SCIENTIFIC DISCUSSION

Introduction

According to UNAIDS, around 40 million people are presently living with HIV. The estimated number of AIDS-related deaths was 3 million during 2006, and around 5 million people were newly infected. The number of people with HIV in central/western Europe and North America is close to 2 million.

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

- NRTIs (nucleoside/nucleotide reverse transcriptase inhibitors) inhibiting the reverse transcriptase (RT) of HIV by structural similarity with the substrate of RT.
- NNRTIs (non-nucleoside reverse transcriptase inhibitors) inhibiting the reverse transcriptase of HIV without being nucleoside analogues.
- PIs (protease inhibitors) inhibiting the HIV protease, which is an enzyme required for the assembly and release of mature HIV particles from the cell after the replication cycle.
- Entry inhibitors preventing the entry of HIV into the cell hence inhibiting the infection of these cells; currently there is only one compound authorised which is a fusion inhibitor.

Regimens containing compounds from one or more of these classes are required for building combination antiretroviral therapy (CART). The choice of the combination regimens depends on the status of the patient particularly in terms of plasma vial load (HIV RNA), CD4 cell counts, previous treatment(s), prior relapse and intolerance to treatment.

The long-term use of all these products is however hampered by different factors such as emergence of resistance, potential toxicity and in some cases inconvenient dosing schedules or formulations. Further therapeutic agents are therefore needed, particularly in patients who have failed their therapy.

CELSENTRI, which contains maraviroc, is a CCR5-antagonist preventing CCR5-tropic HIV-1 from entering cells. It has been developed for treatment-experienced HIV-infected patients who have only CCR5-tropic HIV-1 detectable.

The rationale behind the use of CCR5-antagonists in treatment of HIV infection is based on the fact that HIV requires the binding to both the CD4-receptor and a co-receptor to enter a cell. The two relevant co-receptors are CCR5 and CXCR4. HIV can be either CCR5-tropic ("R5-virus") or CXCR4-tropic ("X4-virus"), so called tropism. Virus isolates replicating on both CCR5- and CXCR4-positive cells may do so either because they contain a mixture of R5- and X4-virus, or they use both CCR5 and CXCR4 (so called dual-tropic). If the CCR5 receptor is blocked by CCR5-antagonists, CCR5-tropic HIV cannot enter the cell.

A so-called full application has been submitted for the marketing authorisation. The assessment was initially made under accelerated review based on a request by the applicant; however the timetable was reverted to "normal" centralised timetable during the procedure.

CELSENTRI is available in film-coated tablets containing 150 mg or 300 mg maraviroc; the recommended dose is 150 mg, 300 mg or 600 mg twice daily depending on interactions with co-administered antiretroviral therapy and other medicinal products.

The approved indication is:

> "CELSENTRI, in combination with other antiretroviral medicinal products, is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable (see section 4.2).
>
> This indication is based on safety and efficacy data from two double-blind, placebo-controlled trials in treatment-experienced patients (see section 5.1)."

Quality aspects

Introduction

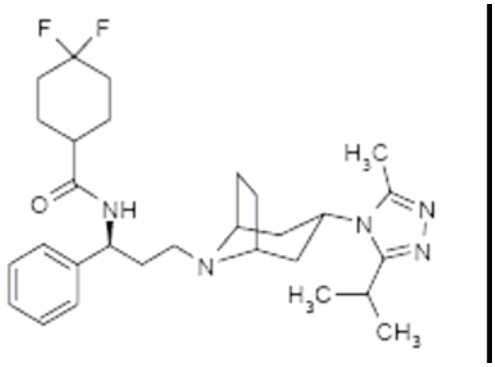
Celsentri is presented as immediate release film-coated tablets containing 150 mg or 300 mg of maraviroc (active substance). The excipients used in the formulation of Celsentri are those typically used in tablet formulations. The tablet core contains cellulose microcrystalline, calcium hydrogen phosphate anhydrous, sodium starch glycollate and magnesium stearate. The film-coat is a conventional Opadry II Blue film-coating system which consists of polyvinyl alcohol, titanium dioxide, talc, macrogol 3350, soya lecithin and indigo carmine aluminium lake (E132).

Celsentri 150 and 300mg film-coated tablets are blue, biconvex and oval, debossed with "Pfizer" on one side and "MVC 150" or "MVC 300" on the other. The tablets are packed in HDPE bottles (with PP closure) or PVC/Al blisters.

Active Substance

Maraviroc is chemically designated as 4,4-difluoro-*N*-[(1*S*)-3-[(3-*exo*)-3-[3-methyl-5-(1-methylethyl)-4*H*-1,2,4-triazol-4-yl]-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-cyclohexanecarboxamide (CAS) or 4,4-difluoro-*N*-{(1*S*)-3-[*exo*-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclohexanecarboxamide (IUPAC). The structure of maraviroc is presented in figure 1.

Figure 1 Chemical structure of maraviroc



Maraviroc is white to pale coloured, non-hygroscopic solid which is highly soluble across the physiological pH range. According to the biopharmaceutical classification system (BCS) maraviroc is clasified as a high solubility compound. Its pKa are 3.3 and 7.9 corresponding to the protonation of the 1,2,4-triazole ring and tropane nitrogen, respectively. Maraviroc has one chiral centre, which has the *S* absolute configuration. It is also an *exo* isomer with respect to the configuration on the tropane unit. Two crystalline forms, A and B and an amorphous form of maraviroc are known.
Form B is the thermodynamically more stable and is the only form used in the formulation. The amorphous form is metastable with respect to Form B.

- Manufacture

A four-stage synthetic process has been well-described and the critical parameters and accompanying in process controls have been defined. Specifications and control methods of the starting materials are satisfactory. Three intermediates are isolated throughout the synthesis. Possible impurities in drug substance have been characterized with respect to their origin, occurrence, detection and removal.

The manufacturing process has been developed by performing risk assessment. Potential impact of process parameters on the quality of the drug substance has been assessed. The concept of Design of Experiments (DoE), including computer modelling, have been utilised to establish a so called Design Space (DS) for the manufacture of the drug substance. The selected ranges for synthesis parameters ("Proven Acceptable Ranges" (PAR)) have been established based on evaluation on the impact on the impurity profiles so as to reach acceptable impurity levels for each of the manufacturing steps.

Confirmation of the chemical structure of the drug substance routinely produced by the defined method of synthesis has been provided by elemental analysis and spectroscopic methods as UV, IR, MS and NMR (^{13}C, ^{1}H and ^{19}F). The crystal structure has been confirmed by crystal single X-ray diffraction. An assessment of the solid state forms has also been conducted. Two crystalline polymorphs (Forms A and B) and an amorphous form of maraviroc have been identified. Only form B is reproducibly produced by the proposed commercial synthetic route.

- Specification

The active substance specification includes tests for physical appearance, identification (FT-IR and HPLC), assay (HPLC), impurities (HPLC), residue on ignition, heavy metals, palladium content (ASA), water content (Karl Fisher), residual organic solvents (GC).

Analytical control methods have been validated with regard to relevant guidelines and include specificity, linearity and precision, limit of quantification, accuracy and robustness as appropriate.

Data was provided on 26 batches of maraviroc all of which were manufactured using the commercial route. All the batches complied with the requirements in the active substance specification.

- Stability

Stability studies have been performed on three batches of drug substance manufactured at 10 % of the proposed maximum commercial batch size. Data have been provided for 12 months at 25°C/60 % RH (long term storage conditions) and 30°C/65 % RH (immediate conditions) and 6 months at 40°C/75 % RH (accelerated conditions). Additionally, data from photostability study, shorter periods under stressed storage conditions (25°C/80 % RH and 50°C/20 % RH) and forced degradations studies (as *e.g.* acidic, alkaline, oxidative elevated temperature and humidity) were also presented.

The stability studies showed that the active substance is stable and confirm the proposed re-test period.

Medicinal Product

- Pharmaceutical Development

The focus has been on the development of immediate release tablets disintegrating and dissolving rapidly under physiological conditions in the stomach. The concepts of risk based analysis have been used during development in order to identify critical parameters and attributes associated with the processing of tablets. For the manufacturing process a so called "Design Space" has been established. Development of the manufacturing process has been divided into four "focus areas", (1) pre-blend, (2) granulation, (3) compression and (4) film-coating. A cause-and-effect analysis identified the parameters with highest possibility to affect product quality (potency, uniformity, dissolution and appearance). The evaluation performed resulted in design space, within which tablets of acceptable quality can be produced.

- Adventitious Agents

None of the excipients used in the formulation of maraviroc film-coated tablets are of human or animal origin.

- Manufacture of the Product

Maraviroc 150 mg and 300 mg film-coated tablets are made from a common granulation procedure. The process consisted of blending, screening, blending, and blend lubrication, to generate a homogenous lubricated mixture of the drug substance and excipients, followed by roller compaction and milling, to produce granules which are then blended and lubricated prior to tablet compression. Finally the tablet cores are film-coated with a blue film-coat.

- Product Specification

The product specification is standard for tablets, and contains tests with suitable limits for identity of active substance (UV and HPLC), assay (HPLC), dissolution (HPLC), content uniformity (HPLC), impurities (HPLC) and skip-test for microbial bioburden and excipients identification.

Batch analytical results for 45 batches indicate satisfactory uniformity and compliance with the agreed specification.

All methods have been satisfactorily validated. The analytical methods and acceptance criteria have been established to confirm the identity, purity and quality of the drug product and to ensure its suitability for their intended use.

- Stability of the Product

In accordance with ICH guideline Q1A (R2), a stability program consisting of one batch of 150 mg strength maraviroc tablets, and three batches of 75 mg and 300 mg strength maraviroc tablets was set up on stability. The 75 mg strength tablets have been used for bracketing the 150 mg strength tablets. All three strengths were manufactured from the common blend formulation and were manufactured and packaged at the commercial manufacturing site.

The stability program for the seven batches of tablets has been completed at 25°C/60 % RH and 30°C/65 % RH through 12 months and 40°C/75 % RH through 6 months. In addition one batch of each strength of tablets was placed on a 'stressed conditions' stability program, evaluated at 25°C/80 % RH and 50°C/20 % RH through 3 months. In accordance with ICH guidelines Q1B one batch of each strength was also exposed to the photostability conditions described for option 2.

Based on the stability data the proposed shelf-life and storage conditions, as defined in the SPC, are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

The active substance and finished product have been adequately described. Excipients used in the formulation of the finished product and the manufacturing process selected are typical for tablets. The results of the tests indicate that the active substance and the finished product can be reproducibly manufactured and therefore the product should have a satisfactory and uniform performance.

At the time of the CHMP opinion, there was a minor unresolved quality issue which have no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve it as a Follow-up Measure after the opinion, within an agreed time-frame.

Non-clinical aspects

Introduction

Maraviroc is a new compound for combined antiretroviral therapy and acts as CCR5-antagonist. It blocks the host cell co-receptor CCR5 that is utilized by CCR5-tropic viral strains in the process of viral entry and infection, which involves several steps including binding of the viral envelope glycoprotein gp120 to the cellular CD4 receptor, the subsequent engagement with CCR5, and membrane fusion between HIV and host cell.

The non-clinical programme consisted of a range of pharmacological and toxicological studies in line with current recommendations and under consideration of European and international guidelines as appropriate.

Pivotal studies on pharmacology (safety) and toxicology were conducted in compliance with GLP and quality assurance statements were provided.

Pharmacology

- Primary pharmacodynamics

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

Primary pharmacology related to the antiviral mode of action

The mode of action of maraviroc was studied at three levels in *in vitro* studies. a) Characteristics of receptor binding of maraviroc (^{3}H-labelled) to recombinant human CCR5 using HEK-293 cell membrane preparation; b) Inhibition of viral protein attachment and fusion; c) viral replication assays.

The affinity of maraviroc for the human CCR5 was reflected in a K_D 0.86 nM, which is comparable to that for the macaque CCR5 receptor (K_D 1.36 nM). The non-competitive binding to the CCR5 receptor leading to inhibition of viral protein attachment and fusion was characterised in two assays (gp120/CD4 binding assay and gp160-CCR5 mediated cell-cell fusion assay) by an IC_{50} of 11 nM and 0.22 nM, respectively. Inhibition of viral replication against 43 primary isolates in PBMC culture was expressed by a geometric mean of the IC_{90} of 2 nM.

The two major human metabolites, a secondary amine product of N-dealkylation (UK-408,027) and the carboxylic acid (UK-463,977) were tested for inhibition of gp160-CCR5 mediated cell-cell fusion (IC_{50}>10 μM) and a general receptor/ion channel/enzyme screen did not indicate any biologically relevant secondary activity.

Primary pharmacology not related to the antiviral mode of action

Studies using site directed mutagenesis were consistent with that the putative binding site for maraviroc on CCR5 included interactions with amino acids within the transmembrane region of the receptor. Sequence comparisons of human data at a radius of 2Å from the perimeter at the putative binding site, indicated a 94.4% identity for the macaque and a range from 61.1% (rabbit) to 77.8% (dog) in other species. The kinetics of maraviroc at the macaque CCR5 (K_D of 1.36 nM and an IC_{50} of 17.5 nM for inhibition of MIP-1β binding) were overall similar to its interactions with the human receptor except for a dissociation half-life of 1.5 h to compare with 16 h for the human receptor. Using homogenates of HEK-293 cells expressing dog and rat recombinant CCR5 it was shown that inhibition reached 38.7 and 33.3%, respectively at concentrations of 10 μM maraviroc.

Studies on the potential to block binding of endogenous human CCR5 ligands and to interfere with the functional activity of the receptor were conducted. Receptor binding studies reported IC_{50} values of maraviroc in the range of 3.3 to 7.2 nM for inhibition of binding of MIP-1α, MIP-1β and RANTES and no intrinsic agonist activity. Functional activities as reflected in assays of calcium flux and cAMP levels were inhibited with IC_{50} values in the 4-30 nM.

- Secondary pharmacodynamics

The selectivity profile of maraviroc with respect to chemokine receptors CCR1 to CXCR4 (CCR6 and CXCR3 not tested) representing an amino acid identity with CCR5 from 68.5% (CCR2) to 31.5% (CXCR4) assayed in different *in vitro* systems showed no significant inhibitory activity of maraviroc up to 10 μM or 25 μM. In assays for selectivity in human immune system functions that may also involve multiple signal transduction, no relevant activity of maraviroc up to 10 μM was reported with the exception of interleukin-4 induced IgE synthesis in isolated human blood lymphocytes from one donor. Although human homozygous for Δ32 CCR5 have not been associated with any particular immune pathology there are reports of subtle physiological effects of altered gene expression. In CCR5 knockout mice defective clearance of infectious agents has been reported as well as reduced corneal neovascularisation and mice may have increased levels of CD4+ and NK.1.1+ in the colonic lamina propria and increased IL-4, IL-5 and IL-10 expression but decreased IFN-γ. No assays for potential to interfere with activity/function of chloride channels or IL-5 pathways were available in the pharmacology screening programme.

- Safety pharmacology programme

The potential of maraviroc to interfere with major physiological systems was investigated in a series of *in vitro* and *in vivo* studies. In most studies maraviroc was tested at concentrations of 0.1 μM to 100 μM and doses estimated to provide unbound plasma levels of 154 ng/ml (300 nM). Standard radioligand techniques were used.

In *in vitro* tests for potential affinity of maraviroc on physiological receptors, ion channels and enzymes, a moderate inhibitory activity for human μ opioid (mean IC_{50} 294 nM), human δ opioid (48% inhibition at 10 μM), rat non-selective muscarinic receptors (39-47% inhibition at 10 μM) and the human α2A adrenergic receptor (52% inhibition at 10 μM) was evident. Functional adrenergic activity was not affected. *In vitro* studies were not indicative of maraviroc having an affinity for a range of receptors responsible for binding vasoactive peptides (angiotensin II, atrial naturietic peptide, bradykinin-2, endothelins A&B, ghrelin, thromboxane, urotensin-1, vasopressin-1A).

In studies *in vitro* in isolated tissue and whole cell a 22% stimulation of functional activity of human μ receptor at 10 μM was reported. In other functional assays indicative of muscarinic activity, maraviroc

was tested up to 1 μM with no effect. Against human recombinant HERG (Ikr) a 43% inhibition was observed at 10 μM and in a patch clamp assay at the same concentration 19% inhibition was achieved. In a dog Purkinje fiber assay, prolongation of ADP_{90} occurred at 10 μM and was initially ascribed to an impurity not further detailed. A second study was negative up to 1 μM. No early afterpolarizations were reported.

The activity of maraviroc at adrenergic receptors was further evaluated as a possible mechanism for postural hypotension seen in clinical trials. Maraviroc caused dilation of isolated canine venous tissue that had been constricted with phenylephrine, but not potassium chloride; some *in vitr*o rat and human data is not consistent with this finding. In canine saphenous veins maraviroc functioned as a competitive antagonist at alpha adrenergic receptors, but no effect was observed in equivalent human preparations. In human vasculature MIP-1β from 0.1 μM caused a concentration dependent vasoconstriction of isolated endothelium denuded human saphenous vein tissues with a pEC_{50} 7.7±0.17. Preincubation for 30 minutes with 300 nM maraviroc had no effect, but in the presence of maraviroc, MIP-1β failed to cause contractions. In an *in vivo* postural challenge study in dog, maraviroc reduced systolic blood pressure and pulse pressure response possibly due to antagonism at the alpha adrenergic receptor. Maraviroc, at levels giving free plasma concentration from 1030 to 2410 nM had "subtle effects" on control of blood pressure during postural challenge.

In vivo safety pharmacology studies included tests for potential to interfere with CNS, cardiovascular, respiratory and renal systems (Table 1). No relevant effects were reported, but doses selected for these studies were overall rather low. At 2000 mg/kg in rats, adverse effects consisted of decreased activity, piloerection, salivation, wet chin, irregular and laboured breathing, jaw movement and vocalisation. At low oral doses (corresponding to Cmax levels below expected clinical) maraviroc had no effect on haemodynamic or ECG parameters in the conscious dog. In the restrained dog, intravenous doses of maraviroc caused slight reduction in systolic and increase in diastolic blood pressure while pulse pressure was reduced. Intravenous doses of 1 mg/kg in rat produced decreases in blood pressure and heart rate. With the exception of rat renal study, male animals only, were used.

