)
Central / South Amer.	23 (9.9)	11 (9.3)	34 (9.7)	38 (16.5)	20 (16.8)	58 (16.6)
Asia Pacific	38 (16.4)	20 (16.9)	58 (16.6)	0	0	0
Europe	171 (73.7)	87 (73.7)	258 (73.7)	0	0	0
Age (years)						
Mean (SD)	46.1 (8.5)	43.7 (8.2)	45.3 (8.5)	45.3 (8.6)	46.5 (7.8)	45.7 (8.3)
Median (min, max)	45.5 (16 to 74)	43.0 (19 to 64)	45.0 (16 to 74	45.0 (16 to 67)	47.0 (17 to 70)	45.0 (16 to 70)
CD4 Cell Count (cells/mm^3)						
Mean (SD)	156.4 (139.0)	152.8 (152.0)	155.2 (143.3)	146.4 (143.4)	163.2 (149.3)	152.1 (145.5)
Median (min, max)	140.0 (1 - 792)	104.5 (3 - 759)	130.0 (1 - 792)	101.5 (1 - 757)	132.0 (0 - 674)	111.0(0 - 757)
Plasma HIV RNA (log_{10} copies / ml)						
Mean (SD)	4.6 (0.8)	4.5 (0.8)	4.6 (0.8)	4.7 (0.8)	4.7 (0.7)	4.7 (0.8)
Median (min, max)	4.8 (3 to 6)	4.6 (2 to 6)	4.7 (2 to 6)	4.8 (2 to 6)	4.7 (2 to 6)	4.7 (2 to 6)
Plasma HIV RNA (copies / ml)						
Geometric Mean	40519.2	31827.9	37351.7	48366.1	47788.6	48168.4
Median	61750.0	42700.0	50950.0	56750.0	46700.0	52900.0
(min, max)	(441 - 750000)	(200 - 750000)	(200 - 750000)	(200 - 750000)	(200 - 750000)	(200 - 750000)
History of AIDS n (%)						
Yes	217 (93.5)	106 (89.8)	323 (92.3)	209 (90.9)	110 (92.4)	319 (91.4)
Prior Use of ART						
Year of ART Use: Median (min, max)	10.6 (0.3 to 8.8)	10.3 (1.3 to 5.4)	10.5 (0.3 to 8.8)	9.6 (0.0 to 18.9)	10.1 (0.0 to 9.4)	9.7 (0.0 to 19.4)
Number of ART: Median (min, max)	12.0 (2 to 19)	12.0 (3 to 18)	12.0 (2 to 19)	12.0 (0 to 21)	12.0 (0 to 22)	12.0 (0 to 22)
Hepatitis Co-infection[H] n (%)						
No Hepatitis B or C	183 (78.9)	91 (77.1)	274 (78.3)	202 (87.8)	110 (92.4)	312 (89.4)
Hepatitis B only	14 (6.0)	3 (2.5)	17 (4.9)	22 (9.6)	4 (3.4)	26 (7.4)
Hepatitis C only	31 (13.4)	22 (18.6)	53 (15.1)	6 (2.6)	5 (4.2)	11 (3.2)
Hep Co-inf of B + C	4 (1.7)	2 (1.7)	6 (1.7)	0	0	0
Stratum n (%)						
Enfuvirtide in OBT	88 (37.9)	43 (36.4)	131 (37.4)	87 (37.8)	46 (38.7)	133 (38.1)
Resistant to ≥ 2 PI	225 (97.0)	112 (94.9)	337 (96.3)	222 (96.5)	114 (95.8)	336 (96.3)

[H] Hepatitis B surface antigen positive or hepatitis C antibody positive.

Further important baseline data were as follows:

- In study 018, 52.6% raltegravir and 45.8% placebo patients had baseline plasma HIV RNA >50,000 copies/ml while 33.2% and 28.0% in respective groups had >100,000 copies/ml. CD4 counts ≤ 50 cells/mm^3 were seen in 29.7% and 33.9%. 43.1% in the raltegravir group and 46.6% of patients in the placebo group had no active PI in the OBT based on phenotypic sensitivity test results. About 30% per group had no active agent in OBT based on GSS and about 20% had no active agent in OBT based on PSS scores.

– In study 019, about 54% and 49% in respective groups had baseline plasma HIV RNA >50,000 copies/ml, 38% in each group had >100,000 copies/ml and 34% and 32% per group had baseline CD4 <50 cells/mm3. 29% raltegravir and 35% placebo group patients had no active PI in the OBT based on PSS. By GSS 20% and 26% had no active agent in their OBT compared to 10% and 19% by PSS.

Numbers analysed

In study 018, of the 352 randomized patients 2 did not receive any study medication. The remaining 350 patients constitute the MITT population and were included in the efficacy analyses. All treated patients received the correct assigned treatment; there were no cross-treated patients.

In study 019, of the 351 randomized patients 2 did not receive any study medication. The remaining 349 patients constitute the MITT population and were included in the efficacy analyses. 3 patients did receive incorrect therapy for approximately 1 month each due to medication dispensing errors. These patients are included in the efficacy analyses in their assigned treatment groups.

Outcomes and estimation

In the primary analysis at Week 16 (% with < 400 c/ml) of both studies individually, raltegravir was statistically significantly superior to placebo ($p<0.001$) based upon a logistic regression model adjusted for baseline HIV RNA level, enfuvirtide use in OBT in enfuvirtide-naïve patients, active PI in OBT determined by phenotypic resistance test and darunavir use in OBT in darunavir-naïve patients. The model adjusted odds ratio (95% CI) for this primary endpoint between raltegravir and placebo were 10.6 (5.60, 20.25) and was 9.6 (5.02, 18.25) for studies 018 and 019, respectively. The results are presented in Table 14.

Table 14 Treatment outcome at Week 16 in studies 018 and 019 (All randomized and Treated Patients)

Outcome at Week 16	Protocol 018		Protocol 019	
	Raltegravir 400 mg b.i.d. (N = 232) n (%)	Placebo (N=118) n (%)	Raltegravir 400 mg b.i.d. (N = 230) n (%)	Placebo (N=119) n (%)
Patients with HIV RNA less than 400 copies/ml	178 (76.7)	48 (40.7)	177 (77.0)	51 (42.9)
Patients with HIV RNA less than 50 copies/ml	141 (60.8)	39 (33.1)	142 (61.7)	43 (36.1)
Patients with greater than 1 log_{10} drop in HIV RNA or HIV RNA less than 400 copies/ml	197 (84.9)	49 (41.5)	190 (82.6)	60 (50.4)
Mean HIV RNA change from baseline (Log_{10} copies/ml)	-1.85	-0.78	-1.92	-1.06
Mean CD4 cell count change from baseline (cells/mm^3)	82.7	31.3	85.1	39.7
Virologic failure (confirmed)[H]	32 (13.8)	63 (53.4)	38 (16.5)	57 (47.9)
Non responder	4 (1.7)	44 (37.3)	9 (3.9)	34 (28.6)
Rebound	28 (12.1)	19 (16.1)	29 (12.6)	23 (19.3)
Death	3 (1.3)	1 (0.8)	3 (1.3)	0 (0.0)
Adjudicated AIDS-Defining Conditions (ADC)	6 (2.6)	2 (1.7)	5 (2.2)	3 (2.5)
Discontinuation due to clinical adverse experiences	4 (1.7)	4 (3.4)	3 (1.3)	1 (0.8)
Discontinuation due to laboratory adverse experiences	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Discontinuation due to other reasons [‡]	1 (0.4)	0 (0.0)	5 (2.2)	1 (0.8)

[H] Virologic failure: defined as non-responders who did not achieve > 1.0 log_{10} HIV RNA reduction or < 400 HIV RNA copies/ml by week 16, or viral rebound, which was defined as: (a) HIV RNA > 400 copies/ml (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA < 400 copies/ml, or (b) > 1.0 log_{10} increase in HIV RNA above nadir level (on 2 consecutive measurement at least 1 week apart).
[‡] Includes loss to follow-up, patient withdrew consent, non-compliance, protocol violation and other reasons.

Ancillary analyses

Tables 15 and 16 show that proportions who achieved < 400 and < 50 c/ml were lower in both treatment groups when baseline viral load was > 50,000 or > 100,000 c/ml and when CD4 counts were less than 50 mm-3. However, response rates at both levels were higher in the raltegravir group.

