2.5 CLINICAL OVERVIEW

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AIDS	Acquired immune deficiency syndrome
AFSSAPS	Agence Francaise de Securite Sanitaire des Produits de Sante, the French regulatory agency
ANCOVA	Analysis of co-variance
AUC	Area under the plasma concentration-time curve
BID	Twice daily treatment regimen
CCR5	CC Chemokine Receptor 5
CD	Cluster of differentiation
CFR	Code of Federal Regulation
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CXCR4	CX Chemokine Receptor 4
CYP3A4	Cytochrome P450 Enzyme 3A4
DSMB	Data safety monitoring board
FDA	United States Food and Drug Administration
GSS	Genotypic susceptibility score
HAART	Highly active antiretroviral therapy
HCV	Hepatitis C virus
HIV-1	Human immunodeficiency virus subtype 1
IC_{50}	The molar concentration at which in vitro viral replication was inhibited by 50%
IC_{90}	The molar concentration at which in vitro viral replication was inhibited by 90%
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
LOCF	Last observation carried forward
LOQ	Limit of quantification
MPA	Medical Products Agency, the Swedish regulatory agency
MVC	Maraviroc
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside/nucleotide reverse transcriptase inhibitor
OBT	Optimised background therapy
OSS	Overall susceptibility score
PBL	Peripheral blood leucocytes
P-gp	P-glycoprotein
PI	Protease inhibitor
PSGT	Phenosense™ GT assay for determination of virus susceptibility to antiretroviral agents (PIs, NRTIs and NNRTIs)
PSS	Phenotypic susceptibility score
QD	Once daily treatment regimen
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
TAD	Time averaged difference

2.5. CLINICAL OVERVIEW

There is a clear unmet medical need for antiretroviral agents with novel mechanisms of action to treat patients infected with HIV-1 who have few or no remaining treatment options available to them due to current class-resistant virus.

Maraviroc (formerly known as UK-427,857) is potentially the first agent of a new pharmacological class of antiretroviral agents known as CCR5 antagonists acting on a human cellular target to prevent infection of the cell by HIV-1. Maraviroc has demonstrated efficacy in vitro against a wide range of CCR5 tropic clinical isolates, including Clade B and non-Clade B strains of HIV-1, as well as those resistant to any of the four existing drug classes of antiretroviral medicinal products. The two Phase 3 studies, A4001027 and A4001028, have demonstrated that a 300 mg dose equivalent of maraviroc, given once or twice daily, when dosed in combination with optimised background therapy (OBT) in treatment-experienced patients infected with CCR5 tropic HIV-1, leads to a greater and clinically relevant decline in viral load than OBT alone (placebo), with a mean reduction in HIV-1 RNA from baseline to Week 24 of at least 1.8 $\log_{10}$ copies/mL compared to approximately 1.0 $\log_{10}$ copies/mL with OBT alone. These studies also demonstrated an acceptable safety and tolerability profile with no significant effect on QTc interval nor an increase in the incidence of heptatoxicity, infections or malignancies, relative to placebo.

This clinical overview provides a summary of the unmet medical need and scientific rationale for the development of maraviroc, a compound with a novel mechanism of action, as well as a critical discussion of the clinical data from the maraviroc development programme, which supports the conclusion that maraviroc:

- Is safe and effective when administered in combination with other antiretroviral agents;
- Offers a positive risk-benefit to treatment-experienced patients infected with CCR5 tropic HIV-1 and very few or no remaining treatment options available;
- Did not appear to result in harm when administered to patients infected with dual/mixed tropic HIV-1 and may provide some benefit in terms of an increase in CD4 cell count, despite no significant effect on viral load.

This document is structured according to the ICH guidance document The Common Technical Document for the Registration of Pharmaceuticals for Human Use EFFICACY – M4E.