Table 1 General pharmacological effects of maraviroc

Study System	Species (n)	Dose (mg/kg)	Result/Observation
Maximum Tolerated Dose	Rat (M) (2), PO	1000, 2000	1000 mg/kg: Salivation, transient ↑ respiration, ↓activity (normal at 30 min) Unbound Cmax 5.0 μM, total Cmax 10.1 μM. 2000 mg/kg: Piloerection, transient ↑ respiration, ↓activity (normal at 45 min). Marked salivation, respiratory distress for 1 h (in 1 rat 2h postdose).
CNS- pentobarbitone induced sleeping time	Mouse (M) (20), PO	1, 3, 10	No effect.
CNS motor coordination (accelerating rotarod)	Mouse (M) (12-20), PO	1, 3, 10	No effect.
Renal excretion of fluid and electrolytes	Rat (F) (12), PO	10, 20, 60	No effect.
Respiratory system	Rat (M) (4), IV	1	No effect-arterial blood pH, pO_2 and pCO_2. Mean arterial pressure, heart rate ↓ 10 min postdose
CVS (haemodynamics, electrocardiogram)	Dog (M), Beagle (4) PO	0.05, 0.15, 0.5, 1.5	No effect. Mean unbound Cmax=168 nM (86 ng/ml) Total 464 nM (238 ng/ml)

CG/009/00, CG/005/01, CG/002/01, CG/004/01, CG/001/01, CG/003/00, CG/008/00 (all studies GLP)

In summary, with respect to the safety pharmacology data no relevant effects were seen at low doses on the renal, respiratory and central nervous system, however the following aspects are of note:

- Non-clinical tests showed that maraviroc has potential to inhibit or block the Ikr current and prolong cardiac repolarisation hence exhibiting a potential to cause QT prolongation. Clinically significant QT interval prolongation was not reported in healthy subjects exposed to maraviroc. Direct comparisons/extrapolations of in vitro concentrations to therapeutic plasma levels with

calculations of "safety factors" may not always be meaningful, but literature data indicate that a factor of 30 for in vitro/in vivo concentrations can be interpreted as reassuring. The in vitro results could thus indicate a lower level of concern for potential cardiovascular effects.

- The mechanism of action involved in the postural hypotension seen in the clinical studies is not clear, but CCR5 mediated effects on vasculature was presented as a possible hypothesis. While activity at adrenergic receptors also could be involved in these effects, data is not consistent with maraviroc causing dilatation in phenylephrine preconstricted canine saphenous vein tissue, but having no effect in the equivalent human preparation. The antagonism by maraviroc of MIP-1β mediated contractile response suggests a functional role of CCR5 ligand-receptor system in vascular function in human saphenous veins. Published data indicate a role of chemokines and their receptors in the regulation of blood pressure.
- The primary and secondary pharmacology studies provide extremely limited data on the potential for any gender dependent interactions of maraviroc with receptor. In mouse systems, estrogen has been discussed in regulation of CCR gene expression and enhanced chemotactic response to MIP-1β. The consequences of partial and altered signalling via CCR5 (or other CCRs) may however not be directly comparable with genetic CCR5 (CCRs) variations.
- No study on gastrointestinal tolerance was conducted, however repeated dose toxicity studies show a potential for local effects.

- Pharmacodynamic drug interactions

For drug interactions see clinical section 4. Additive or slightly synergistic interactions were reported with compounds of the various classes used for CART. There is no evidence that maraviroc antagonises the antiviral activity of these compounds. Specific non-clinical studies to investigate pharmacodynamic drug interactions have not been conducted.

Pharmacokinetics

The pharmacokinetics of maraviroc have been evaluated *in vitro* as well as in several species (mouse, rat, rabbit, dog and cynomolgus monkey) that were also used in the non-clinical pharmacology and toxicology programme. Mostly male animals were used except for dog and rat. *In vivo* studies comprised the investigation of single and multiple dosing, respectively.

Validated chromatographic (HPLC) methods with mass spectrometric detection of maraviroc and relevant metabolites in biological fluids were used. In tissue distribution studies as well as in studies on metabolism, three forms of radiolabelled marviroc were used: (^{3}H), single and dual labelled carbon-14 compound. Metabolic loss of the (^{3}H) label occurred and the carbon-14 studies were considered definitive.

Absorption/Bioavailability

In rat bioavailability was low at 5% while in dog corresponding value was around 40%. Generally there was no difference in plasma exposure in male and female animals, but at lower doses in mouse and rat studies, females appeared to have up to two-times the exposure of males. In mouse and dog there was a dose-proportional increase in exposure after multiple doses while in the rat, a proportional increase in Cmax, but a supra-proportional increase in AUC (increase by 1.4 to 2.2 with duration of study from day 0 to day 181) was recorded. In monkey increases in AUC and Cmax were greater than dose.

Distribution

Ex vivo plasma protein binding by equilibrium dialysis and using (^{14}C)-maraviroc indicated plasma protein binding ranged from 48.4% to 75.5% in various species (58.0%, 51.0%, 66.0%, 63.7%, 48.4% and 75.5% for mouse, rat, rabbit, dog, cynomolgus monkey and human, respectively). Moderate and similar binding to albumen and α-1-acid glycoprotein (56 and 69%) was recorded. Low partitioning into human red blood cells with a mean blood plasma ratio of 0.59 was noted. In some pharmacokinetic and pharmacology studies (^{3}H)-maraviroc was used and while no major effect of

labelling at this position was identified (66%, 46%, 50%, 52% and 78% for mouse, rat, rabbit, dog and human, respectively) studies using (^{14}C)-maraviroc were considered definitive. The mean proportion of drug bound was similar across the concentration range of 1, 30 and 1000 ng/ml.

Maraviroc is a substrate for P-gp as indicated in *in vitro* studies and Km and Vmax values of 37±6.4 µM and 55±3.4 nmol/mg/min were recorded. Studies on the permeability of ^{14}C-maraviroc across Caco-2 cell monolayers in the presence of P-gp and MRP inhibitors showed reduction of efflux by verapamil, MK-571 (an MRP inhibitor), ketaconazole, ritonavir, nelfinavir, saquinavir and indinavir.

In tissue distribution studies in pigmented male Lister Hooded rats given 3 mg/kg of (^{3}H)-maraviroc intravenously, binding to melanin in the eye was evident. Highest concentrations were detected in bladder, prostate gland, kidney, small intestine wall and contents, liver and seminal vesicles.

The distribution to pharmacologically relevant gut associated lymphoid tissues was studied in male Long-Evans rats. Radiolabel from (^{14}C)-maraviroc was detected in lymph nodes including gut-associated lymphoid tissues, axial and sublingual lymph nodes, gastro-intestinal tract mucosa, spleen, liver, kidney, mesenteric adipose and vena cava blood 1 hour postdose. Highest concentration was found in spleen, liver and intestinal mucosa.

Limited penetration into brain occurred with CSF to plasma ratios of 0.01 for unbound drug.

Metabolism/Excretion

Metabolites were identified from excretion studies using (^{14}C)-maraviroc and mass spectrometry combined with chromatographic retention time as well as NMR. Preliminary studies used (^{3}H)-maraviroc resulting in some metabolic loss of the (^{3}H)-label.

Metabolism studies showed unchanged maraviroc as the major excreted component, accounting for 33-39 (human male volunteer, male mouse) to 58-65% (male cynomolgus monkey, male TgrasH2 mouse) of dose. A secondary amine (UK-408,027) produced by N-dealkylation accounted for 3 to 9% in various species and in addition, products of (mono-) oxidation and some other minor components were detected. In urine, an acid metabolite UK-463,977 accounted for 2-3 (mouse, human) to <0.1% (rat). In the rabbit (female) unchanged maraviroc was the major excreted component (78%) and in addition, the secondary amine (UK-408,027), and a product of mono-oxidation (UK-437,719) accounting for 6 and 2%, were identified.

Circulating components in plasma consisted primarily of unchanged maraviroc, ranging from 40-42% (rabbit, human) to 67-74% (rat, Tgras mouse). Major metabolites included the secondary amine UK-408,027, accounting for 6-9% in mouse and rat to 12-22% in rabbit, monkey and human. In rat a major metabolite was an uncharacterised polar metabolite for 23%. In female rabbit the major metabolite (38%) remained unidentified. The acid metabolite UK-463,977 was detected at levels from 2.48 ng/ml (Cmax) in rat, to 45.2 ng/ml in monkey and 37.3 ng/ml in humans. In addition several products of mono-oxidation and other minor components were detected in all species at levels of 1-11%.

The *in vitro* metabolism of maraviroc was studied in hepatic microsomes from human livers and in microsomes prepared from cells expressing individual cytochrome P450 enzymes. In microsomes prepared from cells expressing individual cytochrome P450 enzymes, it was only possible to detect metabolism in incubations with CYP3A4 and CYP2D6. In studies using human hepatic microsomes the disappearance half-life of maraviroc was extended in the presence of ketoconazole, a specific CYP3A4 inhibitor (13.1 min to 79 min). The use of recombinant enzyme systems confirmed a role for CYP3A4 (and its orthologue, CYP3A5) in the metabolism of maraviroc, and showed that neither of the polymorphic P450 enzymes CYP2C19 or CYP2D6 contribute significantly to its metabolism.

The potential for maraviroc to inhibit the activity of five drug metabolising cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) was studied using recombinant enzymes and human liver microsomes. In the recombinant enzyme systems, maraviroc did not inhibit any of the cytochrome P450 enzymes investigated except for weak inhibition of CYP2D6 (IC_{50} 87$\pm$2 µM). The

potential for maraviroc to inhibit the activity of seven drug metabolising cytochrome P450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) has been studied in human liver microsomes. Maraviroc was demonstrated to be a weak inhibitor of cytochrome P450 activity with estimated IC_{50} values of >30μM against each enzyme investigated.

Maraviroc was mainly excreted in faeces (76-95%) in all species. It is secreted into rat milk and in lactating female rats; radioactivity was detected in milk at all time points and 86% of the label excreted was unchanged compound while the secondary amine accounted for 4%. Milk:plasma ratios of 2.5 to 2.7 were recorded.

Toxicology

The toxicity of single and repeated doses of maraviroc was studied in mouse, rat, dog and cynomolgus monkey. In terms of metabolism and general pharmacokinetics these species can all be considered as useful models for humans; however considering pharmacology at the target receptor level the monkey is closest to the human.

Doses used in the studies ranged from 5 to 1500 mg/kg/day with dog being the most sensitive species and rodents and monkey tolerating high doses. One 6 month rat study included a 3 month reversibility period. Administration was once a day except in monkey where doses were administered twice a day to compensate for a faster receptor dissociation rate in monkey compared with human ($t1/2_{off}$ 1.5 h and 16 h, respectively).

The lots used in toxicology studies generally contained impurities representative of clinical batches and overall covered the proposed specification limits.

- Single dose toxicity

Single dose toxicity has been investigated in three GLP studies in mouse and rat. Oral doses up to 2000 mg/kg were well tolerated in mouse and rat while a single intravenous dose of 200 mg/kg resulted in deaths within 5 minutes.

Overall, maraviroc had low acute toxicity. At high intravenous doses deaths occurred within minutes possibly suggesting acute cardiovascular effects.

- Repeat dose toxicity (with toxicokinetics)

Pivotal GLP toxicity studies after repeated doses were conducted over 3 months in the mouse (doses of 200-750 mg/kg), 6 months in the rat (doses of 30-900 mg/kg), 6 months in the dog (doses of 5-40 mg/kg) and 9 months in the cynomolgus monkey (doses of 40-400 mg/kg). At the high dose in mouse, rat, dog and monkey the systemic exposure levels achieved corresponded to approximately x50-80, x32-44, x6-7 and x29-30 the expected clinical exposure, respectively. Corresponding values at the lowest doses used were x4-5, <1, <1 and <1.

<u>Mouse</u>

In the five oral mouse studies few effects of toxicological significance were reported. Histopathology indicated degeneration of superficial epithelium in cecum, probably related to local effects. Sporadic increases in cholesterol, AST, ALT, neutrophils and fibrinogen at doses of 2000 mg/kg/day were noted.

No toxicologically significant effects were evident in the 3 month dose range-finding study in mouse. Females exhibited a dose related increase in body weight. At the high dose there was a slight increase in absolute and relative kidney weights. There was a 10 to 50% increase in absolute and relative ovary weights but as the range for ovary weights were similar in all groups and no correlation to a histopathological finding could be recorded and the changes were considered fortuitous. The

compound was administered in 0.5% methylcellulose and 0.1% Tween 80 by oral gavage. Plasma levels of drug were determined in parallel groups of 12 mice/sex/dose level.

Rat

Three repeat-dose toxicity studies were conducted in rats (2 oral by gavage, 1 parenteral).

In the 6 month oral toxicity study a 13 week reversibility period was incorporated and satellite animals (5/sex/group) were included for blood sampling. In addition to standard parameters monitored, the study incorporated ophthalmological examinations, examinations for postdosing hypersalivation and T3, T4 and TSH determinations. Bone marrow smears were prepared at necropsy. Three deaths occurred during the study, none was considered treatment related. Decreased body weight, salivation and increased water consumption was evident; this could reflect the compounds activity at muscarinic receptors and/or blockade of α2-adrenoceptors. The liver was the primary target organ for toxicity in rat and hepatic effects included increased cholesterol, AST, ALT, decreased bilirubin and triglycerides, possibly indicative of interference with hepatic metabolism and transportation of lipids. Increased liver weight, bile duct vacuolation, bile duct hyperplasia, multinucleated hepatocytes, altered cell foci and hepatocellular necrosis were recorded with a NOAEL of 100 mg/kg/day representing an 8-9 fold multiple to expected clinical exposure, or roughly estimated to provide an approximate 30% inhibition of CCR5.

The mechanism of the liver toxicity is not known. Clarification has been provided by the applicant as to the identification of bile duct changes in different species. The CHMP concurred that interactions on the level of the CCR5 receptor are not likely to be involved in the effects observed, but rather these could be a reflection of non-selectivity at the pharmacological level. Different species appeared to exhibit different sensitivities and bile duct hyperplasia was not reported in toxicology studies other than in rat. However studies in literature suggest that suggest an important role of CCR5 in the pathophysiology of T cell-mediated liver diseases with specific emphasis on auto-immune and viral liver diseases (J Immunol. 2006 Aug 15;177(4):2039-45, Hepatology. 2005 Oct;42(4):854-62). The non-clinical findings are included in section 5.3 of the SmPC. Furthermore, pharmacovigilance activities will further address potential for hepatic toxicity clinically (see section 3.5 Pharmacovigilance).

Further, in rats, increased TSH and T4, thyroid follicular cell hypertrophy, vacuolation of adrenal glands and dilation of cecum were reported, the former likely a result of liver enzyme induction.

Inflammation at the stifle joint was reported at a high dose of 1500 mg/kg in a 1 month oral study with an uncertain relation to treatment and in the male fertility study mononuclear infiltrates along the synovial lining of the joint was noted at high doses.

A 7 day intravenous irritation study in rat indicated no irritating potential of the compound at doses of 0.6, 2 and 10 mg/kg corresponding to concentrations of 0.06 to 1.0 mg/ml.

Dog

Four oral repeat-dose toxicity studies were conducted in beagle dogs.

Emesis, salivation, skin reddening and ocular effects (protruding nictitating membrane, lacrimation, mydriasis, red conjunctiva) could be related to μ-opioid action and antimuscarinic activity. Generalised skin reddening was observed. While vasodilatation *in vitro* has been discussed in terms of activity at adrenergic receptors a possible role of histamine cannot be excluded. The QTc interval increased at doses of 15 mg/kg/day. There was a slight increase in heart rate and decrease in systolic blood pressure. The NOAEL in dog studies was 5 mg/kg/day although some ocular signs were evident. At this dose plasma levels (unbound) were in the clinically relevant range.

Monkey

Three oral repeat-dose toxicity studies were conducted in cynomolgus monkeys.

High doses of 400 mg/kg/day caused reduced activity, prostration, half-closed eyes, decreased body weight, vomiting and liquid faeces. There were increases in triglycerides and ALT and decreases in red blood cell parameters at the high dose. Systolic and diastolic blood pressure decreased as did heart rate with administration of maraviroc. Cardiovascular reaction was evident as QTc interval increase with a NOAEL of 120 mg/kg/day (x3-5 the expected clinical exposure). No cardiac arrhythmias were recorded.

- Genotoxicity

Maravioc has been tested for genotoxicity in three GLP studies, which is in accordance with applicable guidelines.

In vitro tests for gene mutation in bacterial systems (Salmonella strains TA1535, TA1537, TA98, TA100, *E.coli* WP2 uvrApKM101) were negative as was the chromosome aberration test in human lymphocytes. In this assay in mammalian cells, a slight increase in polyploidy cells was evident, but overall not considered relevant.

The *in vivo* mouse micronucleus study for clastogenic potential was negative. A satellite group was included in this test for the determination of plasma levels. There were no reductions in mean percent polychromatic erythrocytes (PCE) suggesting that bone marrow toxicity did not occur and there was no significant increase in numbers of PCE with micronuclei up to the highest dose that was coupled to Cmax levels of 13 and 13 5 µg/ml and $AUC_{0\text{-}24h}$ values of 185 and 174 µg·h/ml in males and females, respectively. The positive and negative controls gave expected responses.

- Carcinogenicity

The carcinogenic potential of maraviroc was evaluated in two studies:
- a long-term 104 week rat study (0, 50, 100, 500, 900 mg/kg/d PO; 60/sex/group);
- a mid-term 26 week TgrasH2 mouse study (0, 200, 800, 1500 mg/kg/d PO; 25/sex/group).

In both studies maraviroc could be detected in a proportion of samples from control animals. This was most prominent in the transgenic study where 33% of control samples were positive for maraviroc and control, low and mid dose animals showed comparable plasma levels of maraviroc. The phenomenon was essentially inexplicable, but determined to originate post sampling (inferred from detection of metabolites in samples from treated animals but not from control animals).

Long-term study

High mortality in vehicle control females led to dosing discontinuation after 96 weeks and all females were necropsied. Dosing continued in males to 104 weeks. Maraviroc treatment had no effect on mortality. Percent survival was 38, 33, 42, 47 and 32% in males in the control, 50, 100, 500 and 90 mg/kg/day groups, respectively. Corresponding values for females was 33, 42, 39, 50 and 48%.

Systemic exposure was determined on day 198 in satellite groups of animals. The mean combined Cmax on day 198 was 0.468, 1.27, 3.49 and 3,84 µg/ml for the 50, 100, 500 and 900 mg/kg/day groups, respectively. Corresponding $AUC_{0\text{-}24h}$ in µg·h/ml were 3.03, 9.97, 39.7 and 54.7. Two of 30 vehicle animals and 1 of 10 untreated animals had quantifiable levels of maraviroc.

Total incidences of benign and malignant neoplasms were similar across all groups. The incidence of biliary hyperplasia was high in all groups, also controls, approaching 80%, whereas a treatment related increase was noted in the rat 6 month repeated toxicity study. Thyroid follicular cell adenoma occurred at a higher incidence in high dose animals and could be related to decreased levels of T4 and increased TSH in plasma, related to liver enzyme induction and this kind of changes are considered of low

human relevance. The trend test was significant for the rare tumours cholangiocarcinoma (2 high dose males) and cholangioma in a high mid dose female. These kinds of tumours have been known to occur in historical controls, but data is not sufficient to conclude on a spontaneous etiology.

Mid-term study

A positive control group of 15 mice/sex, administered a single intraperitoneal dose of N-methyl-N-nitrosurea (75 mg/kg) was included in the study.