Table 14 Proportion of patients with plasma HIV RNA < 400 Copies/ml at Week 16 by prognostic factors in study 018 (Observed Failure Approach)

	Response				Difference in Percent Response % (95% CI)
	Raltegravir 400 mg b.i.d. (Group A)		Placebo (Group B)		
Prognostic Factor	n/N	% (95% CI)	n/N	% (95% CI)	
Total	178/225	79.1 (73.2, 84.2)	48/113	42.5 (33.2, 52.1)	36.6 (25.9, 46.8)
Baseline Plasma HIV RNA (copies/ml)					
≤ 50,000	98/105	93.3 (86.7, 97.3)	35/62	56.5 (43.3, 69.0)	36.9 (23.9, 50.0)
> 50,000	80/120	66.7 (57.5, 75.0)	13/51	25.5 (14.3, 39.6)	41.2 (25.3, 54.4)
Baseline Plasma HIV RNA (copies/ml)					
≤ 100,000	135/150	90.0 (84.0, 94.3)	42/83	50.6 (39.4, 61.8)	39.4 (27.6, 50.9)
> 100,000	43/75	57.3 (45.4, 68.7)	6/30	20.0 (7.7, 38.6)	37.3 (16.8, 53.2)
Baseline CD4 Cell Counts (cells/mm^3)					
≤ 50	38/67	56.7 (44.0, 68.8)	10/37	27.0 (13.8, 44.1)	29.7 (9.8, 46.6)
> 50 and ≤ 200	74/87	85.1 (75.8, 91.8)	15/41	36.6 (22.1, 53.1)	48.5 (31.0, 63.4)
> 200	65/70	92.9 (84.1, 97.6)	23/55	65.7 (47.8, 80.9)	27.1 (11.6, 44.6)
missing	1/1	100.0 (2.5, 100.0)			(N/A)
Enfuvirtide (ENF) Use in OBT					
No	109/140	77.9 (70.1, 84.4)	27/72	37.5 (26.4, 49.7)	40.4 (26.7, 52.7)
Yes in ENF exp. patients	27/40	67.5 (50.9, 81.4)	4/18	22.2 (6.4, 47.6)	45.3 (17.7, 65.1)
Yes in ENF naïve patient	42/45	93.3 (81.7, 98.6)	17/23	73.9 (51.6, 89.8)	19.4 (2.2, 40.9)
Darunavir Use in OBT					
No	116/149	77.9 (70.3, 84.2)	29/81	35.8 (25.4, 47.2)	42.0 (29.1, 53.7)
Yes in Darunavir exp. pts	7/14	50.0 (23.0, 77.0)	0/5	0.0 (0.0, 52.2)	50.0 (-0.7, 73.7)
Yes in Darunavir naïve pts	55/62	88.7 (78.1, 95.3)	19/27	70.4 (49.8, 86.2)	18.3 (1.2, 38.6)
Number of Active PI in OBT by Phenotypic Resistance Test[H]					
0	67/93	72.0 (61.8, 80.9)	9/54	16.7 (7.9, 29.3)	55.4 (40.2, 67.2)
1 or none	104/123	84.6 (76.9, 90.4)	38/57	66.7 (52.9, 78.6)	17.9 (4.8, 32.1)
Missing	7/9	77.8 (40.0, 97.2)	1/2	50.0 (1.3, 98.7)	27.8 (-30.1, 77.5)
Phenotypic Sensitivity Score (PSS) ‡					
0	24/40	60.0 (43.3, 75.1)	1/21	4.8 (0.1, 23.8)	55.2 (33.0, 70.5)
1	51/65	78.5 (66.5, 87.7)	16/37	43.2 (27.1, 60.5)	35.2 (15.8, 52.7)
2	60/66	90.9 (81.3, 96.6)	14/31	45.2 (27.3, 64.0)	45.7 (26.7, 63.1)
3 or more	35/44	79.5 (64.7, 90.2)	14/20	70.0 (45.7, 88.1)	9.5 (-11.9, 34.1)
Missing	8/10	80.0 (44.4, 97.5)	3/4	75.0 (19.4, 99.4)	5.0 (-36.8, 56.6)
Genotypic Sensitivity Score (GSS) ‡					
0	40/66	60.6 (47.8, 72.4)	4/34	11.8 (3.3, 27.5)	48.8 (30.3, 62.8)
1	63/74	85.1 (75.0, 92.3)	20/45	44.4 (29.6, 60.0)	40.7 (23.5, 56.2)
2	53/56	94.6 (85.1, 98.9)	16/21	76.2 (52.8, 91.8)	18.5 (2.7, 40.5)
3 or more	19/26	73.1 (52.2, 88.4)	8/12	66.7 (34.9, 90.1)	6.4 (-22.4, 38.6)
Missing	3/3	100.0 (29.2, 100.0)	0/1	0.0 (0.0, 97.5)	100.0 (-12.3, 100.0)

[H] Darunavir use in OBT in darunavir naïve patients was counted as one active PI

‡ The Phenotypic Sensitivity Score (PSS) and the Genotypic Sensitivity Score (GSS) were defined as the total oral ARTs in OBT to which a patients viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide naïve patients was counted as one active drug in OBT and added to the GSS and PSS. Darunavir use in OBT in darunavir na¨ve patients was counted as one active drug in OBT and added to the PSS and GSS.

Inclusion of enfuvirtide or darunavir in the OBT for patients who were naïve to these agents improved the responses in raltegravir and placebo groups compared to patients without these agents in the OBT. While the response rates were higher in the raltegravir group the relative effects of including enfuvirtide and darunavir in the OBT in naïve patients were greater in the placebo group. That is, the patterns observed suggested that while darunavir and enfuvirtide made some contribution to overall response rates in the raltegravir group these two agents probably accounted for much of the response seen in the placebo group. An analysis of changes in CD4 counts according to the same prognostic factors showed a generally similar pattern of effects.

Table 15 Proportion of patients with plasma HIV RNA < 400 Copies/ml at Week 16 by prognostic factors in study 019 (Observed Failure Approach)

	Response				Difference in Percent
	Raltegravir 400 mg b.i.d. (Group A)		Placebo (Group B)		Response % (95% CI)
Prognostic Factor	n/N	% (95% CI)	n/N	% (95% CI)	
Total	177/222	79.7 (73.8, 84.8)	51/117	43.6 (34.4, 53.1)	36.1 (25.5, 46.2)
Baseline Plasma HIV RNA (copies/ml)					
≤ 50,000	89/104	85.6 (77.3, 91.7)	37/59	62.7 (49.1,75.0)	22.9 (9.2, 37.1)
> 50,000	88/118	74.6 (65.7, 82.1)	14/58	24.1 (13.9, 37.2)	50.4 (35.7, 65.4)
Baseline Plasma HIV RNA (copies/ml)					
≤ 100,000	118/138	85.5 (78.5, 90.9)	43/72	59.7 (47.5, 71.1)	25.8 (13.3, 38.6)
> 100,000	59/84	70.2 (59.3, 79.7)	8/45	17.8 (8.0, 32.1)	52.5 (35.7, 65.4)
Baseline CD4 Cell Counts (cells/mm^3)					
≤ 50	50/73	68.5 (56.6, 78.9)	8/38	21.1 (9.6, 37.3)	47.4 (28.7, 62.1)
> 50 and ≤ 200	71/81	87.7 (78.5, 93.9)	23/41	56.1 (39.7, 71.5)	31.6 (15.2, 48.1)
> 200	56/68	82.4 (71.2, 90.5)	20/38	52.6 (35.8, 69.0)	29.7 (11.5, 47.3)
missing					
Enfuvirtide (ENF) Use in OBT					
No	107/140	76.4 (68.5, 83.2)	25/71	35.2 (24.2, 47.5)	41.2 (27.5, 53.5)
Yes in ENF exp. patients	31/41	75.6 (59.7, 87.6)	8/22	36.4 (17.2, 59.3)	39.2 (13.7, 60.3)
Yes in ENF naïve patient	39/41	95 (83.5, 99.4)	18/24	75.0 (53.3, 90.2)	20.1 (3.5, 40.9)
Darunavir Use in OBT					
No	89/119	69.7 (60.7, 77.8)	13/53	24.5 (13.8, 38.3)	45.2 (29.7, 58.0)
Yes in Darunavir exp. pts	1/3	33.3 (0.8, 90.6)	0/4	0.0 (0.0, 60.2)	33.3 (-31.4, 81.1)
Yes in Darunavir naïve pts	93/100	93.0 (86.1, 97.1)	38/60	63.3 (49.9, 75.4)	29.7 (17.0, 43.1)
Number of Active PI in OBT by Phenotypic Resistance Test[H]					
0	39/64	60.9 (47.9, 72.9)	7/42	16.7 (7.0, 31.4)	44.3 (26.1, 59.0)
1 or none	133/149	89.3 (83.1, 93.7)	43/74	58.1 (46.1, 69.5)	31.2 (19.2, 43.5)
Missing	5/9	55.6 (21.2, 86.3)	1/1	100.0 (2.5, 100.0)	-44.4 (-74.5, 46.0)
Phenotypic Sensitivity Score (PSS) ‡					
0	14/22	63.6 (40.7, 82.8)	1/23	4.3 (0.1, 21.9)	59.3 (34.5, 77.4)
1	56/76	73.7 (62.3, 83.1)	12/31	38.7 (21.8, 57.8)	35.0 (14.5, 53.0)
2	62/72	86.1 (75.9, 93.1)	17/32	53.1 (34.7, 70.9)	33.0 (14.4, 51.4)
3 or more	37/40	92.5 (79.6, 98.4)	18/27	66.7 (46.0, 83.5)	25.8 (7.1, 46.0)
Missing	8/12	66.7 (34.9, 90.1)	3/4	75.0 (19.4, 99.4)	-8.3 (-47.6, 45.0)
Genotypic Sensitivity Score (GSS) ‡					
0	23/45	51.1 (35.8, 66.3)	2:29	6.9 (0.8, 22.8)	44.2 (24.5, 60.0)
1	81/96	84.4 (75.5, 91.0)	20:48	41.7 (27.6, 56.8)	42.7 (26.5, 57.3)
2	47/53	88.7 (77.0, 95.7)	21:27	77.8 (57.7, 91.4)	10.9 (-5.4, 30.9)
3 or more	22/24	91.7 (73.0, 99.0)	5:10	50.0 (18.7, 81.3)	41.7 (10.6, 70.2)
Missing	4/4	100.0 (39.8, 100.0)	3:3	100.0 (29.2, 100.0)	0.0 (-52.8, 59.9)