2.5.1. Product Development Rationale

2.5.1.1. Introduction

AIDS has killed more than 25 million people since it was first recognised in 1981, making it one of the most destructive epidemics in recorded history. Despite recent, improved access to antiretroviral treatment and care in many regions of the world, the AIDS epidemic is estimated to have claimed 3.1 million (2.8 to 3.6 million) lives in 2005. The number of people living with HIV-1 reached its highest level in 2005: an estimated 40.3 million (36.7 to

45.3 million) people were living with HIV-1 at that time. Close to 5 million people were newly infected with the virus in 2005 (UNAIDS, 2005).

Currently the only way to slow disease progression is to use a multi-drug combination strategy that targets 1 or more HIV targets; namely protease, reverse transcriptase and gp-41. This strategy reduces virus replication rate and prevents further decline in CD4 cell counts and disease progression to AIDS. Some of these combinations are initially highly successful in first-line care. However, the significant side-effect profiles and pill burden can reduce compliance over time allowing virus replication and treatment failure by selection for drug resistant virus. A recent study of antiretroviral treatment-experienced HIV-1 patients with detectable viremia demonstrated that 88% were infected with virus containing at least one genotypic resistance mutation, with a median of 3 mutations observed per patient (Napravnik S, 2005). As patients fail a multi-drug regimen their virus often acquires resistance to more than 1 component of that regimen. Therefore, the respective options are further compromised due to drug class resistance, as well as drug-drug interactions preventing concomitant use of certain drugs. To a large extent, the situation in the treatment-experienced patient population today reflects the era prior to the introduction of highly active antiretroviral therapy (HAART), when fully suppressive regimens were unavailable.

Thus there is a high medical need for better tolerated, conveniently administered agents to prevent progression to AIDS in HIV infected individuals, reduce susceptibility to secondary infections and return patients to a normal lifestyle. New drugs are also needed that target different stages of the virus life cycle, which both delay the emergence of resistance in patients with wild-type virus, as well as provide genuine treatment options for the growing numbers of patients with HIV-1 infection due to drug-resistant virus. Due to the various reasons stated above the urgency to meet this medical need is immediate.

The first step in the process of HIV-1 entry into the host cell is the specific binding of viral gp120 to CD4, the primary receptor for HIV-1. However, the binding of gp120 to CD4 alone is not sufficient for HIV-1 entry (Maddon PJ, 1986). The observation that human chemokines are capable of inhibiting HIV-1 infection of T-lymphocytes (Cocchi F, 1995), and the identification of polymorphisms in the CCR5 gene that protect some highly exposed individuals from being infected with HIV-1 (Liu R, 1996), led to the discovery that a human chemokine receptor is an essential co-receptor for HIV-1 infection (Feng Y, 1996). The binding of gp120 to CD4 causes a conformational change in gp120 that exposes the bridging sheet and forms a co-receptor binding site (Kwong PD, 1998, Rizzuto CD, 1998, Wyatt R, 1998). Once this has occurred, co-receptor binding triggers conformational changes in gp41, which drives the remaining steps in fusion and entry of the viral core (reviewed by (Chan DC, 1998)). The chemokine receptors most commonly utilised by HIV-1 in vivo are CC chemokine receptor 5 (CCR5) and/or CX chemokine receptor 4 (CXCR4) (Choe H, 1996, Deng H, 1996, Dragic T, 1996, Feng Y, 1996). A schematic model of the HIV-1 entry process is shown in Figure 1. The ability of gp120 to bind to either one or both receptors defines the tropism of the virus. HIV-1 strains are therefore categorised as R5 (CCR5-tropic), X4 (CXCR4-tropic) or R5X4 (strains using both CCR5 and CXCR4; also referred to as 'dual-tropic') (Berger EA, 1998). Patient serum samples may also contain a heterogeneous population of viruses with different tropism termed 'mixed tropism'. CCR5 antagonists only inhibit strains which are obligate users of CCR5, while CXCR4 and dual

tropic strains ("CXCR4-using") can infect cells in the presence or absence of a CCR5-specific antagonist.