In 33% of control samples (8 of 24) maraviroc was detected above the lower limit of quantification 0.05 µg/ml (levels up to 4.18 µg/ml, comparable to Cmax levels in low and mid dose group), likely due to *ex vivo* contamination. Toxicokinetic data showed highest plasma levels recorded at day 184 with 4.64, 2.89 and 8.54 µg/ml, for low, mid and high dose males, respectively. Corresponding values for females were 4.81, 10.6 and 16.0 µg/ml. Systemic exposure levels as AUC(0-24h) were 22.5, 33.4 and 117 µg·h/ml, for low, mid and high dose males, respectively. Corresponding values for females were 29.0, 71.6 and 213 µg·h/ml. High variability in plasma levels was evident.

The positive control animals in the TgrasH2 mouse study all exhibited neoplastic changes while no unexpected histopathological changes was reported for negative control and maraviroc animals, except a slight increase in glycogen storage in liver.

- Reproduction Toxicity

The potential of maraviroc to affect reproductory systems was studied in rat and rabbit.

Fertility and early embryonic development

Oral doses of up to 1000 mg/kg, corresponding to Cmax levels of 7.2 µM, a concentration estimated to provide an approximately 30% inhibition of MIP-1β binding to rat (and rabbit) CCR5, had no significant effects on estrus cycle, pre-coital time, copulation and pregnancy rates, spermatozoid count in epididymides or spermatic motility. At the high dose a statistically significant increase in preimplantation loss occurred.

Embryo-foetal development

Studies on embryofoetal development in rat reported a NOAEL for pregnant females of 300 mg/kg and 1000 mg/kg for the foetuses in rat and no relevant effects on reproduction parameters. In the definitive rabbit embryofoetal study the NOAEL was determined to 75 mg/kg for maternal animals and 200 mg/kg for foetuses. At the high dose 7 foetuses in 6 litters had external anomalies, two foetuses had a bent forepaw coupled, one foetus had cleft palate, 3 foetuses in 3 litters had short tail and one foetus had cutis aplasia. At 75 mg/kg one foetus had spina bifida occulta and at 30 mg/kg one foetus had single naris and a litter had double placenta.

Based on historical control data the applicant concluded that the findings at the high dose were incidental. The CHMP considered this conclusion questionable. Overall, the studies on potential for reproduction toxicity of maraviroc are deficient in that species used are not relevant from the primary pharmacological aspect for he reasons outlined above. However, although the non-clinical data has limitations it was acknowledged that reproductory effects due to CCR5 inhibition can to some extent be derived from data in CCR5 knockout mouse, which indicate no detrimental effects on fertility, as well as from limited human data that do not indicate any cause for concern. It was noted that substances that cause potent hERG inhibition and foetal hypoxia, have been coupled to increased incidences of malformations such as cardiovascular anomalies and cleft palate.

Prenatal and postnatal development

Peri/postnatal development was evaluated in a study in rats treated from gestation day 6 to lactation day 20 with doses up to 1000 mg/kg/day. The NOAEL for F0 was 300 mg/kg and for F0 reproduction

1000 mg/kg. Based on increased motor activity in F1 males the NOAEL for developmental toxicity was set to 300 mg/kg. The mechanism and significance of the increased motor activity in F1 males is not clear.

In summary, with regard to the potential reproduction toxicity of maraviroc the CHMP concluded that the wording in sections 4.6 and 5.3 of the SmPC adequately reflects the available data.

- Toxicokinetic data

Toxicokinetic data is presented above in relation to the individual studies. In general, similar values were obtained for male and female animals, however there were indications that females had higher exposures at lower doses while at high doses male/female differences were minor.

- Local tolerance

Local tolerance of maraviroc was tested in four studies addressing skin sensitization/irritation, acute dermal toxicity, and eye irritation. The studies were conducted in mouse, rat and rabbit.

Maraviroc was devoid of skin irritating potential, but in the eye irritation test caused iritis and pain response. Limited distribution studies in the male pigmented rat showed distribution to eye and pigmented skin. Maraviroc does not absorb in the range of 290-700 nm indicating that photosafety is not an issue.

- Other toxicity studies

Immunotoxicity

A 4 week BID immunotoxicity study was conducted in the cynomolgus monkeys. Doses of 0, 15, 50 and 150 mg/kg (in 0.5% (w/v) methylcellulose +0.1% Tween 80) were administered twice a day to groups of 5 male and 5 female animals each.

Absolute white blood cell and lymphocytes (due to elevated T(CD3+) lymphocytes) were significantly increased at ≥100 mg/kg/day in males and absolute and relative CD4+/CD45RA+ lymphocytes counts were increased in all treated male groups and in mid-dose females. In the Keyhole Limpet Haemocyanin assay, mid and high dose males had significantly lower IgM titers. Natural Killer activity (as percent lysis) showed a trend towards increase with dose. No relevant statistically significant effects were evident and ranges were wide. High dose males had lower thymus weight while spleen weight was increased. At the dose of 300 mg/kg/day CCR5 occupancy was complete at all time points while at the dose of 30 mg/kg/day occupancy was complete at 1 hour post dose and approximately 79% at 7 and 24 hours post-dose.

Chemokine receptor CCR5 has a role in the development of a protective immune response during acute infection. The potential of maraviroc to increase susceptibility or prolong infections was not evaluated in the study. There were no indications of a higher incidence of infections in toxicology studies, but specific studies were not conducted.

Other studies

No juvenile toxicity studies have been conducted. The section 4.6 of the SPC includes information to indicate that the complete potential for reproduction toxicity has not been evaluated.

The major human metabolites (UK-408,027 and UK-463,977) were tested for antiviral activity in the membrane fusion assay. No relevant activity was evident.

A series of toxicology studies (GLP) were conducted as part of worker safety studies to investigate various compounds and intermediates in the synthesis of maraviroc. Generally the effects seen with

these intermediates were in the same category as effect with the parent compound except for that skin irritation was not evident with maraviroc.

Ecotoxicity/environmental risk assessment

An ecotoxicology/environmental risk assessment (ERA) according to the applicable guidelines was submitted. In Phase I a worst-case PEC in surface water of 3.0 µg/l was calculated using default values for Fpen, WASTEWinhab and dilution. This was higher than the action limit of 0.01 µg/l and a Phase II environmental fate and effects analysis was performed.

The phase II analysis did not indicate any environmental concerns with the use of maraviroc. However, the reports from the following studies related to the ERA will need to be provided as a follow-up measure:

- An aerobic and anaerobic transformation study (OECD 308)
- A 21-day reproduction test using Daphnia magna (OECD211)

Based on these studies as well as the data from the already conducted long-term toxicity test in fish (OECD210) a revised ERA should be submitted and the PEC/PNEC quotients for surface water and groundwater either confirmed or recalculated as appropriate.

Clinical aspects

Introduction

The main clinical programme to support the MAA consisted of:

- two identical phase III double-blind, randomized trials including 1076 *treatment experienced patients with CCR5-tropic virus*, 209 of whom received placebo (A4001027 and A4001028);
- one supportive study to evaluate the safety and antiviral activity of maraviroc in patients with *CCR4-tropic virus* (A4001029);
- two phase II dose-ranging studies for dose-selection (A4001007, A4001015).

Table 2 provides an overview of these studies. Furthermore, studies aiming to characterise the pharmacokinetic profile of maraviroc after single dose and multiple dose administration have been performed.

Table 2 Summary of Studies Providing Support for the Dose Selection and Efficacy

Study/Treatments (Randomisation)	Study Design	Location/no of sites	Main Outcome
A4001007 *Cohort 1*: Maraviroc 25 QD: 100 mg BID: Placebo. (1:1:1) *Cohort 2*: Maraviroc 50 mg BID: 300 mg BID: Placebo. (1:1:0.5)	Randomised, double-blind, placebo-controlled. Asymptomatic patients with CCR5 tropic HIV-1. Study drug as monotherapy for 10 days. Objectives: pharmacodynamics, pharmacokinetics, safety, toleration.	-	All doses of maraviroc superior to placebo (10% significance level). Doses ≥ 100 mg BID produced a similar decrease in viral load.
A4001015 Maraviroc 150 mg BID (fed/ fasted): 100 mg and 300 mg QD (fasted): Placebo (fed/ fasted). (4:4:4:4:1:1)	Design as A4001007. Objectives: effects of food and dose regimen (QD versus BID).	-	Viral load decrease was similar for 150 mg fed and fasted treatment groups and for 300 mg QD group.
A4001027 (N=601) Maraviroc[a] 300 mg QD: 300 mg BID: Placebo. (2:2:1) all in combination with OBT.	Multicentre, randomised, double-blind, placebo-controlled. Antiretroviral-experienced patients with CCR5 tropic HIV-1. Endpoints evaluated at w 24. Duration 48 w.	US 90 Canada 15 Puerto Rico 2	Maraviroc superior to placebo in both primary and secondary endpoints. No relevant difference between maraviroc QD and BID regimens.
A4001028 (N=475) Maraviroc[a] 300 mg QD: 300 mg BID: Placebo. (2:2:1)	See A4001027.	Europe (10 c) 75 Australia 11 US 46	See A4001027
A4001029 (N=186) Maraviroc[a] 300 mg QD: 300 mg BID: Placebo. (1:1:1)	See A4001027. Antiretroviral-experienced patients with non-CCR5 tropic (CCR5/CXCR4, CXCR4-using or non-phenotypable) HIV-1.	US 41 Canada 7 Europe (6 c) 21 Australia 7	Similar decrease in viral load in all groups. Increase in CD4 cell count was significantly higher for maraviroc BID compared with placebo.

The applicant did not seek scientific advice at the CHMP. The development programme did meet the requirements of the applicable EU guideline for the clinical development of medicinal products for the treatment of HIV infection.

A paediatric development programme has not been initiated.

The recommended dose is 150 mg, 300 mg or 600 mg twice daily depending on interactions with co-administered antiretroviral therapy and other medicinal products.

The initially applied indication was "CELSENTRI, in combination with other antiretroviral medicinal products, is indicated for treatment-experienced adult patients infected with CCR5-tropic HIV-1. 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)."

The approved indication is:

> "CELSENTRI, in combination with other antiretroviral medicinal products, is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable (see section 4.2).
>
> This indication is based on safety and efficacy data from two double-blind, placebo-controlled trials in treatment-experienced patients (see section 5.1)."

GCP

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

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

Pharmacokinetics

Maraviroc pharmacokinetics was studied in 28 PhaseI/IIa studies (complete profiles) and 3 Phase IIb/III studies (with sparse sampling). The evaluation was performed after single dose intravenous administration (1-30 mg) as well as oral single dose (1-1200 mg) and multiple dose administration (3-900 mg BID and 1200 mg QD).

The following formulations were used during development: Powder for oral solution in phase I, 5 mg/25 mg/50 mg/100 mg/150 mg tablets in Phase I and IIa, and 150 mg in Phase IIb/III. An IV formulation was used to determine absolute bioavailability. The commercial formulations (150 mg, 300 mg) have not been used in the clinical trials.

The analytical methods used to analyze maraviroc have been adequately validated.

- Absorption

The absorption of maraviroc is highly variable with multiple peaks. The mean Tmax was between 2 and 3 hours with individual values ranging from 0.5 to 8 hours (with food). The absolute bioavailability for maraviroc was 23% at 100 mg and has a predicted bioavailability of 31 % at 300 mg. The absorption of maraviroc is dose dependent, likely attributed to saturated efflux transporters in the intestine. Maraviroc is highly soluble in aqueous media across pH 1-7.5, has an efflux ratio >10 in Caco-2 cell monolayers and is a substrate for P-gp and the Multidrug Resistance Protein (MRP).

Bioequivalence

The research tablet formulation (150 mg) as well as the commercial tablet formulations are completely dissolved within 30 minutes (>90% within 15 minutes) and hence dissolution will not be rate limiting for the absorption of maraviroc. Bioequivalence was shown between the commercial 300 mg tablet and research formulation (2 x 150 mg). The solution had a 12% higher bioavailability than the research tablet.

A bioequivalence study as well as a food effect study with the commercial formulation (300 mg) has been conducted. The results of the bioequivalence study are summarised in Table 3.

Table 3 Results of the Bioequivalence study of the commercial and the research formulations

Parameter (units)	Mean Pharmacokinetic Values (range)		Ratio or Difference (90% CI)[a]
	Maraviroc 300 mg (1 x 300 mg Commercial Tablet) N=43[b]	Maraviroc 300 mg (2 x 150 mg Research Tablet) N=42	
AUCinf (ng.h/ml)[c]	2720 (1470-4740)	2762 (1480-4510)	98.0% (93.9%, 102%)
AUClast (ng.h/ml)[c]	2699 (1460-4650)	2729 (1470-4470)	98.4% (94.3%, 103%)
Cmax (ng/ml)[c]	638 (343-1330)	654 (246-1220)	96.1% (88.1%, 105%)
Tmax (h)[d]	2.47 (0.50-4.00)	2.45 (0.50-4.00)	0.04 (-0.33, 0.40)
t½ (h)[d]	10.4 (8.51-14.7)	10.5 (8.45-13.7)	n/c

[a] The ratios are expressed as percentages for AUCinf, AUClast and Cmax and difference for Tmax
[b] N=42 for AUCinf and t½
[c] Geometric means
[d] arithmetic means
CI=confidence interval, n/c=not calculated.

Since bioequivalence has been demonstrated between 2 x 150 mg research tablets and 1 x 300 mg commercial tablet, the applicant considered it not necessary to investigate bioequivalence of 1 x 150 mg commercial tablet to 1 x 150 mg research tablet on the basis that 150 mg and 300 mg commercial tablets are manufactured from the same blend, and have identical compositions. Furthermore, the 150 mg research tablet and 150 mg commercial tablets are identical in terms of their in vitro dissolution performance. The CHMP concurred that it is not necessary to perform a bioequivalence study with the 150 mg tablet considering the small difference in tablet formulation, the high solubility and rapid dissolution.

Influence of food

The influence of food was studied in four different studies in healthy subjects; A4001001 (solution), A4001003, A4001004 (research formulation) and A4001043 (commercial formulation). Although not formally tested, food effect was also studied in HIV infected subjects in Study A4001015 (research formulation).

AUC and Cmax were reduced by 33% when 300 mg commercial tablet formulation was administered with a high fat, high calorie breakfast. Tmax was prolonged for some subjects but over all the time profiles were not significantly altered. The food effect on the research tablet was dependent on dose and the model predicted food effect was 30% reduced bioavailability for a 300 mg dose and 25% for a 600 mg dose. In HIV-1 infected subjects receiving 150 mg research tablet, AUC was reduced by 50%.

The food effect on the 150 mg commercial tablet is predicted to be 47% in the absence of CYP3A4 inhibitors and would be reduced to 36% in the presence of saquinavir/rtv. The mechanism behind the food effect is likely a combination of more efficient efflux due to slower absorption (less saturation) and to some extent complex formation. The food-effect will not be relevant for maraviroc when co-administered with CYP3A4 inhibitors with large effects on maraviroc e.g. lopinavir/rtv, saquinavir and atazanavir (which in the clinical studies resulted in substantially increased exposure relative to 300 mg BID in the monotherapy study, A4001007). The Phase III data suggests that when taken BID without food restrictions (likely taken as recommended for their other drugs in the OBT) the exposure was not substantially lower than in subjects who had taken maraviroc in a fasted state (monotherapy study), thus supports that maraviroc can be administered with or without food.

- Distribution

Maraviroc binds to both albumin and α_1-acid glycoprotein. The plasma protein binding is between 73 and 78 % and blood plasma ratio around 0.59 suggesting limited distribution into blood cells. Volume of distribution determined after intravenous administration was 194 l.

- Elimination

Maraviroc is mainly eliminated by metabolism. In vitro, CYP3A4 is the main enzyme responsible for maraviroc metabolism (with possible small, but likely not relevant, contribution of CYP2D6, CYP3A5 and CYP2B6). After intravenous administration of 30 mg maraviroc (approximately corresponding to exposure after oral administration of 100 mg) total clearance was 44 l/h and renal clearance 10.2 l/h, thus 23% was excreted unchanged. The terminal half-life was 13 hours after intravenous dose and around 16 hours after multiple oral doses of 300 mg.

The mass balance study (300 mg oral ^{14}C- maraviroc) was performed with maraviroc alone. Simulations were performed to predict the size of the remaining elimination pathways when administered with CYP3A4/P-gp inhibitors with different potency. In the presence of metabolic inhibitors, renal clearance may account for up to 70% of total clearance of maraviroc.

Excretion

In the mass balance study 19.6% of total radioactivity was recovered in urine and 76.4% in faeces. Of the excreted quantities, unchanged maraviroc constituted on average 25% in faeces and 8% in urine.

One unlabelled metabolite, UK-463,977, was present in urine equivalent to 3% of the dose. No information about the concentration –time profiles of the metabolites is available as plasma samples (0-18) hours were pooled before characterisation of metabolites.

Metabolism

The metabolism of maraviroc was evaluated in three healthy male subjects after administration of 300mg ^{14}C maraviroc as an oral solution in a fasted state. Whole blood samples and plasma samples were collected on Days 1 to 6 at specified times up to 120 hours post-dose to measure plasma maraviroc and UK-463,977 concentrations, to measure radioactivity and for metabolite profiling, respectively. Urine and faeces were collected to measure urinary and faecal radioactivity and for metabolite profiling up to at least 120 hours post-dose on Day 1. UK-463,977 concentrations were also determined in urine.

Unchanged maraviroc was the main circulating component in plasma (42% of plasma radioactivity) and the metabolites UK-408,027 (22%), an amine analogue (11%) and UK-463,977 were also identified in plasma. The metabolites UK-408,027 or UK463,977 appear not to accumulate with time.

- Dose proportionality and time dependencies

Non-proportional increase in exposure with increased dose was observed after oral administration. Urine pharmacokinetic results showed that the mean percentage of maraviroc dose excreted unchanged in the urine increased from 1.5% following 1 mg to 12% following 1200 mg; renal clearance did not change notably with dose. The applicant has suggested that the non-linearity is related to increased bioavailability as a result of saturation of intestinal efflux proteins. Disproportional increases in exposure after higher single doses are larger than predicted from increased absorption only but the variability was large and renal clearance did not seem to be altered with higher doses. The CHMP considered the proposed mechanism for nonlinearity at lower doses seems reasonable.

After intravenous administration the kinetics was reasonably linear but the exposure after the highest intravenous dose was much lower than the highest studied oral doses and even if no firm conclusion regarding non-linearity in non-renal elimination can be drawn, multiple dose data at higher doses suggest that nonlinearity at higher doses is limited.

No obvious time dependency was observed.

- Target population

No major differences between healthy subjects and HIV-1 infected have been observed.