[H] Darunavir use in OBT in darunavir naïve patients was counted as one active PI

‡ The Phenotypic Sensitivity Score (PSS) and the Genotypic Sensitivity Score (GSS) were defined as the total oral ARTs in OBT to which a patients viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide naïve patients was counted as one active drug in OBT and added to the GSS and PSS. Darunavir use in OBT in darunavir na¨ve patients was counted as one active drug in OBT and added to the PSS and GSS.

In the OLPVF phase patients initially assigned to placebo had consistently greater numerical responses compared to those who had failed while taking raltegravir (and so could only change their OBT in the OLPVF phase). None of the prior raltegravir patients but 35-40% (study 018) and 23% (study 019) of the prior placebo patients achieved < 50 copies/ml up to the cut-off.

In study 018, nine patients (rate 9.0 per 100 patient-years) on raltegravir and three (rate 5.6 per 100 patient-years) on placebo had confirmed definitive ADCs. Some patients had more than one ADC. In study 019, five patients (rate 5.1 per 100 patient-years) on raltegravir and three (rate 5.6 per 100 patient-years) on placebo had confirmed definitive ADCs. Most had only one ADC.

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

The applicant performed a pre-specified meta-analysis for studies 018 and 019 only after homogeneity tests did not show a heterogeneous treatment effect across protocols (p=0.503 for treatment related discontinuation = failure approach; p=0.518 for non-completer = failure approach; p=0.766 for observed failure approach). In line with the results of the homogeneity tests this meta-analysis demonstrated the same overall efficacy of raltegravir in combination with OBT.

At Week 16 there was no significant treatment interaction detected for the prognostic factors baseline HIV RNA, enfuvirtide use in OBT in enfuvirtide-naïve patients, active PI in OBT determined by phenotypic resistance test, and darunavir use in OBT in darunavir-naïve patients.

At Week 16 those who received both enfuvirtide and darunavir without prior exposure had the highest responses while the lowest occurred in those who received neither agent for the first time.

In addition to Week 16 outcomes, the final data of the Week 24 evaluation has been provided during the assessment on the request of the CHMP. These data are presented in Table 16. For those patients who did respond at Week 16 there was almost always a documented sustained response to week 24.

Table 16 Treatment outcome at Week 24 in studies 018 and 019 combined (all randomised and treated)

Outcome at Week 24	Raltegravir 400 mg b.i.d. (N=462) n (%)	Placebo (N=237) n (%)
Patients with HIV RNA less than 400 copies/ml	347 (75.1)	95 (40.1)
Patients with HIV RNA less than 50 copies/ml	289 (62.6)	80 (33.8)
Patients with greater than 1 Log_{10} drop in HIV RNA or HIV RNA less than 400 copies/ml	371 (80.3)	105 (44.3)
Mean HIV RNA change from baseline (Log_{10} copies/ml)	-1.82	-0.87
Mean CD4 cell count change from baseline (cells/mm^3)	83.7	36.5
Virological Failure (confirmed)	84 (18.2)	127 (53.6)
Non responder	13 (2.8)	77 (32.5)
Rebound	71 (15.4)	50 (21.1)
Death	7 (1.5)	3 (1.3)
Adjudicated AIDS-Defining Conditions (ADC)	16 (3.5)	6 (2.5)
Discontinuation due to clinical adverse experiences	9 (1.9)	5 (2.1)
Discontinuation due to laboratory adverse experiences	1 (0.2)	0 (0.0)
Discontinuation due to other reasons	6 (1.3)	2 (0.8)

To address whether baseline HIV RNA, enfuvirtide use in OBT in enfuvirtide-naïve patients, active PI in OBT determined by phenotypic resistance test and darunavir use in OBT in darunavir-naïve patients were associated with outcome, each factor was assessed as a main effect in the logistic regression model. Table 17 shows that at Week 24 these factors exhibited statistically significant effects on the proportions of patients with HIV RNA < 400 copies/ml.

Table 17 Prognostic factors predicting <400 Copies/ml at Week 24 in studies 018 and 019 combined (Observed Failure Approach)

Prognostic Factor	Odds Ratio for Prognostic Factor[‡]		
	Odds Ratio	95% CI	p-Value
Baseline HIV RNA (log_{10} copies/ml)	0.35	(0.26, 0.47)	<0.001
Enfuvirtide use in OBT in enfuvirtide-naïve patients (Yes: No)	5.05	(2.72, 9.38)	<0.001
Active PI in OBT determined by phenotypic resistance test[§] (Yes:No)	2.34	(1.43, 3.81)	<0.001
Darunavir use in OBT in darunavir-naïve patients (Yes:No)	5.78	(3.55, 9.42)	<0.001
Treatment	9.24	(5.94, 14.37)	<0.001
[‡] An odds ratio of (<1, =1, >1) indicates (decreased, equal, increased) probability to respond at Week 24. Odds ratio and p-value were calculated using a logistic regression model adjusted for: baseline HIV RNA level, enfuvirtide use in OBT with no prior exposure, active PI in OBT determined by phenotypic resistance test, investigational ART use in OBT (darunavir or tipranavir use), study, and treatment.			
[§] Phenotypic resistance test are not available for enfuvirtide and darunavir, both of them are excluded.			

Patients with poor prognostic factors had lower response rates than patients without poor prognostic factors. However, benefits over placebo were maintained. Table 18 shows responses for proportions with <50 copies/ml.

To further evaluate efficacy and durability of the response in patients with a baseline GSS = 0, Table 18 and Figure 3 show the percentage of patients with GSS = 0 who achieved reduction of plasma viral load to <50 copies/ml out to 24 weeks (observed failure approach). In this subset 43% in the raltegravir group achieved a viral load of <50 copies/ml after 8 weeks of therapy and 44.1% had < 50 copies/ml at week 24. In contrast, only 11.1% of GSS = 0 patients receiving OBT alone achieved viral loads of <50 copies/ml at week 8 and 6.3% at week 24.

The proportions of GSS = 0 patients with <50 copies/ml at week 16 and week 24 were lower than observed among patients with GSS > 0. Similar results were observed in patients with PSS = 0.