Figure 1. A model for HIV-1 entry

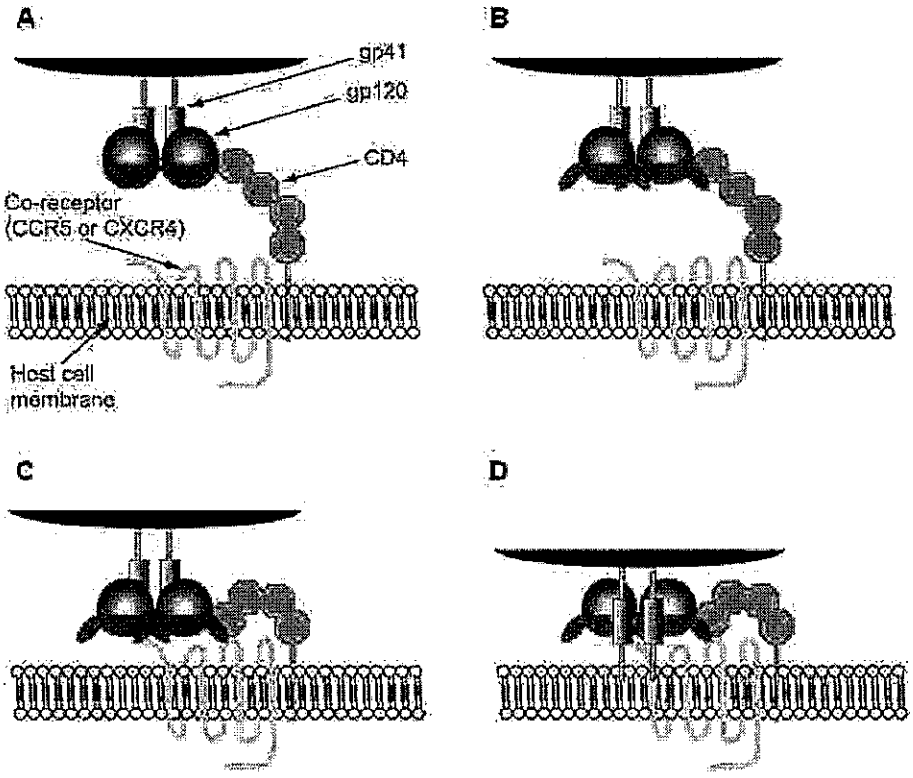


Figure legend. A model for HIV-1 entry. HIV-1 gp120 binds to CD4 (A). This induces conformational changes in gp120 and exposure of the co-receptor binding site (B), which is a complex domain that includes the V3 loop and is collectively termed the 'bridging sheet'. Exposure of the co-receptor binding site permits binding of gp120 to the co-receptor (C). Co-receptor antagonists inhibit this step by binding the co-receptor and changing its shape such that gp120 cannot recognize it. Co-receptor binding induces conformational changes in gp41 and insertion of a 'fusion peptide' into the host cell membrane (D), ultimately resulting in fusion of viral and cell membranes. Multiple gp120-co-receptor interactions are required to form a fusion pore through which the viral core can pass and infect the cell.

Generally, R5 strains are transmitted and establish new infections in a host (Schuitemaker H, 1991, Shankarappa R, 1999, Zhu T, 1993). In some individuals, CXCR4-tropism evolves over time and the emergence of X4 virus has been associated with rapid CD4 T-lymphocyte decline and accelerated disease progression. Although increasing prevalence of X4 virus and decreasing prevalence of R5 virus have been associated with increasing viral load and decreasing CD4 cell counts (Brumme ZL, 2005, Moyle GJ, 2005), the emergence of CXCR4-using virus is not a prerequisite for the development of AIDS. Throughout infection, the detection of R5 virus only is most common; dual/mixed-tropic virus is more likely to be detected in advanced patients than early asymptomatic patients, and the detection of X4 virus only is rare (Moyle GJ, 2005, Whitcomb JM, 2003). Whether emergence of

CXCR4-using strains is a marker for disease progression rather than the cause is not known (Moore JP, 2004).