Population Pharmacokinetics

An extensive modelling program was undertaken. Intravenous data was modelled separately. A 4-compartment model best described the data. Dose, formulation and food effect was initially estimated using AUC and Cmax data obtained from non-compartmental data analysis of orally administered maraviroc as dependent variables. Later a partition model (separating hepatic extraction from absorption bioavailability) was developed using Phase I/IIa data of maraviroc after oral administration with no concomitant drugs allowed. Renal clearance as well as hepatic blood flow was fixed in this model. Interoccasion variability has not been taken into account. No conventional population analysis (e.g. covariate evaluation on a population level) was performed on the Phase IIb/III data. Instead the Phase I/IIa model with minor modifications was applied to Phase I interaction data as well as Phase IIb/III data to obtain empirical Bayes estimates of the pharmacokinetic parameters by fixing all typical values and their variance to the Phase I/IIa typical values except the residual error, hepatic extraction ratio and the parameter describing at which dose the fraction absorbed is 50% which were considered to be potentially affected by interacting agents. The empirical Bayes estimates were then used for evaluation of interaction effects of Phase I interaction data as well as Phase IIb/III data. The empirical Bayes estimates for the Phase IIb/III data were also used to predict Cmin, Cave and equivalent constant concentration, ECC (defined as a constant concentration that gives the same average PD effect as an actual time varying concentration) for the pharmacokinetic-pharmacodynamic evaluation of failure versus non-failure in the same population. Due to presence of shrinkage, data evaluation based on the empirical Bayes estimates should be viewed with some caution.

- Variability

The coefficient of variation for Cmax and AUC was 20-40% based on noncompartmental analysis of phase 1 data. In the population models interindividual variability in hepatic extraction ratios varied between 8% in the Phase 1/2a data to 87% in the Phase 2b/3 data. The latter figure reflects the effects of different OBT, which was not included in the model. Interindividual variability in central and peripheral volumes of distribution was estimated to be 12 and 28% respectively.

- Special populations

Influence of race, sex, weight and age

The influence of race, sex, weight and age was evaluated in the Phase I/IIa population analysis. Asian (23% of total population studied) as compared to non-Asian were estimated to have a 26% higher AUC. As renal clearance was fixed to 12 l/h in this analysis, no covariate effects was tested for that parameter. No significant effect of sex was found (96 women, 23% of the total population studied, was included). No statistically significant effect of weight (range 46-109 kg) was found. Age was found to be statistically significant for intercompartmental clearance (will not affect prediction of total exposure or average concentration) but the studied range was very limited (18-54 years).

In the final population report from the Phase IIb/III studies included subjects between 16 and 75 years of age an attempt to evaluate the relation between age and clearance was made after including effects of OBT on absorption and elimination. There was no statistically significant effect of age, but the data included very few subjects above 65. Thus no conclusion regarding patients above 65 years of age can be drawn from this study.

A specific study was conducted comparing Asian (N=12) and Caucasian (N=12) subjects. A lower renal clearance was observed for Asian subjects but AUC over 24 hours was slightly less although with larger variability.

Hepatic impairment

A study in subjects with mild and moderate hepatic impairment (Child-Pugh A and B) as well as subjects with normal hepatic function has been conducted. Administration of maraviroc (300 mg single dose) to subjects with mild and moderate hepatic impairment resulted in mean values of AUC_{last} which were 25% and 45% higher, respectively than in subjects with normal hepatic function [geometric means and corresponding 90% CIs for the comparisons were 125% (84.7%, 185%) and 145% (100%, 212%)]. Smaller differences in Cmax were noted with mean values 11% and 32% higher for mild and moderate impairment compared to normal function, respectively. As expected mean CL/F decreased with increasing hepatic impairment, although the differences between mild hepatic impairment and normal hepatic function were minimal. Mean CL_R was higher in subjects with moderate hepatic impairment compared to subjects with normal hepatic function. The mechanism for this increase in CL_R is not known. Mean Tmax and t1/2 did not appear to be affected by hepatic impairment.

The data is limited with wide confidence intervals for the comparisons to normal subjects. Also considering the higher CL_R, the effect of hepatic impairment may have been underestimated due to the limited number of subjects with reduced metabolic capacity; this is reflected in the SmPC in sections 4.2, 4.4 and 5.2.

Renal impairment

Studies in subjects with renal impairment have not been performed. In patients without concomitant administration of CYP3A4 inhibitors, renal excretion constitutes a minor elimination pathway (about 23% of total clearance). In these patients decreased renal function will likely have a limited effect on maraviroc exposure. In patients with concomitant administration of CYP3A4 inhibitors, e.g. protease inhibitors, renal clearance will constitute up to approximately 70% of total clearance.

The applicant has proposed prolonged dose intervals for patients with mild, moderate and severe renal impairment which is considered acceptable but due to the variable effects of inhibitors the impact of renal impairment may be exaggerated thus clinical response to treatment should be closely monitored. A respective statement is included in SmPC sections 4.2, 4.4 and 5.2.

- Pharmacokinetic interaction studies

Effect of other substances on maraviroc

Maraviroc is a P-gp substrate and mainly metabolised by CYP3A4, thus, the interaction potential when co-administered with other antiretroviral agents is large. A number of interaction studies with substrates affecting CYP3A4, P-gp as well as renal secretion were performed in healthy subjects. A summary of the observed effects of other substances on maraviroc is presented in Table 4.

The applicant proposed the following dose adjustments:

- 150 mg BID when co-administered with CYP3A4 inhibitors including protease inhibitors (except tipranavir/ritonavir) and ketoconazole, itraconazole, clarithromycin, telithromycin;
- 600 mg BID when co-administered with CYP3A4 inducers (without a CYP3A4 inhibitor) including efavirenz and rifampicin;
- 300 mg BID for other concomitant medications, including all other antiretrovirals and tipranavir/ritonavir.

Dose reductions have been applied in the Phase IIb/III studies and the interaction results were evaluated by obtaining empirical Bayes estimates based on sparse sampled plasma concentration data and the Phase I/IIa population pharmacokinetic model. The applicant claimed that the main limiting toxicity (postural hypotension) has been associated with Cmax. By visual inspection of observed data the attempt to achieve similar Cmax succeeded with the suggested dose adjustment for CYP3A4 inhibitors (150 mg BID). However, as expected from the Phase I interaction studies, where between 2.6 and 9.8-fold increases in AUC was observed, the AUC was not completely corrected by reducing

the dose by half. Long-term safety data is currently lacking. If long-term toxicity may be related to total exposure the strategy for co-administration with CYP3A4 inhibitors may need to be re-evaluated.

Table 4 Summary of the effect of other compounds on maraviroc

Co-administered substance (dose)	N	Maraviroc Dose	Ratio (90% CI) of maraviroc pharmacokinetic parameters with/without co-administered substance (no effect = 1.00)	
			AUC_{tau}	Cmax
CYP3A4 and/or P-gp Inhibitors				
Ketoconazole 400 mg QD	12	100 mg BID	5.00 (3.98, 6.29)	3.38 (2.38, 4.78)
Saquinavir (soft-gelatine capsules) 1200 mg TID	12	100 mg BID	4.25 (3.47, 5.19)	3.32 (2.45, 4.49)
Ritonavir 100 mg BID	8	100 mg BID	2.61 (1.92, 3.56)	1.28 (0.79, 2.09)
Saquinavir (soft-gelatine capsules)/r 1000 mg/100 mg BID	8	100 mg BID	8.32 (6.11, 11.3)	4.23 (2.60, 6.88)
Saquinavir (soft-gelatine capsules)/r 1000 mg/100 mg BID	11	100 mg BID	9.77 (7.87, 12.14)	4.78 (3.41, 6.71)
Lopinavir/r 400 mg/100 mg BID	8	100 mg BID	3.83 (2.81, 5.21)	1.61 (0.99, 2.63)
Lopinavir/r 400 mg/100 mg BID	11	300 mg BID	3.95 (3.43, 4.56)	1.97 (1.66, 2.34)
Atazanavir 400 mg QD	12	300 mg BID	3.57 (3.30, 3.87)	2.09 (1.72, 2.55)
Atazanavir/r 300 mg/100 mg QD	12	300 mg BID	4.88 (4.40, 5.41)	2.67 (2.32, 3.08)
Darunavir/r 600 mg/100 mg BID	15	150 mg BID	4.05 (2.94, 5.59)	2.29 (1.46, 3.59)
CYP3A4 and/or P-gp Inducers				
Efavirenz 600 mg QD	12	100 mg BID	0.552 (0.492, 0.620)	0.486 (0.377, 0.626)
Rifampicin 600 mg QD	12	100 mg BID	0.368 (0.328, 0.413)	0.335 (0.260, 0.431)
CYP3A4 and/or P-gp Inhibitors and Inducers				
Lopinavir/r + efavirenz 400 mg/100 mg BID + 600 mg QD	11	300 mg BID	2.53 (2.24, 2.87)	1.25 (1.01, 1.55)
Saquinavir (soft-gelatine capsules)/r + efavirenz 1000 mg/100 mg BID + 600mg QD	11	100 mg BID	5.00 (4.26, 5.87)	2.26 (1.64, 3.11)
Tipranavir/r 500 mg/200 mg BID	12	150 mg BID	1.02 (0.850, 1.23)	0.86 (0.61, 1.21)
Renal Substrates and/or Inhibitors				
Sulfamehoxazole/Trimethoprim 800 mg/160 mg BID	15	300 mg BID	1.1 (1.04,1.37)	1.19 (1.01, 1.21)
Tenofovir 300 mg BID	12	300 mg BID	1.03 (0.980, 1.09)	1.04 (0.901, 1.19)

In general, the maraviroc dose should be decreased to 150 mg twice daily when co-administered with a PI; except in combination with tipranavir/ritonavir or fosamprenavir/ritonavir where the dose should be 300 mg BID. No dose adjustments are suggested for moderate CYP3A4 inhibitors.

The suggested doubling of the dose with CYP3A4 inducers has not been evaluated at the recommended dose of maraviroc. The applicant claims based on simulations that a dose increment from 100 to 200 mg is directly transferable to 300 to 600mg; however the CHMP considered that it is necessary to include clarifying statements in the SmPC.

Rifampicin is mainly used together with efavirenz (as rifampicin is contraindicated for most boosted PIs) but as it is not known how large the effect of two inducers would be no dose recommendation could be given.

When combinations of inhibitors and inducers are used the suggested dose adjustment is half the dose based on results from combinations of lopinavir/ritonavir or saquinavir/ritonavir with efavirenz (the PIs with large effect on maraviroc pharmacokinetics). Based on the effects on maraviroc in the Phase I interaction studies, the same recommendations could be given for atazanavir and darunavir/ritonavir which had effects similar to lopinavir/ritonavir when administered without efavirenz.

Rifabutin is considered to be a less potent inducer than rifampicin and is likely to have similar or less inducing effect as efavirenz. Therefore the same dose recommendations as for Efavirenz + protease inhibitors could be given.

Recommendations for nevirapine is based on comparison with historical data which suggested that the effects of nevirapine on maraviroc is limited therefore no dose adjustment is suggested.

No significant effects of trimethoprim/sulphamethoxazole or tenofovir were observed. The applicant will further investigate as follow-up measure which transporters are involved in the active renal secretion of maraviroc.

Based on these considerations, the available information relevant for the use of maraviroc in CART is included in SmPC section 4.5.

Since extrapolations are difficult to make and it may be difficult to perform interaction studies with all possible combinations used in the treatment experienced patients, it has been explored with the applicant whether Therapeutic Drug Monitoring (TDM) could be used. However, this was not considered feasible as an alternative option due to the difficulties in defining a target concentration of maraviroc suitable for all situations. Furthermore, TDM is not available in all regions.

The CHMP asked the SAG HIV/Viral Diseases to discuss which drug interaction studies are considered necessary in order to provide adequate data to assist CART in medical practice.

The SAG concluded that interaction data from a study investigating the combination of efavirenz and rifampicin would be needed from a clinical perspective as this combination may be used in some regions (EU and ex-EU) where appropriate alternatives are not available. Furthermore, antifungals other than ketoconazole should be investigated, in particular voriconazole and posaconazole if the target population requires adequate dose recommendation for these antifungals. The experts appreciated that the applicant did already initiate interaction studies with darunavir and etravirine (alone and in combination) as well as raltegravir, and was committed to investigate future compounds as appropriate. Studies with boosted PI (preferably PIs with different degree of effect on maraviroc) + rifabutin (adjusted dose) as well as macrolide antibiotics were not considered necessary.

Despite the recommendations from the SAG, the CHMP concluded that further suggested interaction studies (e.g maraviroc in combination with rifampicin+efavirenz as well as in combination with voriconazole/posiconazole) were not required for the sought indication. Considering that a CCR5-antagonist could potentially have a negative impact on treatment outcomes for certain infections like active tuberculosis and invasive fungal infections, due to the possible immunosuppressive effect of CCR5-antagonists, the use in clinical practise is unlikely. A precautionary statement has been included in section 4.4 of the SmPC.

Effect of maraviroc on other substances

The *in vitro* studies do not give an indication of any relevant inhibition of maraviroc on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 that would require further *in vivo* studies. Maraviroc is a substrate for P-gp but it is unknown whether it inhibits P-gp, which will be

further investigated by the applicant as a follow-up measure. No indication of induction of CYP3A4 by maraviroc has been observed in vivo; therefore the ability of maraviroc to induce CYP450 enzymes is regarded to be limited.

No significant effect of maraviroc on the exposure of lamivudine and stavudine was observed.

Although not evaluated at the recommended dose, but taken together with the observation of no effect on the cortisol/β-hydroxy cortisol ratio, it can be concluded that maraviroc is not likely to have an effect on ethinylestradiol or levonorgestrel exposure.

Very limited effects on oral midazolam pharmacokinetics (18% increased AUC) was observed. It may be concluded that the effect of maraviroc on other CYP3A4 substrates is likely to be limited.

At high exposure level (600mg dose) of maraviroc there was a shift in metabolic ratio for debrisoquine, indicating a possible inhibition of CYP2D6 but the inhibition is not likely to be clinically relevant.

- Pharmacokinetics using human biomaterials

<u>*In vitro* metabolism</u>

In vitro metabolism has been studied in human hepatocytes, microsomes and recombinant enzyme systems. The conclusions from these studies are that CYP3A4 is mainly responsible for the metabolism of maraviroc. One study suggested a small contribution of CYP2B6 but which was 170-fold less than CYP3A4. In another study some metabolism by CYP3A5 (half-life of 99 min as compared to 4.2 min in the CYP3A4 incubation) was observed. In one study maraviroc was easily detectable in all samples but metabolites were only detected in incubation with recombinant CYP3A4 and CYP2D6 samples. The metabolites were approximately 5 fold higher in the CYP3A4 samples indicating a larger turnover rate.

To further investigate the elimination pathway which gave rise to the unlabelled metabolic in the mass balance study (see above) the applicant performed HPLC profiling after incubation of dual-labelled [^{14}C]-maraviroc with pooled human microsomes which showed that the secondary amine (UK-408,027) and a primary alcohol (UK-453,465) represented the two halves of the molecule following N-dealkylation of the parent compound adjacent to the tropane ring. The two metabolites were also identified in the hepatocyte extract. In addition a carboxylic acid metabolite (UK-463,977) was identified resulting from N-dealkylation. The applicant concludes that the presence of cytosolic enzymes promotes the formation of the carboxylic acid and suggests that it should be the major component resulting from this pathway.

Pharmacodynamics

The pharmacodynamics of maraviroc in patients with CCR5-tropic virus (R5-virus) was evaluated in two phase II dose ranging studies and two identical phase III studies. In a supportive study, the viral activity was studied in patients with non-CCR5-tropic virus. For details of these studies see Table 3.

Non-clinical studies related to pharmacodynamics are presented in section 3.3.

- Mechanism of action

Maraviroc is a small molecule CCR5-antagonist, which acts by binding to the transmembrane region of the CCR5 receptor. It is hypothesized, that this binding stabilizes a receptor conformation that is not recognized by the CCR5-tropic HIV. Hereby the virus cannot bind to the co-receptor, and HIV-entry is blocked. Hence, the mode of action is non-competitive allosteric inhibition of HIV co-receptor binding. CCR5-antagonists have no effect on CXCR4-tropic virus.

- Primary and secondary pharmacology

Antiviral activity

In vitro: The *in vitro* IC50 for maraviroc against HIV-1 group M/O was 0.1-8.9 nM (0.05-4.56 ng/mL) in isolated human peripheral blood lymphocyte (PBL) HIV replication assay systems. The geometric mean IC90 was 2.0 nM, correlating to unbound IC90 of 1.0 nM (0.5 ng/mL). This correlated to an in vitro Inhibitory Quotient (IQ) of around 60 for the 300 mg dosage (IQ = Cmin/serum adjusted IC50 value).

The detailed data based on HIV-1 CCR5-tropic primary clinical isolates tested in human peripheral blood lymphocytes (PBL) is summarised in Tables 5 and 6.

Table 5 In vitro antiviral activity obtained in human peripheral blood lymphocytes

Parameter	**Antiviral Activity (ng/mL)**	
	Overall HIV-1 CCR5-tropic primary clinical isolates, n=43 (range)	
EC_{50}	0.26 (0.02 – 3.55)	
EC_{90}	1.04 (0.11 – 19.6)	
Serum adjusted EC_{90}	0.57 (0.06 – 10.7)	
	HIV-1 CCR5-tropic primary clinical isolates	
	HIV-1 group M, n=39 (range)	**HIV-1 group O, n=4 (range)**
EC_{50}	0.27 (0.05 – 3.55)	0.37 (0.21 - 4.62)
EC_{90}	1.08 (0.11 – 19.6)	0.92 (0.46 - 9.42)
Serum adjusted EC_{90}	0.59 (0.06 – 10.8)	0.50 (0.25 - 5.12)

Table 6 In vitro antiviral activity (EC_{90}, ng/mL) for CCR5-tropic HIV-1 group M subtypes obtained in relevant cell types

Subtype tested	Viral Isolate		
	Primary clinical isolates[1] (range; n)	Laboratory adapted strains[2] (range; n)	Recombinant clinical isolates[3] (range; n)
A	0.56 (0.14 - 2.81; **4**)	-	2.06 (1.54-2.78; 2)
AE	0.26 (0.21 - 0.33; 1[4])	-	2.67
AG	-	-	5.04 (1.80- 13.67; 5)
AGJ	-	-	11.51
B	0.94 (0.21 – 12.3; 21)	2.85 (1.26 – 20.4; 1)	7.29 (1.29-48.83; 160)
C	1.54 (0.17 – 7.45; **4**)	-	5.29 (1.0- 95.5; 20)
D	1.36 (0.70 – 3.77; **4**)	-	8.02 (5.76- 11.21; 2)
F	1.52 (1.38 – 1.66; **1**)	-	15.16 (11.87- 19.33; 2)
G	2.28 (0.52 – 19.6; **2**)	-	8.53
J	1.24 (0.11 – 9.20; **2**)	-	16.55

[1]Tested in peripheral blood lymphocytes.
[2]The CCR5-tropic laboratory adapted strain Ba-L was tested in PM-1 cells (n=16), PBL (n=21) and monocyte derived macrophages (n=4).
[3]The CCR5-tropic recombinant clinical isolates were tested in the Phenosense™ HIV entry assay and included isolates from treatment-naïve (n=100) and treatment-experienced (n=100) patients.
[4]Subtype CRF01_AE.93TH073, previously known as subtype E. n = number of different isolates tested. The subtype B CXCR4-tropic laboratory adapted strain IIIB was tested in PM-1 cells and was not inhibited by maraviroc. CXCR4-tropic primary clinical isolates (subtypes B, D & F, n=4) and dual-tropic primary clinical isolates (subtype B, n=2) tested in PBL were not inhibited by maraviroc.