Figure 3 Proportion of Patients with HIV RNA <50 copies/ml Over Time — GSS = 0 in studies 018 and 019 combined (Observed Failure Approach)

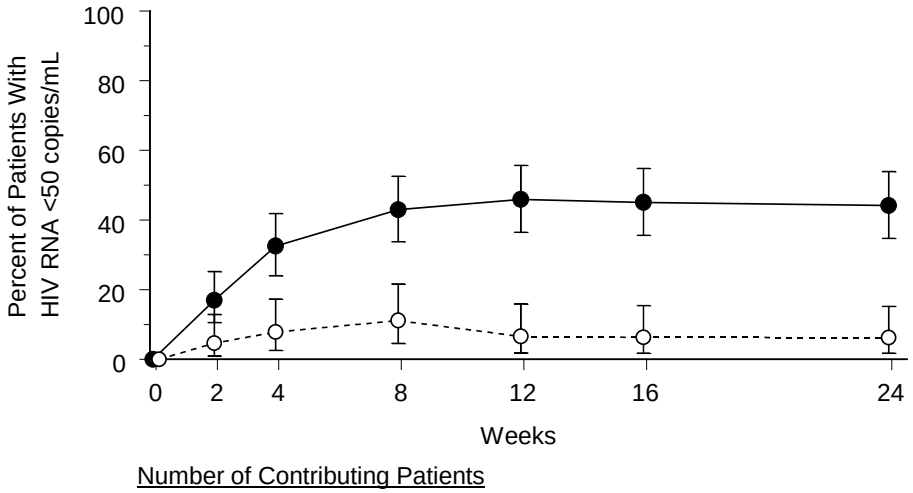


Table 18 Proportion with <50 copies/ml at Week 24 by prognostic factors in studies 018 and 019 combined (Observed Failure Approach)

	Raltegravir 400 mg b.i.d.		Placebo		% Difference in response
Prognostic Factor	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	289/448	64.5 (59.9, 68.9)	80/232	34.5 (28.4, 41.0)	30.0 (22.3, 37.4)
Baseline Plasma HIV RNA (copies/ml)					
≤ 50,000	165/210	78.6 (72.4, 83.9)	58/122	47.5 (38.4, 56.8)	31.0 (20.4, 41.2)
> 50,000	124/238	52.1 (45.6, 58.6)	22/110	20.0 (13.0, 28.7)	32.1 (21.7, 41.3)
Baseline Plasma HIV RNA (copies/ml)					
≤ 100,000	215/289	74.4 (69.0, 79.3)	69/156	44.2 (36.3, 52.4)	30.2 (20.7, 39.2)
> 100,000	74/159	46.5 (38.6, 54.6)	11/76	14.5 (7.5, 24.4)	32.1 (20.0, 42.4)
Baseline CD4 Cell Counts (cells/mm^3)					
≤ 50	61/140	43.6 (35.2, 52.2)	13/75	17.3 (9.6, 27.8)	26.2 (13.5, 37.4)
> 50 and ≤ 200	116/169	68.6 (61.1, 75.5)	36/83	43.4 (32.5, 54.7)	25.3 (12.3, 37.6)
> 200	111/138	80.4 (72.8, 86.7)	31/74	41.9 (30.5, 53.9)	38.5 (25.1, 50.9)
missing	1/1	100 (2.5, 100)			(N/A)
	Raltegravir 400 mg b.i.d.		Placebo		% Difference in response
Prognostic Factor	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Enfuvirtide Use in OBT					
No	173/278	62.2 (56.2, 68.0)	43/145	29.7 (22.4, 37.8)	32.6 (22.8, 41.5)
Yes	116/170	68.2 (60.7, 75.2)	37/87	42.5 (32.0, 53.6)	25.7 (12.9, 37.8)
Yes in naïve patients	73/90	81.1 (71.5, 88.6)	29/47	61.7 (46.4, 75.5)	19.4 (3.8, 35.6)
Yes in exp. patients	43/80	53.8 (42.2, 65.0)	8/40	20.0 (9.1, 35.6)	33.8 (15.6, 48.7)
Darunavir Use in OBT					
No	169/271	62.4 (56.3, 68.2)	32/135	23.7 (16.8, 31.8)	38.7 (29.0, 47.3)
Yes	120/177	67.8 (60.4, 74.6)	48/97	49.5 (39.2, 59.8)	18.3 (6.2, 30.2)
Yes in Darunavir naïve patients	114/159	71.7 (64.0, 78.5)	48/88	54.5 (43.6, 65.2)	17.2 (4.7, 29.6)
Yes in Darunavir exp. patients	6/18	33.3 (13.3, 59.0)	0/9	0.0 (0.0, 33.6)	33.3 (-0.8, 56.7)
Number of Active PI in OBT by Phenotypic Resistance Test[†]					
0	88/161	54.7 (46.6, 62.5)	13/96	13.5 (7.4, 22.0)	41.1 (30.1, 50.8)
1 or more	189/269	70.3 (64.4, 75.7)	66/133	49.6 (40.8, 58.4)	20.6 (10.5, 30.6)
Missing	12/18	66.7 (41.0, 86.7)	1/3	33.3 (0.8, 90.6)	33.3 (-20.7, 69.8)
Phenotypic Sensitivity Score(PSS)[‡]					
0	29/62	46.8 (34.0, 59.9)	2/44	4.5 (0.6, 15.5)	42.2 (27.3, 55.5)
1	93/143	65.0 (56.6, 72.8)	23/69	33.3 (22.4, 45.7)	31.7 (17.5, 44.4)
2	99/140	70.7 (62.4, 78.1)	26/64	40.6 (28.5, 53.6)	30.1 (15.5, 43.6)
3 or more	53/81	65.4 (54.0, 75.7)	25/47	53.2 (38.1, 67.9)	12.2 (-5.2, 29.5)
Missing	15/22	68.2 (45.1, 86.1)	4/8	50.0 (15.7, 84.3)	18.2 (-18.9, 53.2)
Genotypic Sensitivity Score(GSS)[‡]					
0	49/111	44.1 (34.7, 53.9)	4/64	6.3 (1.7, 15.2)	37.9 (26.0, 48.4)
1	122/173	70.5 (63.1, 77.2)	35/94	37.2 (27.5, 47.8)	33.3 (21.0, 44.6)
2	81/108	75.0 (65.7, 82.8)	29/48	60.4 (45.3, 74.2)	14.6 (-0.9, 30.7)
3 or more	30/49	61.2 (46.2, 74.8)	10/22	45.5 (24.4, 67.8)	15.8 (-9.0, 39.0)
Missing	7/7	100.0 (59.0, 100.0)	2/4	50.0 (6.8, 93.2)	50.0 (0.4, 85.8)

[†] Darunavir use in OBT in darunavir-naïve patients was counted as one active PI.
[‡] The Phenotypic Sensitivity Score (PSS) and the Genotypic Sensitivity Score (GSS) were defined as the total oral ARTs in OBT to which a patients viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide-naïve patients was counted as one active drug in OBT and added to the GSS and PSS. Darunavir use in OBT in darunavir-naïve patients was counted as one active drug in OBT and added to the PSS and GSS.

Clinical safety

- Patient exposure

In 18 Phase I studies, including healthy subjects and subjects with renal or hepatic impairment, 315 were treated with at least a single dose of raltegravir. Single doses up to 1600 mg and multiple dosing regimens with up to 800 mg b.i.d. for 10 days were employed.

Overall 758 patients were randomised to receive raltegravir. With addition of those who continued on to open-label raltegravir treatment there were 875 patients exposed in the four studies in ART-experienced patients (004, 005, 018 and 019).

The safety database was updated during the assessment, including data up to 1Q2007. The update included 899 patients. Most had been treated for at least 24 weeks and some for up to 90 weeks. Median durations of double blind treatment were 35 weeks for raltegravir and 27 weeks for placebo with corresponding times at risk of 332.2 patient-years (raltegravir 400 mg b.i.d.) and 150.2 patient-years for placebo. Time at risk in the OLPVF phase was 106.8 patient-years.

- Adverse events

In study 005, 152/178 patients (85.4%) reported in the initial submission had a clinical adverse events but rates and patterns were generally similar between the two sub-studies (with and without atazanavir in OBT). Rates of all and drug-related adverse events were slightly higher with the 600 mg b.i.d. dose compared to lower dose groups although the rate for drug-related adverse events was similar to that in the placebo group.

In a pooled analysis across studies 005, 018 and 019, there were no drug-related clinical adverse events that occurred at frequencies at least 2% greater in the pooled raltegravir group compared to the pooled placebo group. Diarrhoea was the commonest AE reported with raltegravir use in ART-experienced patients, occurring in at 16.6% compared to 19.5% in the control groups, as shown in Table 19.