Support for CCR5 as a therapeutic target in the treatment of HIV-1 came from studies demonstrating that patients with a homozygous 32 base-pair deletion in the CCR5 gene (CCR5Δ32), resulting in a non-functional CCR5 receptor protein, appeared to be resistant to developing HIV-1 infection and patients with a heterozygous CCR5Δ32 deletion demonstrated some resistance to infection and had slower progression to AIDS in patients infected with HIV-1 compared with patients with a wild type genotype (de Roda Husman AM, 1998, Marmor M, 2001).

Maraviroc is a selective and slowly reversible CCR5 antagonist that has shown potent antiviral activity in vitro against a wide range of clinical isolates, including clade B and non-clade B strains, as well as those resistant to any of the four existing drug classes (details provided in Module 2.4 Non-Clinical Overview). The dose limiting adverse event in Phase 1 studies was postural hypotension, observed at a greater incidence than placebo at unit doses >300 mg. Maraviroc also demonstrated potent antiretroviral activity when given as monotherapy to patients infected with CCR5-tropic HIV-1 with no significant adverse effects compared with placebo. Total daily doses ranging from 200 mg to 600 mg per day, given for 10 days, resulted in a mean maximum reduction in HIV-1 RNA of 1.60-1.84 $\log_{10}$ copies/mL. Based on these studies, a Phase 2b/3 clinical programme was designed to explore the safety and efficacy of two maraviroc doses (300 mg dose equivalent once and twice daily) in antiretroviral treatment-naïve and treatment-experienced patients infected with CCR5 tropic HIV-1 and treatment-experienced patients infected with non-CCR5 tropic (dual/mixed-tropic, CXCR4-tropic or non-phenotypable) HIV-1.

The indication sought by the Applicant in this submission is for maraviroc to be administered in combination with other antiretroviral agents for the treatment of treatment-experienced adult patients infected with CCR5 tropic HIV-1. This indication is based on analyses of safety and efficacy data from two independent double-blind, placebo-controlled Phase 3 studies in treatment-experienced patients infected with CCR5 tropic HIV-1 conducted in accordance with the recommendations for development of antiretroviral agents in the US and EU (FDA Guidance for Industry Antiretroviral Drugs using Plasma HIV RNA Measurements – Clinical Considerations for Accelerated and Traditional Approval, October 2002 and CHMP Guideline on the Clinical Development of Medicinal Products for the Treatment of HIV Infection, November 2005). Supportive safety data are presented in this submission from a smaller Study A4001029, designed to address the safety of maraviroc in treatment-experienced patients infected with non-CCR5 tropic (dual/mixed tropic, CXCR4-tropic or non-phenotypable) HIV-1.

2.5.1.2. Maraviroc Clinical Development Programme

2.5.1.2.1. Overview of Maraviroc Phase 2b/3 Studies

More than 2000 HIV-1 infected patients received blinded study drug in the maraviroc Phase 2b/3 development programme, which includes long-term studies of maraviroc in combination with other antiretroviral drugs in both treatment naïve patients infected with CCR5 tropic

HIV-1 (A4001026) and treatment experienced patients infected with CCR5-tropic HIV-1 (A4001027 and A4001028) and non CCR5-tropic HIV-1 (A4001029). To ensure the safety of study participants a Data Safety Monitoring Committee (DSMB) was formed to oversee all the studies in the maraviroc Phase 2b/3 clinical development programme.

The pre-specified 24-Week interim analyses for the two independent, double-blind, randomised, placebo-controlled Phase 3 registrational trials (A4001027 and A4001028) evaluating maraviroc 300mg QD and BID dose equivalents) provide the efficacy and safety data for treatment-experienced patients infected with CCR5 tropic HIV-1 and form the basis of this application, which is discussed in the following sections of this overview. The clinical study reports for Studies A4001027 and A4001028 are included in Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication. These two Phase 3 studies were identical in study design and only differed by overlapping geographic region (A4001027 was conducted exclusively in North America and A4001028 was conducted in Europe, Australia and North America). Over 1,000 patients in total were treated in these 2 studies. The study design and description of patient populations are described in detail in Section 2.7.3.1.4 Module 2.7.3 Summary of Clinical Efficacy.