In vivo: During 10 days of maraviroc monotherapy HIV-RNA decreased 1.6 $\log_{10}$ copies/mL.

Resistance

Resistance to maraviroc can occur in two main ways – with X4-virus or R5-virus. Failure with X4-virus can theoretically be due to X4-virus already present but not previously detected, or by mutagenesis of R5- to X4-virus. Failure with R5-virus can be due to "traditional resistance", with a mutated virus with a reduced sensitivity to the compound – or due to a suboptimal substance exposure/other unknown reasons.

In vitro resistance

Phenotypic resistance: In selection experiments, using both lab strains and clinical isolates, a reduced sensitivity was observed for some strains/isolates after 4 months (16 passages) or longer. All strains, with or without reduced sensitivity, remained R5-positive - no X4-virus was found. Traditional phenotypic fold-change was not a suitable marker for reduced sensitivity; the dose-response curves in samples with reduced sensitivity did not shift to the right with increased concentration, but rather showed a "plateau in maximal percent inhibition". The rank-order of this plateau of maximal percentage inhibition (MPI) was the same regardless of assay used.

Genotypic resistance: In clonal analyses of isolates with reduced sensitivity to maraviroc (after selection experiments) mutations were found to have accumulated in the gp120 genome. The mutations were not found at the same positions in different strains.

Cross-resistance: the maraviroc-resistant clinical isolates were fully sensitive to other CCR5-antagonists (aplaviroc, vicriviroc) as well as enfuvurtide and other antiretrovirals in vitro.

In summary, it was possible to induce reduced sensitivity to maraviroc in clinical isolates (still CCR5-tropic) during long time serial passage in vitro. It is hypothesized that maraviroc resistant CCR5-tropic virus are still able to recognise the CCR5-receptor conformations despite the presence of maraviroc (which is present in the transmembrane region), and can therefore not be inhibited even at high substance levels. No shift to CXCR4-tropic virus was seen in vitro.

In vivo resistance

Due to the (adequate) blinded fashion of the analyses, and the complexity of the resistance assessment, the analyses of resistance in vivo are based on a low number of patients.

- For patients with CCR5-tropic virus at failure (no CXCR4-tropic virus present at rebound), drug susceptibility was assessed and sequencing of the envelope genome was performed (looking for mutations correlating to resistance).
- For patients with CXCR4-tropic virus at rebound baseline samples were re-assessed for CXCR4-tropic virus. This was followed by phylogenetic analyses performed to compare the sequences of the virus found at failure and that found at baseline (X4 if actually present at baseline, otherwise the R5-virus).

1. Maraviroc treated patients failing with CXCR4-virus present *(55% of patients with maraviroc treatment failure in the main studies)*

   In 10 out of 16 patients studied phylogenetically similar CXCR4-tropic virus was shown to be present at baseline (previously not detected), when reassessing the samples with a higher sensitivity. In remaining 6 patients (baseline CXCR4-tropic virus still not found) the CXCR4-tropic virus at failure was shown to be phylogenetically distant from the baseline CCR5-tropic virus, such that emergence of pre-treatment archived CXCR4-tropic virus was the most likely explanation. Hence, in line with the findings in vitro, patients failing with CXCR4-tropic virus during maraviroc treatment seem to rebound with CXCR4-tropic virus already present in minor populations prior to starting maraviroc therapy, rather than with R5-virus that mutated to X4-virus.

2. Maraviroc treated patients failing with CCR5-tropic virus only *(30% of patients with maraviroc treatment failure in the main studies)*

   Phenotypic analysis: In patients with exclusively CCR5-tropic virus at time of treatment failure with maraviroc, 15 out of 36 patients studied had a virus with reduced sensitivity to maraviroc (MPI < 95%). The IC_{50} values for the same 15 samples varied from unchanged to above maximum. In the remaining 21 patients, there was no evidence of virus with reduced sensitivity as identified on a representative group of patients. The latter appears to be related to poor compliance.

   A clinically validated cut-off value for reduced virological response has not yet been established. Therefore, continued use of maraviroc after treatment failure can not be generally recommended regardless of the viral tropism seen.

   Baseline samples and samples from the 25 patients failing with placebo were all sensitive to maraviroc.

Genotypic analyses: Patients with CCR5-tropic virus at failure and a reduced MPI (<95%), all had amino acid changes in the gp120 genome compared to baseline. However, the mutations were in different positions for each patient.

Cross-resistance: The viruses from patients failing with maraviroc remained sensitive to enfuvirtide, unless enfuvirtide was a part of the failing regimen.

In summary, some patients failing with CCR5-tropic virus (no CXCR4-tropic virus present at failure) show reduced sensitivity to maraviroc, while others fail with R5-strains still fully sensitive in vitro. Maximal percentage inhibition, rather than traditional phenotypic fold change, seems to correlate to drug susceptibility. Due to the hypervariablility of the gp120 genome it will be difficult, if at all possible, to find a genotypic correlate of resistance. The present analyses are based on low numbers, and the applicant needs to continue the analyses of CCR5-tropic failure.

The further analyses of the resistance pattern using evolving clinical data is one of the follow-up measures to be addressed by the applicant.

Testing of viral tropism

The assessment of viral tropism was carried out using an in vitro phenotypic assay (Trofile™ HIV Entry Tropism assay).

In mixing experiments, a 10% mix of X4-virus could be detected with 100% sensitivity, while the presence of a 5% mix with 83% sensitivity. The assay has a lower limit of sensitivity for reliable amplification of 1000 copies of HIV-1 RNA/mL.

The following was of special interest for the CHMP:

- The majority of patients failing with maraviroc in the clinical trials had X4-virus at rebound, despite having been negative for X4 at baseline.
- In the main studies 8% of patients negative for X4-virus at screening were found to be X4-positive at baseline (around 6 weeks later). Hence, the sensitivity of the assay in the individual case and the unpredictable course of viral tropism are remaining obstacles.
- Switching therapy (despite full viral suppression) due to side effects etc, is common in clinical practise. For other antiretroviral compounds this can be done by analysis of treatment history and prior resistance tests. In the case of maraviroc this might not be the case; the viral tropism cannot be predicted without the test (minimum viral load of 500-1000 copies/mL), and testing prior (frozen) specimens has not been explored.

Switching therapy with maraviroc was also addressed by the SAG HIV/Viral Diseases on request of the CHMP. The experts were asked for their recommendation with regard to switching a compound to maraviroc in virologically suppressed patients, whether they would consider it appropriate to recommend a short period treatment interruption (i.e. for about 10 days) to enable viral load to increase enough for viral tropism to be tested, and how they would consider their recommendation to be adequately addressed in the SmPC.

The SAG concluded that in general switching of virologically suppressed patients to maraviroc is not recommended since tropism cannot be determined. Treatment interruption strategies to detect viral tropism in virologically suppressed patients was considered not appropriate due to the risk of clinical events, possible emergence of resistance and future treatment options. The SmPC should include wording regarding this issue stating that switching from a medicinal product of a different antiretroviral class to CELSENTRI in virologically suppressed patients is not recommended as viral tropism cannot be determined in fully suppressed patients. It was nevertheless supported that this topic is going to be investigated further by the applicant in future clinical trials.

The CHMP was concerned about the availability of the tropism assay for the use of the medicinal product. The applicant did commit to ensure that adequate logistical arrangements are set up in all EU/EEA Member States to provide physicians with necessary access to the assay.

Furthermore, the applicant will be exploring possible alternative assays as a follow-up measure.

Pharmacodynamic interactions with other antiretroviral compounds

There was no evidence of antagonistic interactions with the 22 licensed and developmental compounds tested. The effects were additive for all compounds tested.

Pharmacogenomic interactions

The primary endpoint (HIV-RNA change from baseline) by CCR5 Δ32-carriage was analysed. Around 7% of patients were heterozygous for the deletion. The efficacy by week 24 was not significantly affected by this genotype.

Secondary pharmacology

The (host cell) CCR5- receptor belongs to a family of chemochine-binding receptors, CCR5 being the receptor for MIP-1-alpha/beta, RANTES and several other chemochines. These chemochines are involved in the inflammatory response at several levels. These chemochines are involved in the inflammatory response at several levels including priming of innate/adaptive immune response, chemotaxis and cell migration. In the presence of maraviroc, CCR5-mediated chemochine activity is blocked, as measured by intracellular calcium release in vitro. Whether a block of this receptor is a potential safety concern is currently unknown and will need to be addressed by pharmacovigilance measures.

Pharmacokinetic-Pharmacodynamic relationship

No conventional population PKPD modelling has been performed on the Phase IIb/III data. The effect of maraviroc and other prognostic factors on failure/non-failure by univariate and stepwise search using logistic regression and generalized additive models has been evaluated. Exposure was more informative than dose group but no distinction between the concentration parameters Cave, Cmin and ECC was observed due to high correlation between the estimates. The univariate analysis suggested that the probability of failure (>50 copies/ml) is constant above an average concentration of maraviroc of approximately 150-200 ng/ml and that the probability of failure increases dramatically below an average concentration of approximately 100 ng/ml, which would imply that dose adjustments resulting in lower exposure should not be done without proper supporting data.

A semi-mechanistic model based on receptor binding theory was developed which could explain the difference in concentration where 50% of the receptors are occupied (0.089 ng/ml) and concentration where 50% of the infection rate is inhibited (7.65 ng/ml, obtained from modelling and simulation). The virus can be regarded as a CCR5 agonist (as well as the response) and depending on the system efficiency only a small amount of free receptors is needed to keep the viral load intact which means that antagonists like maraviroc need to occupy a large extent (possibly >80%) of the receptors before an effect on viral load is seen.

The developed plasma concentration - QTc model suggests that an increase in maraviroc concentration of 1000 ng/ml is expected to increase QTc interval duration with 0.97 msec within the studied concentration range (up to 2360 ng/ml).

The estimated relations between maraviroc plasma concentration and standing systolic or diastolic blood pressure suggest a decrease of 3.87 mmHg (systolic) or 1.79 mmHg (diastolic) per 1000 ng/ml within the studied range of concentrations (0-2000 ng/ml)

Clinical efficacy

- Dose response studies

Two dose response studies were performed in patients infected with CCR5 tropic HIV-1 who were either treatment-naïve or had been off antiretroviral treatment for a minimum of 8 weeks prior to study start were included (A4001007 and A4001015). The studies were randomised, double-blind, and placebo-controlled; both studies were of a similar design regarding drug administration and duration. Dose response was studied during 10-days monotherapy (n=84), at doses ranging from 25 mg QD to 300 mg BID.

The study objectives were to investigate:

- Short term viral efficacy (monotherapy);
- PK/PD relationship with regard to: plasma drug concentration, CCR5 saturation, in vitro IC50/90;
- Efficacy seen with QD vs BID dosing;
- Effect of food.

Viral tropism was determined by an in vitro phenotypic assay (Trofile™ HIV Entry Tropism assay). Patients received double-blind study drug daily at the study visit for 10 days with follow up visits at Days 11-13, 15, 20, 25 and 40.

The dosing was for

- Study A4001007: 25 mg QD, 50 mg BID, 100 mg BID, 300 mg BID or placebo (all in fasted state);
- Study A4001015: 150 mg BID (fasted and fed state), 100 mg QD (fasted), 300 mg QD (fasted) or placebo.

The baseline demographics were similar between treatment arms and studies (Table 7).

Table 7 Baseline demographics, studies A4001007 and A4001015 combined

Age, mean	*A4001007:* 34 *A4001015*: 38
male gender	80/82
white race	76/82
Cd4+ cells/mL, mean (range)	544 (205-1137)
HIV-RNA $\log_{10}$ copies/mL	4.6 (3.6-5.6)

A statistically significantly larger decrease (10% significance level) in HIV-1 RNA level from baseline compared with placebo was seen for all maraviroc dose groups, Figure 2 and Table 8.

Figure 2 Change from Baseline in HIV-1 RNA (log_{10} copies/mL)

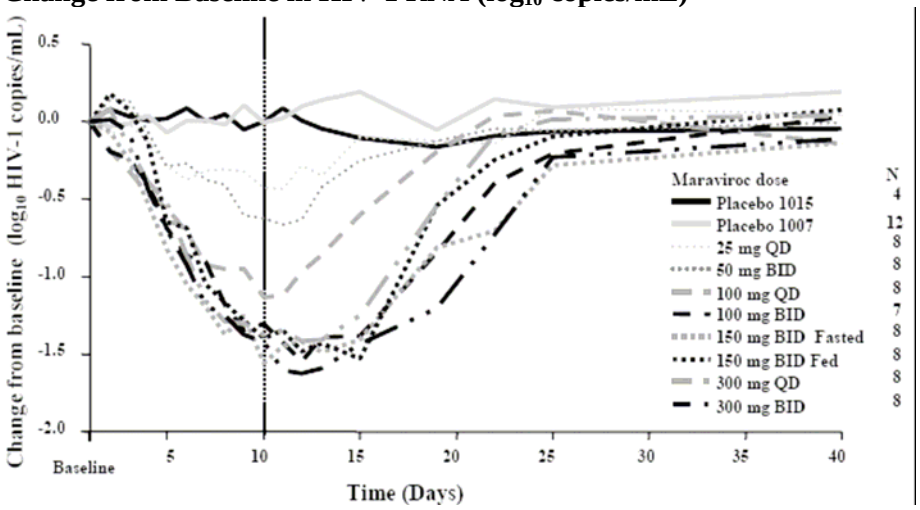


Table 8 Mean Change from Baseline in HIV-1 RNA at Day 11

Dose	No. of Patients		Mean (Range) Change in HIV-1 RN
	Randomised	Treated for 10 Day	(log_{10} copies/mL)
25 mg QD	9	8	-0.43[a] (-1.08, 0.02)
50 mg BID	8	8	-0.66 (-1.37, 0.40)
100 mg QD	9	8	-1.13 (-1.70, -0.43)
100 mg BID	8	7	**-1.42** (-1.84, -1.04)
150 mg BID	8	8	**-1.45** (-1.71, -0.90)
150 mg BID **(fed)**	8	8	**-1.34** (-1.79, -0.51)
300 mg QD	8	8	**-1.35** (-1.62, -0.95)
300 mg BID	8	8	**-1.60**[b] (-2.42, -0.78)
Placebo (1007)	12	12	0.02 (-0.45, 0.56)
Placebo (1015)	4	4	0.09 (-0.20, 0.27)

[a] P=0.056 compared with placebo; [b] P<0.01 compared with placebo (Williams step down test).
NB: Fasted when not otherwise stated

Maraviroc as 10-day monotherapy resulted in a mean maximum reduction in HIV-1 RNA of ≥1.6 log_{10} copies/mL at all doses ≥200 mg total daily dose, with a maximum reduction occurring at a median of 10-15 days. These effects on viral load appeared to be independent of dosing frequency (QD or BID). Evaluation of safety data from the Phase 1/2a studies identified postural hypotension as the dose-limiting adverse event, occurring at a frequency greater than placebo at unit doses of >300 mg and was associated with Cmax rather than AUC.

Based on these data, it was decided that exposure at a 300 mg dose equivalent would give an optimal balance between safety and efficacy, and doses of 300 mg QD and 300 mg BID were selected for further study. This dose selection was acceptable for the CHMP. Although no difference was seen with doses of 100 mg BID and higher, maraviroc is a substrate for both CYP3A and p-glycoprotein hence it appears reasonable to choose a dosage that is likely to provide a safety margin of exposure with other concomitant interacting compounds.

- Main studies

Two identical double-blind randomized trials in treatment experienced patients with CCR5-tropic HIV-1 comparing maraviroc 300 mg QD versus maraviroc 300 mg BID versus placebo (2:2:1; n=1076), all in combination with Optimised Background Therapy (OBT), have been conducted:

- MOTIVATE 1 (A4001027)
- MOTIVATE 2 (A4001028)

The studies were performed in North America, Europe and Australia at 239 study sites.

METHODS (FOR BOTH STUDIES)

Study Participants

The main inclusion criteria were:

- CCR5 tropic HIV-1 at baseline (Trofile™ HIV Entry Tropism assay)
- Minimum 6 months of prior treatment with at least 1 agent (2 agents for PIs) from 3 of the 4 antiretroviral drug classes *or* documented resistance to three of the four antiretroviral drug classes (by virologic genotypic/phenotypic assay).
- Plasma HIV-1 RNA ≥5000 copies/mL while failing therapy *or* while not on therapy.
- Stable regimen (or no regimen) for a minimum of 4 weeks prior to screening.
- Age > 16 years.

The detection of CXCR4 tropic HIV-1 at baseline (dual/mixed) led to exclusion from participation.

Other main exclusion criteria were

- prior treatment with maraviroc or other CCR5-inhibitor for more than 14 days
- patients requiring > 6 antiretroviral agents (excluding low-dose ritonavir) in the OBT
- active untreated OI, acute hepatitis
- moderate to severe ischemic cardiac disease (these criteria withdrawn by amendment 2)

Treatments

Patients were randomised to receive maraviroc 300 mg QD or BID *dose equivalent* or placebo all in combination with Optimised Background Therapy (OBT), without food restrictions (Table 9).

Maraviroc is a substrate for CYP3A4/P-gp and therefore, the dose was adjusted to maraviroc 150 mg QD or BID in those patients receiving a PI (except for tipranavir/ritonavir – by amendment 2) and/or delavirdine in their OBT due to the increased exposure of maraviroc observed in the presence of these co-administered antiretrovirals.

Table 9 Daily blinded study treatments administered

Treatment Group	Morning Treatment Regimen	Evening Treatment Regimen
Maraviroc 300 mg[a] QD + OBT	Placebo	Maraviroc 300 mg
Maraviroc 300 mg[a] BID + OBT	Maraviroc 300 mg	Maraviroc 300 mg
Matching Placebo + OBT	Placebo	Placebo

[a] Patients whose OBT included a PI (except tipranavir/ritonavir) and/or delavirdine received maraviroc 150 mg QD or 150 mg BID.