Table 19 Number (%) of patients with specific clinical adverse events (≥10%) by system organ class (double-blind cohort 005, 018, 019; cumulative data)

	400 mg b.i.d. (Group A) (N=507)		Placebo (Group B) (N=282)		400 mg b.i.d. vs. Placebo Difference From Placebo	
	n	%	n	%	% Diff.	95% CI
Patients With One or More Adverse Experiences	426	84.0	243	86.2	-2.15	-7.1, 3.2
Patients With No Adverse Experiences	81	16.0	39	13.8	2.15	-3.2, 7.1
Gastrointestinal Disorders	201	39.6	124	44.0	-4.33	-11.5, 2.8
Diarrhoea	84	16.6	55	19.5	-2.94	-8.8, 2.5
Nausea	50	9.9	40	14.2	-4.32	-9.5, 0.3
General Disorders And Administration Site Conditions	162	32.0	86	30.5	1.46	-5.4, 8.1
Injection Site Reaction	52	10.3	28	9.9	0.33	-4.4, 4.5
Pyrexia	25	4.9	29	10.3	-5.35	-9.8, -1.6
Infections And Infestations	240	47.3	136	48.2	-0.89	-8.2, 6.4
Metabolism and Nutrition Disord.	52	10.3	24	8.5	1.75	-2.7, 5.8
Musculoskeletal And Connective Tissue Disorders	77	15.2	38	13.5	1.71	-3.6, 6.6
Nervous System Disorders	112	22.1	64	22.7	-0.60	-6.9, 5.3
Headache	49	9.7	33	11.7	-2.04	-6.9, 2.3
Psychiatric Disorders	55	10.8	34	12.1	-1.21	-6.2, 3.3
Respiratory, Thoracic And Mediastinal Disorders	64	12.6	35	12.4	0.21	-4.9, 4.9
Skin And Subcutaneous Tissue Disorders	119	23.5	57	20.2	3.26	-2.9, 9.1

Based on the safety update that was received during the assessment period, clinical adverse events that occurred at frequencies at least 2% greater in the raltegravir group were limited to fatigue (7.9% versus 4.6%), herpes zoster (4.1% versus 0.7%), nasopharyngitis (6.1% versus 3.9%) and rash (5.3% versus 2.5%). Rates of these adverse events in patients who received atazanavir and/or tenofovir as part of the OBT regimen, which would be expected to increase raltegravir plasma levels, were compared to patients who did not receive these agents. In the raltegravir group receiving atazanavir and/or tenofovir rates were 8.6%, 4.3%, 5.1% and 6.1% for these respective adverse events compared to 5.4%, 3.6%, 9.8% and 2.7% of patients not taking atazanavir and/or tenofovir.

Of the 21 patients with herpes zoster in the raltegravir group irrespective of atazanavir and/or tenofovir use none was serious, most were of mild intensity and none caused interruption of discontinuation of study medication. Herpes zoster in patients beginning HAART has been reported as a manifestation of Immune Reconstitution Syndrome (IRS). The rate of herpes zoster seen with raltegravir was in the range of published rates among HIV-infected patients recently commenced on HAART.

In the initial application documentation, the proportion of patients with rash was 6.7% (34/507) for the raltegravir group and 3.9% (11/282) for the placebo group. Several patients reported more than one rash (3 raltegravir and one placebo). Drug related rash was reported in 2.0% (10/507) of the raltegravir arm and 2.5% (7/282) of the placebo arm. There were no discontinuations due to rash or serious adverse events of rash. In the raltegravir group the intensity of rash was mild-moderate for 33/34 and 25/34 recovered. In the placebo group all rashes were mild to moderate and 8/11 recovered. In the raltegravir group 23/34 took two or more concomitant medications commonly associated with rash (e.g. atovaquone, sulfonamides, trimethoprim, abacavir, amprenavir, atazanavir, darunavir, efavirenz, fosamprenavir and tipranavir) compared with 3/11 in the placebo group who took two or more of these agents.

The safety update showed that the rate of rash remained higher in the raltegravir group. Drug-related rash was reported for 2.2% (11/507) raltegravir patients in the cumulative period. There were seven additional OLPVF phase patients with rash during the safety update report period of which four were considered drug-related but only one patient interrupted study therapy and the investigator considered that the rash was related to delavirdine.

Because of a serious adverse event of rash in an ongoing Phase I study of raltegravir with darunavir and ritonavir rash was examined according to use darunavir in OBT. In the double-blind cohort in the cumulative period there were 294 patients who used darunavir in OBT and 495 patients who did not. Among those who darunavir in OBT the proportions with rash in the cumulative period were 13.5% (26/193) in the raltegravir group compared to 4/101 (4%) in the placebo group. Drug-related rash was reported in 3.1% (6/193) and 2% (2/101). Among patients who did not use darunavir rash occurred in 4.5% (14/314; related in 5) and in 3.9% (7/181) in respective groups. The intensity of drug-related rash was mild to moderate for all patients and all patients recovered from drug-related rash.

The safety update also revealed that rash occurred in 9.4% (37/395) patients in the raltegravir group who used atazanavir and/or tenofovir in OBT. The frequency of drug-related rash in this subset was 2.8%. In contrast, rash occurred in 2.7% (3/112) in the raltegravir group patients who did not use atazanavir and/or tenofovir in OBT and none of the three cases was considered to be drug-related.

At present there appear to be several possible explanations for the higher rates of rash observed in the raltegravir group overall and on co-administration with particular other antiretroviral agents. Rash is included as a specific issue in the Risk Management Plan.

In the pooled 400 mg b.i.d. double-blind cohort of 005, 018 and 019 there were 8/789 patients (4 raltegravir) with a report of drug hypersensitivity or hypersensitivity. The four reported from the raltegravir group seem unlikely to have been related to this medicinal product.

Adverse events with onset during the OLPVF phase are reported for 177 patients of whom 100 (56.5%) reported an adverse event. Drug-related adverse events were reported by 19.2% (34/177). In general, the adverse event profile was similar to that for raltegravir during the double-blind phase.

- Serious adverse event/deaths/other significant events

There was one serious adverse event reported from a Phase I study (029), which involved co-administration of raltegravir with darunavir and ritonavir. On co-administration a patient had a diffuse maculopapular rash on the trunk and extremities and discontinued all study medications. A punch biopsy indicated superficial perivascular chronic inflammation with rare intravascular neutrophils, which was consistent with a delayed hypersensitivity reaction. When the rash worsened to include facial and periorbital oedema the subject was admitted to hospital for 2 days. Recovery was almost complete by Day 38. At the time of the safety update there had been four discontinuations due to rash from this study. These were moderate (3) or severe (1) grade 2 pruritic rashes determined to be definitely related to co-administration of the three agents by the investigator. Rash occurred after at least 9 days of co-administration, was similar in nature across the four subjects and was considered to be similar to that seen in other darunavir studies. All four subjects have recovered.

In study 004 serious adverse events were reported by 2-5 patients per dose group but none was considered drug-related. In the safety update one patient had a serious adverse event of Kaposi's sarcoma but no patient had died.

Six of the seven deaths in the 400 mg b.i.d. double-blind phases of 005, 108 and 019 occurred in patients who had been assigned to raltegravir. None was considered to be drug-related. There were two additional deaths reported in the safety update - one had a fatal serious adverse event of coronary artery disease and one had pleural effusion, splenic abscess and lymphadenopathy.

Across these studies the most frequent serious adverse events were infections and infestations, which were of a very varied nature. In the safety update additional serious adverse events included the additional patients who died and a patient with a second bout of pancreatitis

There were eight raltegravir patients with drug-related serious adverse events but in 5/8 the serious adverse events were ascribed to the OBT. In the other three cases the serious adverse events were renal failure, gastritis and hepatitis that recurred on re-starting therapy after treatment interruption. In the safety update there were four more drug-related serious adverse events in the double-blind cohort of studies 018 and 019 (herpes simplex, renal failure, gastritis and overdose)

Three raltegravir patients were reported to have serious adverse events of IRS, of which one occurred in the OLPVF phase and was considered to be drug-related. Study therapy was interrupted for one patient. Two had a documented recovery but the other was ongoing at the cut-off.

One patient died as a result of progressive multi-focal leuco-encephalopathy in the OLPVF phase with onset detected at day 177. Also, in the OLPVF phase serious adverse events were reported by 10.7% (19/177) of patients of which one case of immune reconstitution syndrome was considered to be drug-related. Two more serious adverse events in the OLPVF phase (depression and diarrhoea) were reported in the safety update.

In the safety update serious adverse events had been reported by 36/827 patients in the expanded access programme. These included a B-cell lymphoma and three cases of PME. One case of hypersensitivity resolved after stopping the medicinal product while another continued with therapy and the episode resolved.

Neoplasms

During the assessment updates were provided on numbers of malignancies reported during the clinical development (Table 20).