Study A4001029 was designed as a safety study to assess the use of maraviroc (300 mg QD and BID dose equivalents) in 186 patients infected with dual/mixed-tropic, CXCR4-tropic or non-phenotypable HIV-1. This study was conducted primarily to provide assurance that maraviroc would not cause virologic or immunologic harm in this population when given in combination with OBT. This study is now completed and patients who were still responding to maraviroc QD or BID were offered open label maraviroc BID and remain in study. The A4001029 clinical study report is included in Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication.

Study A4001026 is an ongoing study in 917 treatment-naïve patients infected with CCR5 tropic HIV-1. An interim analysis of this study was evaluated by the DSMB when 205 patients had been treated with blinded therapy (maraviroc 300 mg QD, 300 mg BID or efavirenz 600 mg QD) in combination with zidovudine/lamivudine for 16 weeks. The DSMB recommended discontinuation of the maraviroc 300 mg QD treatment group as it failed to meet pre-specified statistical endpoints compared with the efavirenz treatment group. On the recommendation of the DSMB, patients who had been responding to the maraviroc QD regimen were offered treatment with maraviroc 300 mg BID in an unblinded manner. The remaining maraviroc BID and efavirenz QD treatment groups remain blinded to the Applicant. Efficacy assessments for this study are not compared with the registrational studies in treatment-experienced patients. This study, if positive, will form the basis of a later supplemental filing for the treatment of treatment-naïve patients infected with CCR5 tropic HIV-1. Efficacy data from the unblinded maraviroc QD treatment group is presented in Section 2.7.3.1.3 Module 2.7.3 Summary of Clinical Efficacy and safety data for the unblinded patients are provided in an abbreviated clinical study report (A4001026 Module 5.3.5.4 Other Study Reports).

2.5.1.2.2. Ongoing or Planned Studies of Maraviroc

The ongoing and planned studies of maraviroc are presented in Table 1 below.

Table 1. Ongoing and Planned Studies of Maraviroc

Study	Comment
Ongoing Studies	
A4001027 and A4001028 Phase 3 Studies	These registrational studies, on which the safety and efficacy for this submission were based, are currently ongoing until the 48 week study end when patients and Investigators will be unblinded to treatment. The completed 48 week analyses should be available approximately 3Q 20[redacted]
A4001026 Phase 3 Study in Treatment-Naïve Patients Infected with CCR5 HIV-1	A4001026 is an ongoing Phase 3 study to determine the safety and efficacy of maraviroc 300 mg BID versus efavirenz 600 mg QD, both combined with zidovudine/lamivudine, in treatment-naïve patients infected with CCR5 tropic HIV-1. Following the Week 16 interim analysis conducted by the DSMB this study is ongoing to a formal statistical analysis at 48 weeks to which the Applicant (but not the patients or Investigators) will be unblinded and will be continued out to 96 weeks study end.
Hepatic Impairment Study (A4001023)	A study of maraviroc use in subjects with hepatic impairment is currently ongoing, but is not complete at the time of this submission and therefore is not included.
TMC-114 (Darunavir) Drug-drug Interaction Study (A4001052)	This Phase 1 drug-drug interaction study is designed to investigate the effect of TMC-114 (darunavir) on maraviroc pharmacokinetics. Darunavir was an investigational drug during the development programme of maraviroc and was only approved by the FDA in June 20[redacted]
UK-453,061 Drug-drug Interaction Study (A5271018)	This Phase 1 drug-drug interaction study is designed to investigate the effect of a Pfizer investigational NNRTI agent, UK-453,061, on maraviroc pharmacokinetics.
Planned Studies	
Expanded Access Programme (A4001050)	Following this submission, an expanded access programme for the use of maraviroc will be available for treatment-experienced patients infected with CCR5 tropic HIV-1. This EAP study will be available multi-nationally and provision is available to recruit up to 6000 patients. The inclusion/exclusion criteria will be similar to the proposed label. Maraviroc will be administered as 300 mg dose equivalent BID, with a dose adjustment to 150 mg in the presence of CYP3A4 inhibitors and 600 mg in the presence of CYP3A4 inducers without an inhibitor.
TMC-125 (Etravirine) Drug-drug Interaction Study (A4001041)	This planned Phase 1 drug-drug interaction study is designed to investigate the effect of multiple oral doses of etravirine (TMC-125), and the combination of etravirine and darunavir/ritonavir (TMC-114/r) on maraviroc pharmacokinetics.
Maraviroc Genital Secretion Study (A4001059)	This planned Phase 1 study is designed to investigate the extent of maraviroc exposure in blood, cervicovaginal fluid and vaginal tissue and to investigate the CCR5 receptor saturation in cervicovaginal mononuclear cells and peripheral blood mononuclear cells following single and multiple maraviroc dosing.
Paediatric Study (A4001030)	At the present time maraviroc has not been studied in patients below the age of 16 years. A paediatric study is planned for commencement in 3Q 20[redacted]