Choice of Optimised Background Therapy (OBT): Investigators chose OBT with 3-6 approved antiretroviral agents (low dose ritonavir not counted), based on the results of resistance testing, treatment history and safety/tolerability considerations. The protocol recommended that patients with efavirenz in their OBT should also receive a boosting PI (by amendment 2), to balance the CYP-induction by efavirenz. Experimental antiretroviral agents available through pre-approval access programs or other means were permitted as part of OBT provided that adequate information was available to allow for safe co-administration. Changes to background therapy could be made within the first two weeks, in consultation with the medical monitor, due to mistakes in interpretation of screening resistance results. After the first two weeks changes to background therapy could only be made for reasons of toxicity, when a drug could be switched for another compound from the same anti-retroviral drug class.

Rescue therapy: Subjects meeting the criteria for treatment failure or stopping for other reasons (pregnancy, adverse event) and requiring an alternative regimen, are followed until week 48 according to protocol. For patients whose virus still remains CCR5-tropic and potentially sensitive to maraviroc, open-label (OL) study drug may be continued during this period.

Objectives

- Primary objective: to confirm superior viral reduction (mean changes from baseline in $\log_{10}$ plasma HIV-1 RNA) with maraviroc + OBT compared to OBT alone at week 24.
- Secondary objective: safety and tolerability of maraviroc when given in combination with OBT versus OBT alone.

Outcomes/endpoints

Primary Endpoint: Change from baseline in $\log_{10}$ HIV-1 RNA at week 24.

Secondary Endpoints: For each of the two maraviroc dosing regimens (QD and BID) versus the placebo regimen, to compare:

(a) The percentage of subjects with an HIV-1 RNA <400 copies/mL at Week 24;
(b) The percentage of subjects with an HIV-1 RNA <50 copies/mL at Week 24;
(c) The percentage of subjects who achieved at least a 0.5 $\log_{10}$ reduction in HIV-1 RNA from baseline or <400 copies/mL at Week 24;
(d) The percentage of subjects who achieved at least a 1.0 $\log_{10}$ reduction in HIV-1 RNA from baseline or <400 copies/mL at Week 24;
(e) The differences in the magnitude of change in CD4 cell count from baseline to Week 24;
(f) The differences in the magnitude of change in CD8 cell count from baseline to Week 24;
(g) The Time-Averaged Difference (TAD) in $\log_{10}$ HIV-1 RNA at Week 24;
(h) To assess HIV-1 genotype and phenotype at baseline and at the time of failure.

Additional Endpoints:

- To assess HIV-1 tropism at baseline and at the time of failure;
- To assess the association between baseline resistance and virological response;
- To compare the safety and tolerability of each of the two maraviroc regimens versus the placebo regimen.

Treatment failure was defined by any one of the following virological endpoints:

1) An increase to at least 3 times the baseline (mean of 3 values before start of dosing) plasma HIV-1 RNA level at the Week 2 visit or thereafter (confirmed by a second measurement taken no more than 14 days after the first measurement);
2) HIV-1 RNA <0.5 $\log_{10}$ decrease from baseline (mean of 3 values before start of dosing) on two consecutive measurements starting at Week 8 (second measurement taken no more than 14 days after the first measurement);
3) HIV-1 RNA <1.0 $\log_{10}$ decrease from baseline (mean of 3 values before start of dosing) on two consecutive measurements starting at Week 8 (second measurement taken no more than 14 days after the first measurement), in a patient who had previously achieved a ≥2.0 $\log_{10}$ decrease from baseline; or
4) An increase in HIV-1 RNA to ≥5,000 copies/mL on two consecutive measurements taken no more than 14 days apart, in subjects previously confirmed to have undetectable levels of <400 copies/mL on 2 consecutive visits.

Sample size

A total of 1000 patients were to be randomised into the two studies to provide adequate numbers to demonstrate safety and efficacy. Initial plans were to recruit 500 patients into each study. However, difficulties in recruitment into study 1028 meant that differences in the recruitment rate between the studies were increasing over time. This was felt to be problematic, as patients recruited later may differ, due to access to new drugs Hence North American sites were included into study 1028, which was initially restricted to Europe and Australia. Sample sizes were adjusted accordingly (600 and 400 patients respectively).

Randomisation

Randomisation was performed by computer generated pseudo-random code using the method of permutated blocks, balanced within each randomisation strata (screening HIV-1 RNA ≥100,000 copies/mL and using enfuvirtide, screening HIV-1 RNA ≥100,000 copies/mL and not using enfuvirtide etc).

Blinding (masking)

The study was conducted double-blind. The maraviroc/placebo treatment was unblinded to the sponsor at week 24, while the investigators/patients remain blinded until the last subject has completed 48 weeks of therapy. Investigators could only break the blind in case of emergency.

The OBT was administered as open-label therapy.

Statistical methods

Two analysis populations were used to determine efficacy at 24 weeks – Full Analyses Set *and* Per Protocol Population.

The Full Analysis Set (FAS) population: all randomised patients who received at least 1 study drug dose. Two patients were, due to mistake, not given the randomized treatment. Hence, in practise 'As Randomised' and 'As Treated' will give the same results. The results of FAS – As Treated population are presented below.

Negative values for change from baseline indicated a benefit of treatment and negative values for the maraviroc comparison to placebo indicated an advantage of treatment with maraviroc compared to OBT alone. If the 2-sided 97.5% confidence interval was completely to the left side and completely excluded zero the superiority of maraviroc in comparison to placebo was concluded.

Primary endpoint: baseline HIV-RNA was calculated as the mean of all three values before start of dosing (screening, randomization, pre-dose). All values were log-transformed before calculation.

An ANCOVA model was used with baseline randomization values (< or > 100.000 HIV-RNA cps/mL, use of enfuvirtide) and treatment group as main effects. The least squares mean difference between maraviroc dose group and placebo is presented. For study subjects who discontinued therapy (apart from protocol defined treatment failure), the final value was imputed as baseline (i.e. no change from baseline). The same was done for subjects with missing baseline values:

- For patients on therapy and with an assessment of baseline viral load, the last observation carried forward approach was used.
- For patients with treatment failure, the last observation carried forward was used.

Secondary endpoints: the last observation carried forward at each visit was used. A Cochran-Mantel-Haenszel test was performed and 97.5% confidence intervals for the difference in percentage between maraviroc treatment arms and placebo are presented, with adjustment based on the randomization data.

The variables were also analyzed using logistic regression including randomization strata.

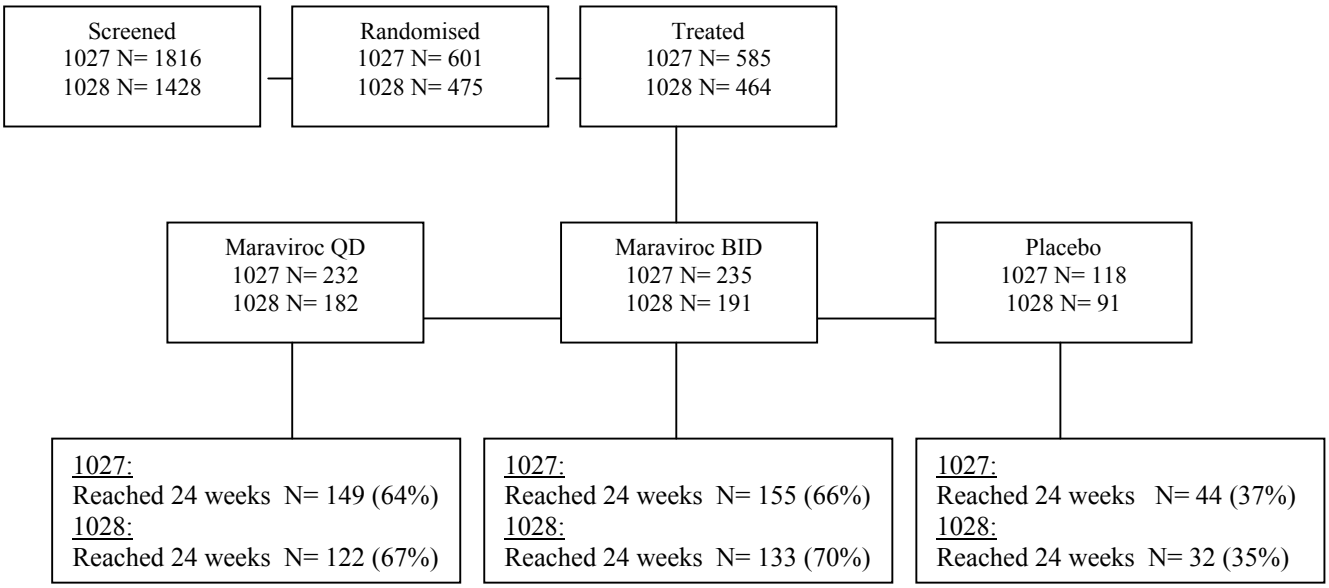
Change in CD4+ cell count was analyzed using an ANCOVA model.

RESULTS

Participant flow

An overview of the patient flow is provided in Figure 3.

Figure 3 Patient flow in studies A4001027 and A4001028



Seven patients were erroneously included in the studies as they did not have a CCR5 tropism result at screening.

Some patients included had a change in viral tropism between screening and baseline (4-6 weeks duration between these two occasions): 79 patients well balanced according to randomization (~8% per treatment arm). They are included in the analyses to follow; if not it is stated as such.

Recruitment

The details regarding recruitment (time periods and locations) are summarised in Table 10.

Table 10 Location and time for study inclusion

Study	Inclusion start	Cut off date	Location	Sites (no)	No´s randomized
A4001027	Nov 11 2004	Sept 15 2006	US	90	528
			Canada	15	67
			Puerto Rico	2 (total 107)	6 (total 601)
A4001028	Dec 17 2004	Sept 15 2006	Europe (10 countries)	75	283
			Australia	11	42
			US	46 (total 132)	150 (total 475)

Conduct of the study

There were no changes in the planned analyses. The applicant provided a statement that the studies were undertaken according to good clinical practise.

Amendments #2 (study 1027: December 2005; study 1028: February 2006) was important for the conduct and analysis of the studies; the key features were:

- Addition of interaction study results with tipranavir/ritonavir:
- Addition of interaction study results with efavirenz:
- Removal of several exclusion criteria with regards to cardiovascular disease.

Baseline data

Baseline characteristics were similar between studies and treatment arms (Table 11). The study population was heavily treatment experienced; i.e. 50% of patients had ≤1 drug considered to be active in the OBT. Demographics were quite homogenous; the vast majority of patients were middle-aged white men with HIV subtype B. The proportion of patients with hepatits B/C co-infection was low.

Table 11 Patient Demographics and Baseline Characteristics (Studies A4001027 and A4001028)

Characteristic	Study A4001027			Study A4001028		
	Maraviroc QD	Maraviroc BID	Placebo	Maraviroc QD	Maraviroc BID	Placebo
N	232	235	118	182	191	91
Male Sex, n (%)	210 (91)	212 (90)	106 (90)	153 (84)	170 (89)	79 (87)
White Race, n (%)	187 (81)	197 (84)	99 (84)	149 (82)	166 (87)	79 (87)
Mean Age (range), yrs	46 (19-75)	46 (25-69)	46 (31-71)	45.2 (17-75)	47.0 (21-73)	45.3 (29-72)
Mean Duration of Diagnosis (years)	14.0 (1.0-27.8)	13.9 (2.3-24.3)	14.3 (3.4-25.1)	14.3 (5.1-23.1)	13.8 (4.1-26.1)	14.4 (4.1-24.0)
Median CD4 Cell Count (range), cells/µL	168 (1– 812)	150 (2 – 678)	163 (1 – 675)	174 (1 – 966)	182 (3 – 820)	174 (2 – 545)
Mean HIV-1 RNA (SD), log_{10} copies/mL	4.85 (0.641)	4.86 (0.614)	4.84 (0.556)	4.87 (0.664)	4.84 (0.621)	4.89 (0.696)
Genotypic Sensitivity Score [1] n (%)						
0	52 **(22.4)**	59 **(25.1)**	31 **(26.3)**	39 **(21.4)**	43 **(22.5)**	20 **(22.0)**
1	82 **(35.3**	80 **(34.0)**	29 **(24.6)**	64 **(35.2)**	58 **(30.4)**	24 **(26.4)**
2	38 (16.4)	48 (20.4)	21 (17.8)	25 (13.7)	32 (16.8)	20 (22.0)
≥3	57 (24.6)	47 (20.0)	34 (28.8)	52 (28.6)	57 (29.8)	25 (27.5)

[1] Monogram Biosciences PhenoSense™ GT assay (for NRTI/NNRTI,PI); British Columbia Centre for Excellence in HIV using gp41 sequencing (for enfuvirtide)

Of patients eligible for screening, 45% were excluded due to the presence of X4-virus. This underlines the central role of a valid and sufficiently sensitive assay.

Numbers analysed

Table 12 outlines the number of patients analysed. Treatment discontinuations were similar between all maraviroc arms, with lack of efficacy as the major cause.

Table 12 Patient evaluation groups

Number of Patients	Study A4001027			Study A4001028		
	Maraviroc QD	Maraviroc BID	Placebo	Maraviroc QD	Maraviroc BID	Placebo
Number Treated	232	235	118	182	191	91
Discontinuations, n (%)	83 (35.8)	80 (34.0)	74 (62.7)	60 (33.0)	58 (30.4)	59 (64.8)
Due to Lack of Efficacy, n (%)	49 **(21.1)**	56 **(23.8)**	59 **(50.0)**	32 **(17.6)**	35 **(18.3)**	47 **(51.6)**
Ongoing at Week 24, n (%)	149 (64.2)	155 (66.0)	44 (37.3)	122 (67.0)	133 (69.6)	32 (35.2)
Evaluated for Efficacy, n (%)	232 (100.0)	235 (100.0)	118 (100.0)	182 (100.0)	191 (100.0)	91 (100.0)

Outcomes and estimation

Maraviroc was overall superior to placebo and in all subsets of patients. The 24-week data included in the initial MAA dossier is summarised in Tables 13-14.

Table 13 Summary of main results at week 24, studies A4001027 and A4001028

	A4001027			A4001028		
	Maraviroc QD (N= 232)	Maraviroc BID (N= 235)	Placebo (N= 118)	Maraviroc QD (N= 182)	Maraviroc BID (N= 191)	Placebo (N= 91)
HIV-RNA change from BL (log_{10} copies/mL) adj mean	-1.80	-1.95	-1.01	-1.94	-1.97	-0.90
CI 97.5% difference	[-1.15, -0.43]	[-1.29, -0.58]		[-1.45, -0.64]	[-1.48, -0.67]	
≥ 1 log change HIV-RNA, n (%)	15 (68.5)	166 (70.6)	55 (46.6)	128 (70.3)	137 (71.7)	32 (35.2)
< 50 cps/mL	98 (42.2)	114 (48.5)	29 (24.6)	84 (46.2)	79 (41.4)	19 (20.9)

Since no relevant difference in baseline characteristics (Table 11), proportion of dropouts (Table 12) and outcome (Table 13) are seen between the two studies, further presentation of outcome parameters will only be provided for the pooled analyses (Full Analyses Set – As treated).

Table 14 Main efficacy results at week 24, studies A4001027 and A4001028 combined

	Maraviroc QD (414)	Maraviroc BID (426)	Placebo (209)
HIV-RNA change from BL adj. mean log_{10} copies/mL, (se)	-1.88 (0.07) [CI 97.5%: -1.15, -0.62]	-1.96 (0.07) [CI 97.5%: -1.24, -0.71]	-0.99 (0.09)
>= 1 log reduction or < 400 cps/mL , %	65.7 (272/414)	69.2 (295/426)	35.9 (75/209)
VL < 400 cps/mL, %	55.1 (228/414)	61.0 (260/426)	27.8 (58/209)
VL < 50 cps/mL, %	44 (182/414)	45.3 (193/426)	23 (48/209)
Increase Cd4+ T-cells; adjusted mean cells/uL (se)	108.6 (5.3)	106.3 (5.3)	57.4 (7.5)

During the assessment and on request of the CHMP, the applicant provided additional 48-week data particularly outlining the proportion of patients with HIV-RNA < 50 copies/mL, total and per CD4-strata (Tables 15-18).

Table 15 Outcomes of randomised treatment at week 48 (pooled studies A4001027 and A4001028)

Outcomes	CELSENTRI 300 mg twice daily + OBT N=426	OBT alone N=209	Treatment Difference[1] (Confidence Interval[2])
HIV-1 RNA Change from baseline (log_{10} copies/mL)	-1.84	-0.78	-1.05 (-1.33, -0.78)
Proportion of patients with HIV RNA <400 copies/ml	56.1%	22.5%	Odds ratio: 4.76 (3.24, 7.00)
Proportion of patients with HIV RNA <50 copies/ml	45.5%	16.7%	Odds ratio: 4.49 (2.96, 6.83)
CD4+ cell count Change from baseline (cells/mm^3)	124.07	60.93	63.13 (44.28, 81.99)

[1] p-values < 0.0001

[2] For all efficacy endpoints the confidence intervals were 95%, except for HIV-1 RNA Change from baseline which was 97.5%

Table 16 HIV-1 RNA <50 copies/mL at Weeks 24 and 48 by CD4+ cell count at baseline, studies A4001027 and A4001028 combined

Baseline Cd4 (cells/μL)		Maraviroc QD (N= 414) %	(n)	Maraviroc BID (N= 426) %	(n)	Placebo (N= 209) %	(n)
All	**Wk 24**	**44.0**		**45.3**		**23.0**	
	Wk 48	**47.8**		**48.5**		**19.3**	
<50	Wk 24	**10.6**	(9)	**20.0**	(17)	2.7	(1)
	Wk 48	**15.5**	(13)	**16.5**	(14)	2.6	(1)
50-100	Wk24	45.1	(23)	40.0	(22)	16.0	(4)
	Wk48	37.7	(19)	36.4	(20)	12	(3)
101-200	Wk24	50.5	(47)	49.0	(51)	28.6	(16)
	Wk48	41.1	(39)	56.7	(59)	21.8	(12)
201-350	Wk24	63.8	(74)	62.9	(73)	29.0	(18)
	Wk48	68.7	(79)	57.8	(67)	21.0	(13)
≥350	Wk 24	66.1	(41)	64.4	(38)	42.3	(11)
	Wk 48	71	(44)	72.9	(43)	38.5	(10)

Table 17 Proportions with HIV-1 RNA <50 copies/mL at Weeks 24 and 48 by baseline viral load, studies A4001027 and A4001028 combined

	Maraviroc QD (N=414)	Maraviroc BID (N=426)	Placebo (N=209)
<100,000			
Wk 24	61.3	57.6	34.2
Wk 48	**58.8**	**58.4**	26.0
≥100,000			
Wk 24	28.2	34.7	10.7
Wk 48	**32.4**	**34.7**	9.5

Table 18 Change in CD4 + cell count (cells/uL, median and range) from baseline to week 48 (LOCF), studies A4001027 and A4001028 combined

Baseline CD4 Cell Count (cells/μL)	**Maraviroc QD (N= 414)**		**Maraviroc BID (N= 426)**		**Placebo (N= 209)**	
<50	43	(-31, 466)	62	(-29, 486)	7	(-13, 421)
50-100	102	(-12, 363)	103	(-70, 324)	20	(-47, 422)
101-200	92	(-52, 564)	125	(-40, 455)	32	(-134, 319)
201-350	116	(-193, 444)	102	(-157, 516)	58	(-185, 522)
≥350	124	(-250, 430)	142	(-218, 778)	123	(-301, 457)

Overall, efficacy results are durable also in patients with low CD4-counts at baseline. The clustering of factors predictive of poor response is notable in the < 50 CD4-count stratum, especially high viral load, but also GSS. For the interpretation of study data in relation to other compounds tested in similar groups of patients, the very poor results in the placebo group should be taken into account (darunavir and partly tipranavir not being used). In this context, the results, including those seen in patients with aggregated risk factors, are considered clinically relevant. As regards dosing, the BID dose appears favourable from an efficacy perspective in those patients at highest risk of treatment failure.