Table 20 Summary of malignancy – double-blind data phase II and III studies (Cumulative update as of 09-Jul-2007)

	Raltegravir N=758; 820 PY			Comparator Group N=323; 261 PY		
	n (%)[†]	Recurrent	Diagnosis ≤ 3 Months[‡]	n (%)[†]	Recurrent	Diagnosis ≤ 3 Months[‡]
Patients with Malignancy	19 (2.5)	8/19	11/19	5 (1.5)	2/5	0/5
Kaposi's Sarcoma	4 (0.5)	3	1	0 (0)	-	-
Non-Hodgkin's Lymphoma[§]	3 (0.4)	1	3	1 (0.3)	-	-
Squamous Cell Carcinoma – Anogenital[‖]	5 (0.7)	2	3	2 (0.6)	-	-
Squamous Cell Carcinoma - Other	1 (0.1)	-	1	1 (0.3)	-	-
Rectal Cancer	1 (0.1)	-	1	0 (0)	-	-
Metastatic Neoplasm NOS	0 (0)	-	-	1 (0.3)	1	
Hepatocellular Carcinoma	1 (0.1)	-	1	0 (0)	-	-
Non-Melanoma Skin Cancer[¶]	5 (0.7)	2	1	1 (0.3)	1	-

[†] Crude incidence (100 x n/N).
[‡] Diagnosis of neoplasm occurred within 3 months of initiating study therapy.
[§] Includes B-cell lymphoma, T-cell lymphoma, and lymphoma – other.
[‖] Includes squamous cell carcinoma – anal and squamous cell carcinoma CIS.
[¶] Includes squamous cell cancer – skin and basal cell carcinoma.
NOS = Not otherwise specified. PY = Patient years of exposure.
Patients with multiple events may be counted more than once in different terms, but only once in one term.

Based on the data from the double blind cohort the patient-year adjusted incidence rates of malignancy were 2.3 for raltegravir and 1.9 for comparator per 100 patient-years, which gives a relative risk of 1.2 with an associated 95% confidence interval of (0.4, 4.1). The difference between raltegravir and control groups that had been calculated based on the initial submission was therefore reduced with further follow-up (Table 21).

Table 21 Summary of malignancy rates and risk ratio (Cumulative update as of 09-Jul-2007)

Timing	Raltegravir (N=758)			Comparator Group (N=323)			Relative Risk (95% CI)
	Cases	PY	Rate[§]	Cases	PY	Rate[§]	
Original MAA[†]	10	508	2.0	1	169	0.6	3.3 (0.5, 144)
Cumulative Update[‡]	19	820	2.3	5	261	1.9	1.2 (0.4, 4.1)
[†] Data through 13-Dec-2006, [‡] Data through 09-Jul-2007. [§] Per 100 PY. PY = Patient years of exposure.							

On inclusion of open label and double blind exposure there were 916 raltegravir patients with 1118 patient-years time at risk, which is approximately 500 additional patient years of exposure compared to the initial analysis (Table 22). The patient-year-adjusted incidence rate of malignancy during all raltegravir therapy was 2.3 with a 95% confidence interval of (1.5, 3.4).

Table 22 Malignancy events in studies 004, 005, 018, 019 combined (DB+OL+OLPVF; cumulative update as of 09-Jul-2007)

	Raltegravir (N = 916) 1118 Patient-Years	
	n (%)[†]	Rate[‡]
Total number of patients with endpoint	**26 (2.8)**	**2.3**
Kaposi's sarcoma	**5 (0.5)**	**0.4**
Non-Hodgkin's lymphoma	**4 (0.4)**	**0.4**
B-cell lymphoma	2 (0.2)	0.2
T-cell lymphoma	1 (0.1)	0.1
Lymphoma - other	0 (0.0)	0.0
Lymphoma-other (CNS)	1 (0.1)	0.1
Hodgkin's lymphoma	**2 (0.2)**	**0.2**
Squamous cell carcinoma - anogenital	**7 (0.8)**	**0.6**
Squamous cell carcinoma - anal	3 (0.3)	0.3
Squamous cell carcinoma - CIS - anal	4 (0.4)	0.4
Squamous cell carcinoma - other	**1 (0.1)**	**0.1**
Rectal cancer	**1 (0.1)**	**0.1**
Metastatic Neoplasm, NOS	**0 (0.0)**	**0.0**
Hepatocellular carcinoma	**1 (0.1)**	**0.1**
Non-melanoma skin cancer	**7 (0.8)**	**0.6**
Squamous cell carcinoma - skin	5 (0.5)	0.4
Basal cell carcinoma	3 (0.3)	0.3
Note: Patients with multiple events may be counted more than once in different terms, but only once in one term. [†] Crude incidence (100×n/N). [‡] Events per 100 PY, PYR calculated based on overall endpoint.		

Patients with active cancer were eligible for 018 and 019 provided that they were clinically stable and not expected to require chemotherapy or immunosuppressive therapy. In the four Phase II/III studies (004, 005, 018 and 019) 17.4% of raltegravir patients and 16.4% of controls had a malignancy or pre-malignant condition prior to enrolment. In 8/19 patients in the double-blind period, the cancer represented a recurrence or progression. All of the patients had a diagnosis of AIDS and most had CD4 cell counts <150 cells/mm^3. Co-existing conditions associated with malignancy were present in

all patients including presence of oncogenic viral infections such as HPV and HBV or tobacco use. Malignant neoplasia features in the Risk Management Plan as a potential risk.

- Laboratory findings

There were no serious laboratory AEs reported in the Phase I studies. The most common laboratory AE was hyperbilirubinaemia but this occurred after initiation of atazanavir in two interaction studies.

In ART-naïve patients in 004 laboratory AEs were reported in 39/198 patients, the most frequent being AST increased (10.5% in the efavirenz group *vs* 5.6 % in the pooled raltegravir groups). The most frequently reported drug-related laboratory AEs were increases in ALT and AST, both of which were reported in 3.8% raltegravir and 5.3% efavirenz patients. There was no apparent association between all or related laboratory AEs and the dose of raltegravir.

In ART-experienced patients the most frequently reported (≥3%) laboratory AEs were increases in ALT, AST, triglycerides and CK.

ALT/AST

In the treatment-experienced raltegravir 400 mg b.i.d. cohort during the double-blind phase laboratory adverse events of increased ALT and increased AST were reported in 4.7% (24/507) and 4.5% (23/507) of patients, respectively, as compared with 2.1 % (6/282) and 2.8 % (8/282) in the placebo group. Drug related increases were reported in 3.2% (16/507) and 2.6% (13/507) of raltegravir patients compared with 0.7% (2/282) and 1.1% (3/282) in the placebo group. On review of laboratory results that exceeded pre-defined limits of change (PDLC) Grade 3 and 4 aminotransferase elevations were uncommon.

In the treatment-experienced raltegravir 400 mg b.i.d. cohort during the double-blind phase, 11.6% (59/507) of raltegravir patients had a Grade 2 or higher AST elevation compared to 8.5% (24/282) in the placebo group. Corresponding rates for ALT were 10.4% (53/507) and 10.3% (29/282). In the OLPVF phase, 5.0% (10/199) of patients had a Grade 2 or higher AST elevation and 6.5% (13/200) of patients had a Grade 2 or higher ALT elevation.

Patients with Grade 2 or higher AST or ALT elevations were further analysed by baseline HBV and/or HCV infection, concurrent CK elevation and tipranavir use in OBT. Raltegravir patients with Grade 2 AST or AST elevations were more likely to have HBV or HCV and a concurrent increase in CK than placebo patients but there was no difference with regard to tipranavir use. A review of patients whose OBT included or did not include tipranavir showed that slightly higher rates of AST and ALT elevations reported as adverse events and recorded as PDLC were seen for both raltegravir and comparator treatment groups among those whose OBT contained tipranavir.

Creatin kinase (CK)

In the treatment-experienced raltegravir 400 mg b.i.d. cohort during the double-blind phase laboratory AEs of increased CK were reported in 3.7% (19/507) compared to 1.1% (3/282) in the placebo group. Drug-related adverse events of increased CK were reported in 1.2% (6/507) and 1.1% (3/282) in respective groups. During the double-blind and the OLPVF phases there were no serious adverse events or discontinuations due to increased CK. Many were isolated increases that returned to normal with time and elevations for several patients were noted by the investigators to be related to physical exercise.

All grades of CK elevations occurred more often in the raltegravir group. There was only one CK elevation of Grade 1 or higher present during 2 visits at least 30 days apart.

Since the cut-off date for the safety update several cases of myopathy and rhabdomyolysis have occurred in ongoing studies. Although the relationship to raltegravir is not clear these events need to be mentioned in the SPC and added as specific issues for attention in the Risk Management Plan.

Lipids

The data from 004 with a fixed NRTI combination regimen indicated no significant elevation of triglycerides, total cholesterol or LDL-cholesterol in the raltegravir groups compared with the efavirenz group. The pooled data in ART-experienced patients with 400 mg b.i.d. showed that the frequency of lipid abnormalities reaching Grade 3 or 4 according to the DAIDS toxicity criteria and the mean change from baseline in fasting lipids were generally similar between raltegravir and placebo groups. However, hyperlipidaemia, dyslipidaemia, hypercholesterolaemia and hypertriglyceridaemia were commonly present at baseline (16.7%, 4.9%, 7.2% and 12.9% of patients, respectively) and lipid lowering agents were commonly used along with ARTs associated with lipid disorders. The frequency of lipodystrophy or lipoatrophy reported as AEs was <1% but the background rates were high (27.4% and 12.0%).