2.5.1.3. Critical Elements of the Design, Conduct and Analysis of the Clinical Studies

The two Phase 3 studies were designed in accordance with the FDA Guidance for Industry Antiretroviral Drugs using Plasma HIV RNA Measurements – Clinical Considerations for Accelerated and Traditional Approval, October 2002 and the CHMP Guideline on the Clinical Development of Medicinal Products for the Treatment of HIV Infection, November 2005. The United States FDA and European agencies (the French Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSAPS) and Swedish Medical Products Agency

(MPA) were consulted and agreed with the design of the Phase 3 studies at meetings held between the Applicant and the agencies in 2004.

The eligibility criteria and add-on to optimised therapy design for these studies were similar to those of the registrational studies for the approval of enfuvirtide, the only currently marketed HIV-1 entry inhibitor (TORO-1 and TORO-2) (Lalezari JP, 2003, Lazzarin A, 2003). However, taking into consideration the US and EU guidance for the development of drugs for the treatment of HIV-1, the maraviroc studies were conducted in a double-blind manner to limit treatment bias, whereas the enfuvirtide studies were open label, as it was administered as a twice daily injection. In addition, noting that dose selection for Phase 3 studies in this therapeutic area is difficult, both QD and BID maraviroc dosing regimens were studied. The maraviroc studies conducted in treatment-experienced patients were placebo-controlled and did not include an active treatment comparator arm. The major reason for this was that patients were failing therapy and were resistant to a variety of currently available antiretroviral agents, which made the choice of a single comparator agent impossible. However, all patients were administered blinded study drug in combination with an optimised regimen, consisting of 3-6 antiretroviral agents (not including low-dose ritonavir), which were chosen by the Investigator on the basis of genotypic and phenotypic susceptibility of the virus to currently available antiretroviral agents (including enfuvirtide), patient treatment history and safety/tolerability considerations. Each patient was therefore provided with a background treatment regimen that was personally optimised to provide the maximum treatment benefit for that patient irrespective of the blinded study drug received. These regimens were reviewed by the Applicant's medical monitors on an ongoing basis. These choices were made by the Investigator prior to randomisation of study drug. Therefore, any potential bias between treatment groups for choice of OBT was very limited. Further support for this is provided by the efficacy observed in the placebo (OBT alone) treatment group of the maraviroc Phase 3 studies, which was comparable or greater than that observed in other registrational studies for antiretroviral agents.

Maraviroc has met the regulatory definition for accelerated review from the FDA; (i) the disease studied is serious or life-threatening, (ii) plasma viral load measurements are an acceptable surrogate marker for demonstrating clinical benefit, and (iii) all patients were treated with a patient-specific OBT chosen on the basis of virus susceptibility testing, irrespective of treatment group. As per the published guidance, maraviroc, in combination with OBT, has demonstrated clear efficacy over OBT alone and a safety profile that is comparable to that of the placebo treatment group at the Week 24 interim data analysis. Given the immediate unmet medical need that exists for a highly treatment-experienced patient population, the Applicant believes that the data provided in this application are adequate for accelerated review.