The majority of patients failing with maraviroc showed X4-virus at rebound, while the vast majority failing with placebo still had R5-tropic virus (Table 19).

Table 19 Viral tropism at time of treatment failure (for patients with R5-virus at baseline)

	R5	X4			Non-typeable
		All	X4	Dual/mixed	
maraviroc QD, n=56	18 **(32%)**	31 **(55%)**	8	23	7 (13%)
maraviroc BID, n=57	17 **(30%)**	32 **(56%)**	7	25	8 (14%)
placebo, n=89	80 **(90%)**	4 **(4%)**	0	4	5 (6%)

X4-virus has been associated with immunological deterioration in the natural course of HIV-infection, although a cause relationship has not been established. The CHMP therefore asked the applicant to provide additional data on patients from the pivotal trials who failed with X4-virus during maraviroc therapy and who were available for follow-up on the viral tropism over time; these data is summarised in Table 20.

Table 20 Viral tropism at last follow up visit following discontinuation for patients with R5-virus at baseline and X4-virus at failure, studies A4001027 and A4001028 combined

Tropism at last follow-up		MVC QD	MVC BID	MVC all	Placebo
R5	N	14	16	**30**	1
	Days of Follow-up, median (range)	182 (19-293)	207 (24-295)	**203** (19-295)	20 (N/A)
DM/X4	N	9	5	**14**	2
	Days of Follow-up, median (range)	11[a] (1-267)	121[b] (1-203[b])	**16** (1-267[a,b])	22 (1-42)

[a]Includes one patient whose virus returned to R5-tropic by day 30 but was DM-tropic at last follow up (day 267)
[b]Includes one patient whose virus returned to R5-tropic by day 35 but was DM-tropic at last follow up (day203) and one patient whose virus returned to R5-tropic by day 22 but was X4-tropic at last follow up (day 196)

When stopping maraviroc treatment, 30/44 reverted back to R5-virus. Of those patients still having X4-virus present, the follow-up time was either quite short (n=11), or the tropism was switching back and forth (n=3).

About 1/3 patients with X4-virus failure left the study, which might introduce a selection bias. However, patient characteristics (e.g CD4 count at baseline and failure, and HIV-RNA at baseline) were similar between those leaving and those remaining in study after X4-failure. Hence, the results seen in the patients studied (remaining in study OFF maraviroc) were considered as representative.

Still the consequences of X4 failure is a subject for further follow-up within the pivotal trials and the ongoing study in treatment naive patients. Data will be hard to interpret not least, and as made evident during the screening phase for the pivotal studies, some of these patients are at risk of spontaneous R5 – X4 switch due to the advanced stage of the HIV infection.

These data were also presented to the SAG HIV/Viral Diseases on request of the CHMP. The experts were asked to discuss whether the proposed follow-up of patients failing with X4-virus during maraviroc therapy in the pivotal studies is adequate and sufficient to address the issue in treatment-experienced patients. Furthermore, it was of interest what the SAG's view is on the re-usage of CCR5-inhibitors including maraviroc in patients who failed with X4-virus and reverted back to R5-virus, and how should this be addressed in the SmPC.

The SAG felt comfortable with the proposal to follow-up treatment-experienced patients from the pivotal trials for 96 weeks in view of the reassuring data regarding X4- to R5 reversion. In addition, the planned 5-year data from naïve patients was considered to provide an important contribution. Together this data set was considered adequate and sufficient to further investigate the issue of tropism change. Due to the lack of availability of sufficient information the experts would not recommend the re-use of CCR5-antagonists, including maraviroc, in these patients. The experts would hence recommend that the SmPC contains information about the fact that maraviroc and other CCR5-antagonists should not be used in patients who fail with X4 virus and revert back to R5 when maraviroc therapy is stopped.

Ancillary analyses

Tables 15-19 provide the result of various ancillary analyses performed in order to address the questions raised by the CHMP during the assessment to further investigate the possible impact of CD4+ cell count at baseline as well as baseline viral load.

The primary endpoint was analysed by CCR5 Δ32 genotype status of the patient. Of all patients randomized 7% were heterozygous for the CCR5 Δ32 deletion. No relevant differences were seen in the primary endpoint for patients with versus without the deletion.

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

Since no relevant difference in baseline characteristics, proportion of dropouts and outcome were seen between the two studies, the above presentation is mainly based on pooled analyses (Tables 14-20).

- Clinical studies in special populations

The patient population in the main studies was quite homogenous and no meaningful analyses can be undertaken regarding outcome by age, gender, race, HIV subtype and co-infection with hepatitis B/C. In the analyses presented no relevant differences in outcome were seen.

- Supportive study

A supportive study was undertaken to evaluate the safety and antiviral activity of maraviroc in patients with non-CCR5 tropic (CXCR4-tropic [i.e. dual or mixed tropic] or non-phenotypeable) HIV-1 virus present at baseline. The design, methods and dosing were identical to those of the main studies (1:1:1, n=186).

At week 24, no harm was seen with regards to CD4-count and viral load in patients treated with maraviroc as compared to placebo.

This study has a limited impact on the overall risk/benefit analysis of maraviroc. The findings were expected – as patients were positive for X4-virus already at baseline. Maraviroc should only be used in patients with CCR5-tropic virus, as assessed with sensitive assays.

Clinical safety

- Patient exposure

In phase I studies 595 healthy subjects and 37 HIV-patients have been exposed to maraviroc in doses ranging from 1-1200 mg. In two multiple dose-finding phase II studies 66 HIV-patients were exposed to maraviroc (25-300 mg) for 10 days.

Long term safety data (minimum 24 weeks) was obtained in the main and supportive studies. In addition to the three previously presented studies in treatment experienced patients (A4001027, A4001028 and A4001029), supportive safety data (n=174) was provided from an ongoing study in treatment naïve patients (A4001026). In this study a maraviroc treatment arm (300 mg QD) was stopped due to an increased incidence of treatment failure and maraviroc 300 mg BID open-label was offered.
For these studies (A4001027 and A4001028) all safety data on all patients to week 24 are reported to 15 September 2006. All other safety data beyond Week 24 are reported to the Week 48 visit or to 11 September 2006, whichever occurred earlier. Table 21 provides a calculation of the safety database.

Table 21 Population for long-term safety assessment

Safety data group	Total treated	Total on maraviroc
Treatment experienced		
CCR5-tropic (A4001027, 1028)	1049	840
Non-CCR5 (A4001029)	186	124
Open-label maraviroc	-	109
Treatment naive (A4001026), supportive	-	174

A total of 964 treatment experienced patients received at least 1 dose of maraviroc, including 840 CCR5-positive patients in the two pivotal studies. In the two pivotal trials (A4001027, A4001028) patients were exposed to maraviroc for a median of 8 months (Table 22); the total exposure (580 patient years) was around 5-fold that of placebo exposure (124 patient years).

Table 22 Maraviroc exposure in treatment experienced patients (studies A4001027, A4001028, A4001029[#])

Duration Categories	Maraviroc QD		Maraviroc BID		Placebo	
(Days)	R5	Non-R5[#]	R5	Non-R5[#]	R5	Non-R5[#]
N	**414**	63	**426**	61	209	62
<1	0	0	1	0	0	1
2-14	5	0	5	1	2	2
15-28	1	0	11	2	2	1
29-90	51	19	53	12	64	20
91-180	104	19	92	17	60	14
181-364	248	25	262	29	80	24
≥365	5	0	2	0	1	0
Median days (range)	**236** (2-381)	119 (64-317)	**239** (1-366)	176 (11-326)	145 (7-427)	127 (1-318)
Total , patient-years	258.7	26.4	266.8	27.9	99.3	25.0

Of these patients, 80-90% received a unit dose of 150 mg, due to concomitant use of a boosted PI in OBT, with similar proportions in each maraviroc treatment arms in the different studies.

The patient population of the main studies was very homogenous (Table 23). Furthermore, patients with verified ischemic heart disease were not allowed to be included until amendment 2 was implemented in December 2005 (study A4001027) and February 2006 (study A4001028). By this time the vast majority of patients were already included. In study A4001029, such patients were never allowed.

Table 23 Homogenous baseline characteristics in main studies (A4001027 and A4001028)

Parameter	
Age < 65 years	98%
Male gender	89%
Race (%) White	84
Black	14
Asian	1
HIV subtype B	94%
HBV, HCV* % (n) (in MVC-arms)	5.9 (50), 5.3 (45)

*Defined as HCV RNA positive; HBsAg positive

- Adverse events

Adverse events were similar in frequency and character in patients treated with maraviroc and placebo, and were those expected in this treatment population. Furthermore, no relevant differences in adverse events (including serious AE) were seen in maraviroc given QD versus BID.

Infections (upper respiratory and herpes simplex) were somewhat more common with maraviroc than with placebo, also after adjustment of exposure. Herpes simplex as a manifestation of immune response inflammatory syndrome (IRIS) is a well-known phenomenon and could be one possible

explanation for this particular finding. AIDS-related infections and malignancies were not more common with maraviroc, and auto-immune disorders were not reported.

The frequency of treatment-related adverse events was similar between treatment arms (Table 24).

Table 24 Treatment-related adverse events reported in ≥2% of patients (studies A4001027 and A4001028), not adjusted for time of exposure.

System Organ Class MedDRA Preferred Term	MVC QD N (%)	MVC BID N (%)*	Placebo N (%)	MVC, all N (%)
Subjects Evaluable for AEs	414	426	209	840
Subjects With AEs	205 (49.5)	213 (50.0)	93 (44.5)	418 (49.8)
Gastrointestinal Dis.				
Abdominal pain	11 (2.7)	11 (2.6)	2 (1.0)	22 **(2.6)**
Abdominal pain upper	11 (2.7)	8 (1.9)	5 (2.4)	19 (2.3)
Constipation	10 (2.4)	13 (3.1)	3 (1.4)	23 (2.7)
Diarrhoea	54 (13.0)	37 (8.7)	25 (12.0)	91 (10.8)
Dyspepsia	2 (0.5)	10 **(2.3)**	2 (1.0)	12 (1.4)
Flatulence	10 (2.4)	10 (2.3)	7 (3.3)	20 (2.4)
Nausea	39 (9.4)	51 (12.0)	24 (11.5)	90 (10.7)
Vomiting	18 (4.3)	17 (4.0)	8 (3.8)	35 (4.2)
General Dis.				
Fatigue	24 (5.8)	31 (7.3)	16 (7.7)	55 (6.5)
Pyrexia	9 (2.2)	7 (1.6)	7 (3.3)	16 (1.9)
Metabolism and Nutrition Dis.				
Anorexia	12 (2.9)	9 (2.1)	5 (2.4)	21 (2.5)
Musculoskeletal/Connective Tissue Dis.				
Muscle spasms	9 **(2.2)**	6 (1.4)	2 (1.0)	15 (1.8)
Myalgia	**12 (2.9)**	2 (0.5)	0	14 (1.7)
Nervous System Dis.				
Dizziness	20 (4.8)	21 (4.9)	8 (3.8)	41 (4.9)
Dysgeusia (taste disturbance)	1 (0.2)	9 **(2.1)**	2 (1.0)	10 (1.2)
Headache	41 (9.9)	30 (7.0)	21 (10.0)	71 (8.5)
Psychiatric Disorders				
Insomnia	10 (2.4)	14 (3.3)	4 (1.9)	24 (2.9)
Respiratory, Thoracic, Mediastinal Dis.				
Cough	9 **(2.2)**	8 (1.9)	1 (0.5)	17 (2.0)
Skin and Subcutaneous Tissue Dis.				
Rash	12 **(2.9)**	18 **(4.2)**	3 (1.4)	30 **(3.6)**

NB: Treatment-related AEs occurring at a higher incidence than placebo (2% or 2-fold) **highlighted.**

- Serious adverse event/deaths/other significant events

Some particular adverse events warrant special assessment. Block of the (host-) CCR5-receptor could cause immune-related side effects (infections, auto-immune disorders, malignancies). Maraviroc causes QT-prolongation at high concentrations, as well as postural hypotension. Furthermore, severe liver toxicity was seen with this class of compounds.

Immune-related adverse events

As indicated above, upper respiratory infections and herpes simplex infections was more common in maraviroc treated patients, also after adjustment of exposure. No "uncommon" infections were reported. No relevant difference of Category C-infections (AIDS-defining) were seen between maraviroc and placebo.

HIV disease itself is associated with an increased risk of a number of malignancies; hence the incidence must be related to a control-group. Although the available data so far is re-assuring, exposure is still short with regards to developing malignancies and hence further measures are warranted to be addressed with the risk management plan (see section 3.5).

The CHMP did consult the SAG HIV/Viral Diseases on the potential risk of immune dysfunction (infections, auto-immunity, malignancies). In order to further investigate specific safety risks it is planned to set up a Maraviroc Safety Registry. The SAG was specifically asked whether they consider that this registry is adequate to further explore the potential risk of malignancies as part of the Pharmacovigilance Plan.

The experts were not convinced that the pharmacovigilance and risk management strategy as proposed by the applicant is sufficient to address the potential risk of malignancies. Concerns were raised regarding the number of patients included as well as the duration of the follow up. Despite the possible ability to miss an important increase in overall risk for malignancies it was noted that the proposed study is unlikely to detect an important signal for specific Non –AIDS tumours. In addition concerns were raised that the proposed observational period of 5 years is too short to investigate the issue adequately.

A revised study proposal including an enlarged number of patients in the registry (2000 with maraviroc and 1000 controls) and a longer duration of follow-up (5 years), which can be extended even longer if found relevant by an external scientific committee, was proposed by the applicant. The data will also be compared to the incidence of malignancies found in a large HIV cohort, e.g. the EUROSIDA or if feasible the D.A.D cohort. Taking into consideration the position of the SAG, the CHMP considered that the changes to the Maraviroc Safety Registry, which is an essential element of the risk management plan, adequately address the issue.

Cardiac/circulatory adverse events

In studies 1027 and 1028 ECGs were recorded at baseline, weeks 24 and 48, and at early termination. Mean change in QTs interval from baseline was similar between maraviroc and placebo. QT-prolongation and postural hypotension was not a significant problem during treatment with maraviroc, including in those patients with the highest exposure (i.e. patients with saquinavir/ritonavir in OBT).

Postural hypotension was slightly more common with maraviroc than placebo. *At week 2* and *at early termination* maraviroc treated patients were reported to have this at frequency of 6-7% and 5-8% respectively, as compared to 4% and 7% with placebo. Of all PIs Saquinavir/ritonavir has the greatest impact on the maraviroc exposure (highest maraviroc exposure). Hence, a specific assessment was carried out for this subgroup of patients. Postural dizziness/hypotension was not more common for patients treated with maraviroc + saquinavir/ritonavir than in patients treated with maraviroc + other PI/ritonavir. Postural hypotension does not seem to be a safety problem with the 300 mg unit dose.

In the main studies 6 maraviroc treated subjects reported 8 serious adverse events, possibly linked to ischemic heart disease (4 QD, 2 BID), while no such event was reported with placebo. These patients all had significant risk factors for cardiac disease. As major cardiovascular disorders were exclusion criteria throughout the supportive study and during most of the inclusion time of the main studies (until amendment 2), cardiovascular safety has to be continuously followed within the ongoing studies and within the risk management plan.

Hepatic adverse events

Exclusion criterias of > 5 x ULN for transaminases and > 2.5 ULN for bilirubin were used in the main studies. Co-infection with hepatits B/C was allowed, but the number of such patients very low (around 5%).

There was no relevant difference of grade 3-4 AEs that might be linked to the hepatobiliary system with maraviroc treatment as compared to placebo. Only 3 possibly treatment-related SAEs, with a possible link to the hepatobiliary system were reported. No deaths were considered related to hepatic events.

Other events

Myalgia and increased creatine kinase (CK) was more common with maraviroc, time adjusted. 5 patients (of 840) treated with maraviroc stopped therapy due to rhabdomyolysis (2), myositis (1) and myalgia. Although increased CK levels are very common in this treatment population myositis/rhabdomyolysis cannot be excluded as a possible uncommon adverse event and will be followed within the risk management plan.

Deaths

As of database cut-off a total of 30 deaths have been reported post randomization of the phase IIb/III studies. All except one of these deaths were not considered related to study drug by the investigators. After adjustment for time of exposure, no difference in the frequency was seen between maraviroc and placebo. Another 12 deaths occurred between screening and randomization (period of around 6 weeks), underscoring the advanced stage of HIV disease in this patient population.

- Laboratory findings

There was no relevant difference of grade 3-4 AEs that might be linked to the hepatobiliary system with maraviroc treatment as compared to placebo. Treatment-related serious AEs, with a possible link to the hepatobiliary system were reported in 3 patients, with values normalized after cessation (1) and continuing therapy (1); the third patient left the study.

No relevant differences were noted, including liver enzymes.

- Safety in special populations

As mentioned above the main study populations were very homogenous. No relevant analyses can be undertaken with regards to special populations. In the analyses presented, no specific safety concerns were identified.

- Discontinuation due to adverse events

Maraviroc was well tolerated, with a low number of patients discontinuing the main studies due to adverse events. No relevant differences were seen between treatment arms (MVC QD 2.9%, MVC BID 2.3%, placebo 2.4%).

- Post marketing experience

No post-marketing data is available as the product is not yet licensed.

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 25.