Glucose

Fasting glucose was routinely monitored. From pooled data with 400 mg b.i.d. hyperglycaemia was reported in one patient in each of raltegravir and placebo groups while diabetes mellitus was reported in 1.0% (5/507) and 1.1% (3/282), respectively. Grade 3 and 4 abnormalities in blood glucose were uncommon.

- Safety in special populations

Adverse events and laboratory abnormalities were generally similar in patient subgroups based on gender, age (<65 or ≥ 65 years) and race. However, interpretations are limited due to the lack of patients aged ≥ 75 years and to relatively small numbers of females, patients aged ≥ 65 and from certain racial groups.

In study 004, one raltegravir patient (400 mg b.i.d. group) reported a pregnancy and discontinued during the extension phase. The outcome of the pregnancy is unknown. The single pregnancy reported in study 005 occurred in a patient randomised to raltegravir 200 mg b.i.d. who switched to open label 400 mg b.i.d. on day 363 even though a pregnancy test on day 350 was positive. On Day 382 additional urine pregnancy tests were positive and all therapy was interrupted. She had an elective abortion and then restarted study medication therapy including OBT. There were no pregnancies reported for female patients in 018 or 019 but the wife of a patient in 019 became pregnant while he was taking blinded study therapy and had an elective abortion. A pregnancy register has been established by the applicant.

- Safety related to drug-drug interactions and other interactions

Diarrhoea was reported more frequently when raltegravir was given with tipranavir (22.5% compared with 13.8% without tipranavir). See above regarding rates of rash when raltegravir was and was no co-administered with other ARTs.

To assess for potential toxicity based on the presumed highest exposure to raltegravir the applicant reviewed the data for 74 patients who received *both* atazanavir and tenofovir DF in OBT with inclusion of 36 in the 400 mg b.i.d. group, 9 in the 600 mg b.i.d. group and 29 in the placebo group. Nausea appeared at a higher frequency (33.3%) in the 600 mg b.i.d. group. There were no adverse events of rash reported in these 74 patients except for a pruritic rash in a raltegravir patient who took 400 mg b.i.d. with atazanavir and tenofovir DF. Laboratory adverse event profiles were generally similar in the patient subgroups.

- Discontinuation due to adverse events

In 004 one patient discontinued raltegravir (600 mg b.i.d.) due to a G4 AST elevation considered to be drug-related. In study 005 three patients in sub-study A discontinued during the double-blind phase,

two of whom had been assigned to raltegravir and died. One raltegravir patient in sub-study B discontinued during the double-blind phase due to increased ALT and AST.

During treatment with 400 mg b.i.d. 13 patients (9 raltegravir) discontinued due to adverse events. In the raltegravir group five adverse events in four patients were considered by the investigator to be drug-related but hepatomegaly and hyperlactacidaemia in one patient were considered related to OBT. The other three patients with drug-related adverse events had hepatitis, renal failure or flatulence. One of the nine raltegravir patients discontinued due to a laboratory adverse event that was not considered to be drug-related.

In the safety update there were another 10 patients in the double blind cohort that discontinued due to adverse events and one in the OLPVF phase. These adverse events were of no clear pattern.

- Post marketing experience

No post-marketing data is available yet.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan

The MAA submitted a risk management plan, which is summarised in Table 23.

Table 23 Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important Identified Risks		
IRIS	• Routine Pharmacovigilance • Monitor reports of IRIS from ongoing clinical trials (004, 005, 018, 019, 021, 022, 023, 032, 033)	• Listed as class labeling warning in Section 4.4 of the SmPC
Drug resistance	• Routine Pharmacovigilance • Monitor resistance in ongoing clinical trials (004, 005, 018, 019, 021, 022, 023, 032, 033)	• Listed under SmPC sections 4.4 and 5.1
Drug interaction with rifampicin and other strong UTG1A1 inducers	• Routine Pharmacovigilance	• Listed under SmPC sections 4.4 and 4.5
Extent of pharmacokinetic (PK) variability and impact, if any, on pharmaco-dynamics (PD)	• Monitor data from ongoing clinical trials (004, 005, 018, 019,)	• Listed under SmPC sections 4.2, 4.4, 4.5 and 5.2
Important Potential Risks		
Malignancies	• Routine Pharmacovigilance • Monitor reports of malignancies from ongoing clinical trials (004, 005, 018, 019, 021, 022, 023, 032, 033) • Observational post authorization safety study	• Listed under SmPC sections 4.4 and 4.8
Serious rash	• Routine Pharmacovigilance • Monitor reports of rash from ongoing clinical trials (004, 005, 018, 019, 021, 022, 023, 032, 033)	• The Applicant will periodically reassess whether product labeling needs to be modified.

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Increase in liver enzymes	• Routine Pharmacovigilance • Monitor reports of increased in liver enzymes and related clinical hepatic events from ongoing clinical trials (004, 005, 018, 019, 021, 022, 023, 032, 033) • Observational post authorization safety study (will monitor selected clinically important liver outcomes, not liver enzyme elevation)	• Listed under SmPC section 4.8
Lipodystrophy/Fat Maldistribution	• Routine Pharmacovigilance • Monitor reports of lipodystrophy/fat maldistribution from ongoing clinical trials (004, 005, 018, 019, 021, 022, 023, 032, 033)	• Listed under SmPC section 4.8
Increase in CK with clinical manifestations; myopathy, rhabdomyolysis	• Routine Pharmacovigilance • Monitor reports of increase in CK with clinical manifestations; myopathy, rhabdomyolysis from ongoing clinical trials (004, 005, 018, 019, 021, 022, 023, 032, 033)	• Increase in CK listed under SmPC section 4.8; rhabdomyolysis and myopathy listed under SmPC sections 4.4 and 4.8
Important Missing Information		
Exposure during pregnancy	• Routine Pharmacovigilance • Participation in the APR	• Listed in SmPC section 4.6
Long-term safety data • Populations Studied	One or more of the following, as relevant to the population: • Routine Pharmacovigilance • Monitor safety data from ongoing clinical trials (004, 005, 018, 019, 021, 023, 032, 033) • Observational post authorization safety study	• To be determined, based on analysis of long-term safety data.
• Populations insufficiently studied/not studied		
o Exposure in children less than 16 years of age	• Routine Pharmacovigilance • Monitor safety data from the ongoing paediatric clinical trial (022)	• SmPC section 4.2 notes that safety and efficacy has not been established in patients below 16 years of age
o Exposure in elderly patients	• Routine Pharmacovigilance • Monitor safety data from ongoing clinical trials, if elderly patients are enrolled (004, 005, 018, 019, 021, 023, 032, 033)	• SmPC section 4.2 includes information about limited information in the elderly
o Exposure in patients with hepatitis B and/or C co-infection and treatment naïve patients	• Routine Pharmacovigilance • Monitor safety data from ongoing clinical trials (hepatitis B/C co-infection: 018, 019, 021, 023, 032, 033; treatment naïve patients: 004, 021)	• Listed under SmPC section 4.8.
o Patients with non-clade B virus	• Routine Pharmacovigilance	• The Applicant will periodically reassess whether product labeling needs to be modified.
o Exposure in patients with severe hepatic impairment	• Routine Pharmacovigilance	• SmPC section 4.2 includes a dosing recommendation in patients with hepatic

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		impairment. The SmPC also includes language in Section 4.4 related to patients with severe hepatic impairment.

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

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product has been evaluated and found to be satisfactory for the intended clinical use as defined in the SPC. There are no unresolved quality issues which may have a negative impact on the benefit/risk balance.

Non-clinical pharmacology and toxicology

Biochemical and *in vitro* studies have demonstrated that raltegravir inhibits integrase strand transfer and consequently inhibits integration of HIV-1 into host cell genomic DNA and inhibits replication of HIV-1 and HIV-2. No significant off-target activities were detected for raltegravir. Several pivotal non-clinical studies have been conducted to evaluate the safety pharmacology of Raltegravir. No significant treatment related effects were found in any of these studies. At higher compound concentrations, typically in excess of their IC_{50} values, Raltegravir displayed synergistic activity with all other antiviral compounds tested, regardless of their mechanism of inhibition.

The pharmacokinetic properties of raltegravir have been evaluated in rat and dog studies with additional studies in rabbits and mice, and a number of *in vitro* assays. Raltegravir is a low to intermediate clearance, and orally bioavailable compound, with a short plasma half-life, a volume of distribution ranging from ~0.4 to 2 L/kg and a rapid absorption. Raltegravir is cleared primarily by glucuronidation and the main route of excretion is by the faeces. The main metabolite of raltegravir is M2, which has no activity against HIV-1. Raltegravir is excreted into the milk of lactating rats.