In the European Union, the European Guideline on the Procedure for accelerated assessment (EMEA/419127/05) adopted by CHMP July 2006 sets out the criteria for accelerated assessment. Maraviroc is a novel potentially first in class orally administered agent that has been shown to be safe and highly effective in a treatment-experienced patient population (as demonstrated by screening viral loads of approximately 4.86 $\log_{10}$ copies/mL, mean baseline CD4 cell count approximately 170 cells/μL and more than 70% of patients with two or fewer active antiretroviral agents, based on resistance testing). Importantly, approximately 45% of

patients receiving maraviroc were found to have a viral load <50 copies/ml (i.e., considered maximally suppressed), compared with just 23% on placebo (OBT alone), thus reducing the risk of resistance emergence and the risk of transmission of a multidrug resistant virus. Based on the novel therapeutic mechanism, the in vitro resistance profile and safety and efficacy data presented in this submission, the Applicant has provided justification for accelerated review.

Clinical studies have been conducted in multiple countries and regions in accordance with the principles of Good Clinical Practice (GCP) issued by the European Commission in 1991 and the Declaration of Helsinki (Hong Kong 1989 revisions), and with the local laws and regulations relevant to the use of new therapeutic agents in the country of conduct, such as United States (US) Food and Drug Administration (FDA) regulations for informed consent and protection of patients rights as described in 21 Code of Federal Regulations (CFR) 50, 56 and 312. These studies have also been approved by ethics/institutional review boards. Written informed consent was obtained from all subjects. All studies have undergone regular monitoring by the Applicant or appointed Contract Research Organizations including site visits to Investigators and regular telephone contact, with review of all serious adverse events reported. All clinical study reports of studies that started have been written to the standards of the ICH Guideline for Structure and Content of Clinical Study Reports (ICH-E3, November 1995) and have been reviewed extensively within Pfizer. The majority of Investigator sites participated in more than one of the clinical studies and 17 study sites (4 for A4001026, 5 for A4001027, 6 for A4001028 and 2 for A4001029) have been audited by the Applicant.

There are sections within the Table of Contents for the maraviroc CTD submission that do not contain documents. As per the guidance these sections contain not applicable statements. These sections are:

- Module 5.3.1.3 In Vitro – In Vivo Correlation Study Reports. This Section is Not Applicable for an immediate release dosage formulation and maraviroc is currently only available as an immediate release formulation.

- Module 5.3.3.2 Patient PK and Initial Tolerability Study Reports. The Phase 2a studies A4001007 and A4001015, which in part investigated patient pharmacokinetics and initial tolerability, are located in Section 5.3.4.2; Patient PD and PK/PD Study Reports. As the cross-reference statement is made in this section it is not populated with duplicate reports.

- Module 5.3.5.2 Study Reports of Uncontrolled Clinical Studies. This section is Not Applicable as there have been no uncontrolled clinical studies performed with maraviroc to support this Marketing Authorisation Application/New Drug Application submission.

- Module 5.3.6 Reports of Postmarketing Experience. This section is Not Applicable as this Marketing Authorisation Application/New Drug Application submission is for a new chemical entity that has not yet been marketed.

The following not applicable statement applies to the European CTD Marketing Authorisation Application (MAA) only, and not to the US New Drug Application (NDA) for which case reports forms will be supplied:

- Module 5.3.7 Case Report Forms and Individual Patient Listings. These are available on request and therefore no documents can be found in this section.

There were no substantive variances of the maraviroc Phase 3 clinical studies from the published guidance.

2.5.2. Overview of Biopharmaceutics

The maraviroc biopharmaceutic development programme consisted of 5 clinical studies; 1 study examined the absolute bioavailability, 1 study examined the relative bioavailability of the research tablet with a solution formulation, 1 study examined the bioequivalence of the commercial and research formulation of maraviroc and 2 studies examined the effects of food on the bioavailability of maraviroc. An additional 2 clinical studies provided supportive data regarding the effect of food.