Table 25 Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified risks: None		
Important potential risks		
Hepatic Safety	**Routine Pharmacovigilance** **Ongoing trials in TE subjects** 48 week analysis Longer term follow up data (until last patient reaches 96 weeks) Observational mortality follow-up until 5 years post starting study drug **Ongoing trials in TN subjects** 48 week data in naïve subjects (A4001026) 5 year follow up if efficacy of maraviroc is similar to efavirenz **EAP initiate 1Q2007** **Maraviroc Safety Registry** (A4001067) **EuroSIDA data** **Additional cohorts** **Data Capture Aid** **Expert panel if required**	-Warning to patients with abnormal hepatic function, known underlying hepatic disease or HCV/HBV is in section (4.4) of the SmPC -Discontinuation rules are defined in Section 4.4 -PIL includes warning regarding hepatic safety
Malignancy (both AIDS and non-AIDS related)	**Routine Pharmacovigilance** **Ongoing trials in TE subjects** 48 week analysis Longer term follow up data (until last patient reaches 96 weeks) Observational mortality follow-up until 5 years post starting study drug **Ongoing trials in TN subjects** 48 week data in naïve subjects (A4001026) 5 year follow up if efficacy of maraviroc is similar to efavirenz **EAP initiate 1Q2007** **Maraviroc Safety Registry** (A4001067) **EuroSIDA data** **Additional cohorts** **Data Capture Aid** **Expert panel if required**	---
Infection (including Category C events, HCV coinfection, encephalitides)	**Routine Pharmacovigilance** **Ongoing trials in TE subjects** 48 week analysis Longer term follow up data (until last patient reaches 96 weeks) Observational mortality follow-up until 5 years post starting study drug **Ongoing trials in TN subjects** 48 week data in naïve subjects (A4001026) 5 year follow up if efficacy of maraviroc is similar to efavirenz **EAP initiate 1Q2007** **Maraviroc Safety Registry** (A4001067) **EuroSIDA data** **Additional cohorts** **Data Capture Aid** **Expert panel if required**	-Listed in the Warning section of the SmPC (4.4), including advice for caution. -Listed as ADR in section 4.8

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Potential to alter rates of autoimmune disease	**Routine Pharmacovigilance** **Ongoing trials in TE subjects** 48 week analysis Longer term follow up (until last patient reaches 96 weeks) Observational mortality follow-up until 5 years post starting study drug **Ongoing trials in TN subjects** 48 week data in naïve subjects (A4001026) 5 year follow up if efficacy of maraviroc is similar to efavirenz **EAP initiate 1Q2007** **Maraviroc Safety Registry (A4001067)** **Expert panel if required** Results from Study A4001045 in the treatment of RA	IRS is listed in the Warning section of the SmPC (4.4).
Off label use in paediatrics and adolescents	**Routine Pharmacovigilance** Including reporting of any reported off label usage and reported SAEs via PSURs **Monitoring literature** for reports of off label usage Producing summary of reports identified in the PSUR **Automated Database** will be explored to examine the extent of off-label use of maraviroc within such a study	-Indication only in adult with CCR5-tropic HIV is listed in Sections 4.1, 4.2 and Warning section of the SmPC (4.4) -Educational materials to guide prescribers on tropism and how to get a tropism test performed to help ensure appropriate use of maraviroc
Change in tropism result from CCR5 to CXCR4 tropic with associated adverse clinical outcome	**Routine Pharmacovigilance** **Ongoing trials in TE subjects** 48 week analysis Longer term follow up data from ongoing TE studies (until last patient reaches 96 weeks) Observational mortality follow-up until 5 years post starting study drug **48 week data in naïve subjects** (A4001026) 5 year follow up if efficacy of maraviroc is similar to efavirenz **EAP** initiate 1Q2007	-Listed in Sections 4.1, 4.2 and Warning section of the SmPC (4.4) -Tropism data is presented in Section 5.1.
Potential imbalance in cardiac ischaemic events	**Routine Pharmacovigilance** **Ongoing trials in TE subjects** 48 week analysis Longer term follow up data (until last patient reaches 96 weeks) Observational mortality follow-up until 5 years post starting study drug **Ongoing trials in TN subjects** 48 week data in naïve subjects (A4001026) 5 year follow up if efficacy of maraviroc is similar to efavirenz **EAP initiate 1Q2007** **Maraviroc Safety Registry** (A4001067)	-Listed as uncommon adverse reactions in the SmPC (Section 4.8). -Warning to patients with severe cardiovascular diseases is listed in section 4.4 of the SmPC.

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	EuroSIDA data **Additional cohorts** **Data Capture Aid**	
Potential for rhabdomyolysis and myositis	**Routine Pharmacovigilance** **Ongoing trials in TE subjects** 48 week analysis Longer term follow up data (until last patient reaches 96 weeks) Observational mortality follow-up until 5 years post starting study drug **Ongoing trials in TN subjects** 48 week data in naïve subjects (A4001026) 5 year follow up if efficacy of maraviroc is similar to efavirenz **EAP initiate 1Q2007** **Maraviroc Safety Registry** (A4001067) **EuroSIDA data** **Additional cohorts** **Data Capture Aid**	Listed as uncommon adverse reactions in the SmPC (Section 4.8).
Missing information		
Exposure during Pregnancy	**Routine Pharmacovigilance** In-utero exposure is captured via the SAE reporting process and will be reported annually in the PSUR In order to perform developmental assessments following inadvertent in-utero exposure of infants it is proposed to enrol such infants where geographically possible into **current long term studies in the US and Europe** following in utero exposed infants. Post authorization in-utero exposure will also be captured within the **US antiretroviral registry.** The registry will provide a report which will be submitted with the PSUR annually.	-Recommendation of use in pregnancy is in SmPC (Section 4.6) -Warning of use during lactation is listed in SmPC (Section 4.6) - Details of pre-clinical safety data are provided in SmPC (Section 5.3).
Other Safety concerns		
Postural Hypotension	Routine Pharmacovigilance	Warning to patients with history of postural hypotension or on concomitant products known to lower blood pressure is included in section 4.4 of the SmPC. -Listed in the Overdose Section (4.9) of SmPC
Potential for QTc prolongation	Routine Pharmacovigilance	Listed in the Overdose Section (4.9) of SmPC

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.

Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

The applicant committed to place on stability study the first three production batches of the finished product and to inform the Authorities if out-of-specification results occur.

Non-clinical pharmacology and toxicology

Maraviroc is a small molecule CCR5 antagonist that binds with an affinity reflected in a K_D of 0.86 nM. It binds CCR5 to promote a conformation that is not recognised by CCR5-tropic HIV i.e. it is an allosteric inhibitor of HIV binding to CCR5. Maraviroc is a CCR5 functional antagonist, with no intrinsic agonist activity, blocking to signals induced by different receptor-binding chemokines. Overall, the compound appeared selective for the human over the murine receptor ortholog. In assays screening for selectivity, some activity towards rat muscarinic, human μ-opioid and human α adrenergic receptors was reported. The interactions of maraviroc with macaque CCR5 receptor were determined to be most similar to the human receptor. From the non-clinical point of view the primary and secondary as well as safety pharmacology of maraviroc has been adequately characterised.

The species used in toxicology studies can be considered as relevant models concerning metabolism and general pharmacokinetic characteristics. In interspecies comparisons of exposure the applicant has used unbound values adjusted for differences in protein binding. Overall this approach was considered acceptable also considering that using total or unbound values does not generally have a major impact on exposure multiples. The metabolism of maraviroc is rather complex, but the major pathways in various species have been identified. Maraviroc is mainly metabolised by CYP3A4, and is considered unlikely to inhibit the metabolism of other cytochrome P450 substrates in clinical practice. Overall, the species used in toxicology studies were exposed to various extents to all major metabolites of maraviroc. Maraviroc is chemically described as having one chiral centre with an S absolute configuration and an *exo* substitution configuration on the tropane unit. *Endo* and *exo*isomers could exhibit differences in pharmacology/toxicology, but stereochemical inversion or inversion of the *exo* configuration seems unlikely.

With regard to the toxicological properties of maraviroc and the respective studies to investigate the general toxicity, reproduction toxicity and carcinogenic potential, respectively, it needs to be considered that possible effects may be a function of the binding to CCR5, i.e. the primary pharmacological effect, and that this has either not or to a limited extent been characterised due to species-dependent differences in receptor affinity resulting in an inhibition of 30% at the most in the species used, mouse, rat, rabbit and dog. Therefore, for toxicity directly related to CCR5 interactions the data from the monkey studies provides the most valuable information.

In particular, the studies on the carcinogenic potential do not address possible tumourigenicity arising from long-term blockade of the CCR5 receptor. Background data from CCR5 knockout mouse is also not available. The applicant was asked by the CHMP to further address the potential tumour "promoting" properties of maraviroc as follow-up measure by use of available primate tissues to conduct investigations for markers of proliferative activity and conducting tests aimed to provide data on tumour proliferating potency.

In addition, further pharmacovigilance activities are mandated as follow-up measure to address this concerns (see section 3.5 Pharmacovigilance).

Efficacy

The applicant states that the studies have been conducted in accordance with Good Clinical Practise. They were approved by ethics/institutional review boards.

The phase III pivotal studies consisted of truly treatment-experienced patients, with a median sensitivity score of 1 at baseline. In this population, maraviroc proved to have a relevant effect, with 45% of patients having undetectable viral load at week 24, which were twice as many as in the placebo arms (23%). The efficacy was lower in patients with the lowest sensitivity score at baseline, and a marked decrease was seen in patients with the lowest Cd4-strata. 10-20% of maraviroc treated patients with a Cd4-count < 50 at baseline had undetectable viral load at week 24, compared to 3% of those who received placebo. 48-week data was provided showing that efficacy results are durable also in patients with low CD4-counts at baseline.

The resistance evaluation of patients failing on therapy with maraviroc is complicated. The majority of failing patients (two thirds) showed X4-virus at rebound. Such emerging X4-virus was shown to be of pre-existing origin, rather than mutated R5-virus. After stopping maraviroc treatment again only R5-virus was detected in the vast majority (30/31) patients with a follow-up of more than 4 weeks.

The patient population of the main studies were very homogenous with respect to age (around 40), gender (89% males), race (84% white) and HIV-subtype (94% subtype B). Although these parameters might not correlate to efficacy on theoretical grounds, further data is warranted regarding the efficacy in subpopulations.

Safety

The safety database is adequate for this stage of development, however further data will need to be generated also as part of the risk management plan.

No major safety concerns were found with maraviroc as part of the antiretroviral regimen in treatment experienced patients. The dose limiting adverse event, postural hypotension, appeared to be clinically manageable with the chosen dosage of a 300 mg. Maraviroc was well tolerated, with the same frequency of study drug discontinuation for maraviroc and placebo. The spectrum of AEs reported, including serious adverse events and deaths, did not reveal any specific issues considering the population studied. The frequency of liver related AEs does not raise any concerns for liver toxicity.

The safety conclusion must be viewed with some caution, due to the homogenous study population with regards to age, gender and race. However, from a mechanistic point of view it appears unlikely that these parameters would have a major impact on the safety aspects of the compound.

It is noteworthy that the number of patients co-infected with hepatitis B/C in the main studies is low (around 5%). Hence, neither the safety of maraviroc in such patients, nor the possible impact of maraviroc on the course of these infections has been adequately studied. Adequate reflection in the SmPC wording is mandated and further studies to explore this issue as part of the follow-up measures is mandated.

Furthermore, it must be highlighted that verified ischemic heart disease, congestive heart failure and prior intracranial vascular events were exclusion criteria through the major part of the inclusion period of the main studies, and throughout the supportive study. Hence, the safety of maraviroc has not been adequately studied in this subgroup of patients. This issue must be specifically addressed in the pharmacovigilance program – especially as the only treatment related cardiac events seen, although at low frequency, occurred in patients treated with maraviroc.

Maraviroc could potentially have a negative impact on immune function through CCR5-receptor blockade. In the population studied, the frequency and severity of infections is complex to assess. This issue should be continuously followed, and later findings in the ongoing study in treatment naïve patients will be helpful for this assessment. It must be emphasized, that the frequency of uncommon

but potentially serious infections, like encephalitis, can only be analysed by looking at large number of maraviroc treated patients included in HIV-cohort studies.

No increased frequency of malignancy was seen at this early stage; this must be followed for longer time periods, as well as signals of auto-immune disorders. The proposed risk management plan addresses these issues.

CXCR4-tropic virus is seldom found during early stages of HIV infection, but is more frequently seen along with increasing immunosuppression. Whether such CXCR4-tropic virus is present in minor reservoirs already after transmission, or if R5-virus is transformed to CXCR4-tropic virus by mutation is unknown. The shift from R5-tropic virus in early stages of HIV-infection to a gradually higher frequency of virus able to use the CXCR4 receptor found at later stages of disease, is a process not fully understood. Although a cause-effect between emergence of CXCR4-tropic virus and immune deterioration has not been established, this issue is of particular interest, as the majority of patients failing with maraviroc do so with the emergence of CXCR4-tropic virus. As discussed, it is reassuring that there seems to be reversion back to a CCR5 using virus population once maraviroc therapy is stopped. The impact of failure with CXCR4-tropic virus on subsequent treatment outcome will be followed within both the pivotal trials and in the ongoing study in treatment naive patients.

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

The applicant has submitted results from user testing of the package leaflet, which was performed in English. Overall, the user test is found acceptable.

Risk-benefit assessment

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.

Benefits

Maraviroc is relevantly superior to placebo in the treatment of heavily experienced patients with CCR5-tropic HIV-1. This was shown in two large, double-blind, randomized studies comparing maraviroc 300 mg QD versus maraviroc 300 mg BID versus placebo (2:2:1, n=1076) all in combination with optimized background therapy. At week 48, the proportion of patients with undetectable viral load was around 48% for both doses of maraviroc as compared to 19% with placebo. Maraviroc was relevantly superior in all subsets of patients analysed.

From a clinical practice perspective it is worth noticing that:

- Maraviroc treatment should not be initiated in patients with detectable CXCR4-tropic virus.
- Patients in advanced failure are at higher risk for detectable CXCR4-tropic virus.
- The Trofile™ HIV Entry Tropism assay (Monogram Sciences) is the only currently available and validated assay. The applicant did commit to ensure that adequate logistical arrangements are set up in all EU/EEA Member States to provide physicians with necessary access to the assay.

- Viral tropism cannot be confidently predicted from treatment history and re-assessment of stored samples. Hence maraviroc is not a suitable agent when switching therapy in virally suppressed patients (due to side effects, etc.).

Risks

Non-clinical data on repeated dose toxicity, reproduction toxicity and carcinogenic potential included dosing regimens providing high exposure multiples in relation to human clinical dose and generally did not indicate any unexpected toxicity of maraviroc. In rat prominent liver effects were reported, but in monkey effects were mild. Animal studies were, though, partially deficient in studying the risks of CCR5-inhibition, as the affinity for maraviroc is low in non-human host cells with the exception of monkey. Sufficient human data therefore need to be generated to overcome this deficiency.

The CCR5-receptor is a host cell chemokine receptor. CCR5-mediated signalling is involved in inflammatory response at several levels including priming of innate/adaptive immune response, chemotaxis and cell migration. This activity is blocked by maraviroc, which therefore carries a potential risk for immune dysfunction (infections, auto-immune disorders, malignancies). In the pivotal studies upper respiratory infections and mucocutaneous herpes simplex was somewhat more common with maraviroc compared to placebo (exposure adjusted). The frequencies of AIDS-defining events and malignancies were similar between groups.

In early studies it was shown that maraviroc has the potential of QT-prolongation at high doses, and postural hypotension is dose limiting. However, postural hypotension, a bit more frequent than with placebo, was uncommon and QT-prolongation not noted in the pivotal studies. The frequency of liver-related AE´s was similar to placebo.

Maraviroc is a substrate of both CYP3A and p-glycoprotein, and hence sensitive to interactions. In treatment experienced patients the number of drugs prone to interactions may be quite extensive. Uncommon combinations of antiretrovirals as well as several other drugs to treat opportunistic infections and other underlying disorders might be used concomitantly. The option of individual cases therapeutic drug monitoring (TDM) was discussed but currently not considered feasible.

The patient population studied was quite homogenous; the vast majority of patients were middle-aged white men, with HIV subtype B. The percentage of patients with HBV/HCV co-infection was low, around 5%. The applicant has therefore not been able to adequately study the impact of maraviroc on the course of hepatitis C co-infection (levels of HCV-RNA levels).

As patients with verified significant cardiovascular disorder were excluded until late when most patients were already included, cardiovascular safety is not adequately studied, but signals were noticed. Similarly, myalgia and increased creatine kinase are considered as signals.

- Safety follow-up long-term is of major importance. The ongoing confirmatory study in treatment-naive patients with planned follow-up for 5 years is considered pivotal, e.g. as regards putative safety issues related to long-term CCR-5 receptor inhibition.
- There are concerns related to the consequences of treatment failure with CXCR4-tropic virus. The advanced to very advanced stage of the patients enrolled in the pivotal trials and the non-availability of effective next-line ART at time of failure in a large proportion of patients probably make these trials the best possible but far from ideal source of information as regards this issue. Available data are considered reassuring as back shift to R5-virus dominates, but data are limited.
- Safety should also to be documented in a wider population than that currently studied, including co-infected patients and patients with cardiovascular disease.

As regards the deficiency with respect to non-clinical toxicity studies (non-relevance of species for assessment of CCR5 inhibition), medium-term clinical safety data are overall sufficiently reassuring, while long-term safety must be addressed within the RMP.

Balance

Maraviroc is a new antiretroviral compound that shows clinically relevant 48-week efficacy as add-on to optimised background therapy in patients with few or no available treatment options and with only CCR5-tropic virus detectable at baseline.

The dose proposed for approval is 300 mg equivalent BID (150, 300 or 600 mg BID depending on interactions with co-administered antiretroviral therapy and other medicinal products). In limited phase 2 dose ranging studies, doses ranging from 25 mg QD to 300 mg BID were given during short-term monotherapy. Maximum activity (-1.6 log10 change in HIV-RNA at day 10) was achieved with all doses of 100 mg BID or above.

The overall activity of the 300 mg equivalent QD regimen compared with 300 mg equivalent BID is similar and actually fulfilled predefined criteria for non-inferiority in the pooled analysis. The activity of the QD regimen, however, is somewhat lower in patients with risk factors for poor response; high viral load, low CD4 T-cell count and a low sensitivity score. In addition, no difference as regards safety comparing the regimens is observed, including the dose-limiting adverse reaction postural hypotension. Maraviroc is also a compound with a large potential for clinically relevant interactions, including food. Based on until now available data, the concerns raised in relation to interactions mainly refer to too low exposure. Altogether, the proposed dose regimen is considered acceptable.

Fully acknowledging the mechanism-based safety concerns and some signals in the rather limited safety database, the benefit/risk is considered favourable for the intended indication

- as no major toxicity or tolerability issues have been shown to be related to maraviroc,
- as the compound provides a new mechanism of action,
- as sustained efficacy (48 weeks) of undoubted relevant magnitude has been clearly shown.

The CHMP is of the opinion that the SmPC adequately reflects the current knowledge about the compound in its intended therapeutic indication. A number of follow-up measures would need to be conducted by the applicant post-licensure.

Recommendation

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

> "CELSENTRI, in combination with other antiretroviral medicinal products, is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable (see section 4.2).
>
> This indication is based on safety and efficacy data from two double-blind, placebo-controlled trials in treatment-experienced patients (see section 5.1)."

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