The toxicology profile of raltegravir was assessed by single-dose and repeat dose studies, genotoxicity, carcinogenicity (in progress), reproductive toxicity studies and a number of non-pivotal additional toxicity studies. Raltegravir was generally well tolerated, with an exposure margin of at least 1.6-fold above the expected exposure of the 400 mg/BID dose in patients. The results of the four GLP genotoxicity studies are negative, indicating the absence of a genotoxic potential for raltegravir.

Two-year carcinogenicity studies in mice and rats are currently on-going. The final study reports will be provided post-approval. No short-term carcinogenicity studies have been conducted.

The “no observed adverse effect levels” of reproduction studies were 600 mg/kg/day for maternal toxicity, ≥600 mg/kg/day for male fertility and 300 mg/kg/day for embryo-fetal development. The safety margin at the “no observed effect levels” for developmental toxicity is approximately 3.4-fold the value at the maximum recommended dose (MRD). In rabbits, no developmental toxicity was found at the maximum dose of 1000 mg/kg/day, resulting in a safety margin of about 3.7-fold relative to the AUC in patients at the MRD.

With respect to local tolerance, raltegravir is not considered a dermal sensitizer and is classified as a mild irritant as the free base and as a severe irritant as the potassium salt. Raltegravir did not show evidence of immunogenicity or antigenicity and it is considered non-phototoxic at doses up to

2000 mg/kg. The specification limits of the impurities have been adequately justified, and their potential for toxicity, including genotoxicity, has been adequately investigated.

A satisfactory revised environmental risk assessment for raltegravir was provided; there was no evidence of a risk to the aquatic environment, nor to micro-organisms. The data did not suggest any potential for raltegravir to bioaccumulate.

Efficacy

The results from the two pivotal phase III studies (018 and 019) at Week 16 demonstrate the superiority of raltegravir over placebo when used in combination with OBT in treatment-experienced patients. The general study designs, including the patient selection criteria, were appropriate except that even in treatment-experienced patients the optimal outcome is to achieve <50 copies/ml hence the choice of primary endpoint of <400 copies/ml at Week 16 could be criticised. Nevertheless data at <50 copies/ml also showing this overall outcome have been provided and show an advantage for raltegravir. Data through to Week 24 showed that for those patients who did respond at Week 16 there was almost always a documented sustained response to Week 24

In studies 018 and 019 about 30% per group had no active agent in OBT based on GSS and about 20% per group had no active agent in OBT based on PSS scores. For those with a PSS score of zero in oral OBTs about half of raltegravir patients achieved <50 copies/ml at Week 24 compared to 5% in the placebo group. In both groups these patients may have been receiving enfuvirtide and so the raltegravir results cannot be interpreted as responses to monotherapy. As expected, the response to raltegravir was lower in those with baseline viral load >50,000 or >100,000 copies/ml and/or CD4 counts <50 mm-3. However, response rates were still much higher in the raltegravir than placebo group.

Inclusion of enfuvirtide or darunavir in the OBT for patients who were naïve to these agents improved the responses in raltegravir and placebo groups compared to patients without these agents in the OBT. Those who received both agents without prior exposure had the highest responses at this level while the lowest occurred in those who received neither agent for the first time. While the response rates were higher in the raltegravir group the relative effects of including enfuvirtide and darunavir in the OBT in naïve patients were greater in the placebo group. The patterns observed suggested that while darunavir and enfuvirtide made some contribution to overall response rates in the raltegravir group these two agents probably accounted for much of the response seen in the placebo group.

There is a low genetic barrier to the selection of raltegravir-resistant mutants; the CHMP requested that further examinations of the resistance profile should be performed post-approval. Thus far the applicant has been able to identify several mutations that correlate with virological failure and reduced susceptibility to raltegravir. Whereas *in vitro* studies suggested that these mutant viruses have a reduced capacity for replication *in vitro* this finding seems to be irrelevant to the clinical situation since failure has occurred. Viruses with these mutations have emerged from about Weeks 2-4 onwards. Factors that decreased the likelihood of developing mutation at either amino acid 148 or 155 included lower viral load, the use of darunavir in OBT, PSS >0 and GSS>0. Having a low CD4 count (≤50 mm-3 vs. >200 mm-3) increased the likelihood of developing a mutation at either amino acid 148 or 155. The SPC specifically advises against use of functional monotherapy.

Safety

The safety database was significantly updated during the assessment with data on 899 patients and corresponding treatment times of 332.2 and 150.2 patient-years for raltegravir 400 mg b.i.d and placebo, respectively.

In the clinical studies the most common side effects seen were diarrhoea, nausea, headache and pyrexia. Important safety issues which require a specific follow-up post-marketing include immune reconstitution inflammatory syndrome, malignancies, serious rash, increase in liver enzymes,

lipodystrophy/fat maldistribution, and increase in creatine kinase with clinical manifestations (myophathy, rhabdomyolysis).

Regarding the risk of malignant neoplasm, patient-year adjusted incidence rates for malignancies were 2.3 for raltegravir vs. 1.9 for placebo per 100 patient-years resulting in a relative risk of 1.2 and 95% confidence interval of (0.4, 4.1). Overall, the numbers are relatively small, the types of malignancies have been diverse and several occurred so early in the course of treatment that a relationship to the medicinal product seems unlikely. Also, the listing of cases shows that these patients included several who achieved good viral suppression and others who seemed to have failed to respond from the start. Malignancies feature in the Risk Management Plan.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

User testing was performed in 26 subjects. The results demonstrated that at least 90% of the participants were able to find each point of information. It also showed that at least 90% of those participants were able to express the information in their own words. The leaflet therefore fulfils the requirements for user testing.

Risk-benefit assessment

Benefits

The differences observed between raltegravir and placebo, both in combination with optimised background therapy, in the Phase II and III studies in treatment-experienced patients indicate that addition of raltegravir to an appropriate optimised background therapy regimen can provide suppression of HIV replication that is sustained to 24 weeks.

With regard to the likely efficacy of raltegravir in routine clinical use in the intended target population there remains a question regarding the possible clinical importance of intermittent or persistent low plasma exposure to raltegravir in terms of risk of selecting for drug-resistant virus and virological failure.

Risks

Thus far the applicant has been able to identify several mutations that correlate with virological failure and reduced susceptibility to raltegravir. The data strongly suggest a low genetic barrier for the selection of raltegravir-resistant mutants that requires further evaluation.

Furthermore, there remains a need for very careful study of the following specific issues in the post-marketing period: malignant neoplasm, increases in liver enzymes or CK, gastrointestinal irritation, immune reconstitution syndrome, interaction with strong UTG1A1 inducers, rash and lipid abnormalities. The Risk Management Plan addresses these issues; an adequately designed observational cohort study is needed to generate appropriate long-term safety data.

Balance

Based on the assessment of the available data, and in particular the 24-week safety and efficacy data from the two pivotal trials, it is considered that the risk-benefit relationship is favourable for a conditional approval according to Article 14(7) of Regulation (EC) 726/2004 in conjunction with Commission Regulation (EC) 507/2006:

- ISENTRESS is proposed to be indicated for treatment of HIV-1 infection, which is a life-threatening disease, and so falls within the scope of the legislative framework on conditional marketing authorisations as defined in Article 2(1) of Regulation (EC) 507/2006.
- In support of the MAA the applicant provided complete 24-week data from two Phase 3 studies. Comprehensive clinical data up to 48 weeks would be needed to further assess important issues including long-term viral suppression, the safety profile and the resistance pattern. Such data will be generated but were not available in the timeframe of the assessment. In addition, it was considered that further monitoring of resistance to raltegravir and the risk for malignancies is required.
- Based on the available data the risk-benefit analysis was considered to be positive. The product fulfils an unmet medical need as it has a novel mechanism of action that results in activity against HIV that is resistant to many other antiretroviral agents. It likely has an acceptable safety profile and a limited potential for drug interactions. On this basis it could be considered that the benefit to public health of allowing ISENTRESS to be marketed without undue delay may outweigh the risks inherent in the fact that additional data are still required. Therefore, the application fulfilled the requirements for a Conditional Marketing Authorisation as defined in Article 4(1) of Regulation (EC) 507/2006.

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

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

Recommendation

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

> "ISENTRESS is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in treatment-experienced adult patients with evidence of HIV-1 replication despite ongoing anti-retroviral therapy.
>
> This indication is based on safety and efficacy data from two double-blind, placebo-controlled trials of 24 weeks duration in treatment-experienced patients (see section 5.1)"

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