Maraviroc has been developed as an oral tablet formulation, which is highly soluble at a physiological pH range of 1-7.5. As such, the solubility of maraviroc should not be affected by the concomitant use of stomach acid suppressing medications, which do not cause stomach pH to rise above 7 (Thomson ABR, 2006). Although in some early Phase 1 studies maraviroc was administered as an oral solution and an intravenous (IV) preparation, there are currently no plans to provide maraviroc in these dosage forms. A study of the oral research (2 x 150 mg) and commercial (1 x 300 mg) tablets demonstrated bioequivalence of these formulations at the therapeutic dose (A4001040, Module 5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports).

Phase 1 bioavailability studies using the research tablet demonstrated that the pharmacokinetics of maraviroc were not dose proportional over the unit dose range 50-600 mg. It was estimated that a doubling of the dose led to a 2.3-fold increase in mean AUC_{inf} over the dose range studied.

Phase 1 food effect studies have demonstrated that there is a dose dependent and time dependent effect of food when maraviroc is administered with a high fat meal, which was independent of dosage form. This food effect was confirmed in a Phase 1 study of the commercial tablet, which showed that food reduced the exposure of maraviroc 300 mg by 33% (Study A4001043, Module 5.3.3.4 Extrinsic Factor PK Study Reports), primarily by reduction of Cmax. The food effect of maraviroc was also assessed in a Phase 2a study, A4001015, to determine whether these effects translated into an effect on antiviral activity (Module 5.3.4.2 Patient PD and PK/PD Study Reports). The results of this study showed that there was little effect of food on the antiviral activity (change from baseline in viral load log_{10} copies/mL) of maraviroc, with a -0.103 (90% CI -0.390, 0.185) difference between maraviroc 150 mg fasted and fed treatment groups on Day 11. The high fat meal provided in these studies was consistent with that recommended by the FDA for food-effect

bioavailability studies (FDA Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies, December 2002).

Simulations (using pharmacokinetic-pharmacodynamic-viral dynamics model) projected that the maximum impact of taking maraviroc 300 mg QD or BID at the same time as a high fat meal every day would diminish response (proportion of subjects with a response of <400 $\log_{10}$ copies/mL) at 48 weeks by 7% and 4% respectively. Taken together with the magnitude of increase in maraviroc exposure when administered with concomitant antiretroviral agents that inhibit CYP3A4 (described in Section 2.5.3 below), the effect of food on exposure of maraviroc was believed to be negligible. No recommendation for food restriction was made in the Phase 2b/3 clinical programme.

A summary of the maraviroc biopharmaceutic studies is described in detail in Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods.

2.5.3. Overview of Clinical Pharmacology

There have been 28 Phase 1 studies completed in over 600 healthy volunteers and HIV-1 infected subjects. For 2 of the studies (A4001032, the paediatric formulation taste test study and A4001047, which studied the potential modified release preparation of maraviroc) only the safety data were reported, as the other endpoints were not applicable to this filing. The pharmacokinetics, metabolism, absolute bioavailability and maximum tolerated dose of maraviroc have been comprehensively evaluated in 7 studies. Thirteen drug-drug interaction studies have been performed, 10 evaluating the effects of other drugs on maraviroc and 3 studies evaluating the effect of maraviroc on other drugs. Two Phase 1 studies were conducted to evaluate the effect of food on maraviroc pharmacokinetics (discussed in Section 2.5.2 above), one study evaluated bioequivalence (also discussed in Section 2.5.2 above), and 2 studies were designed to evaluate specific safety concerns (QTc and haemodynamics). One further pharmacokinetic study evaluated the influence of race on maraviroc pharmacokinetics. There have been two Phase 2a dose ranging studies in asymptomatic patients infected with CCR5 tropic HIV-1, which provided pharmacokinetic-pharmacodynamic data including effects on plasma viral load. The results of these studies were used to select the doses for the Phase 2b/3 clinical programme. A summary of the maraviroc clinical pharmacology studies is described in detail in Module 2.7.2 Summary of Clinical Pharmacology Studies.

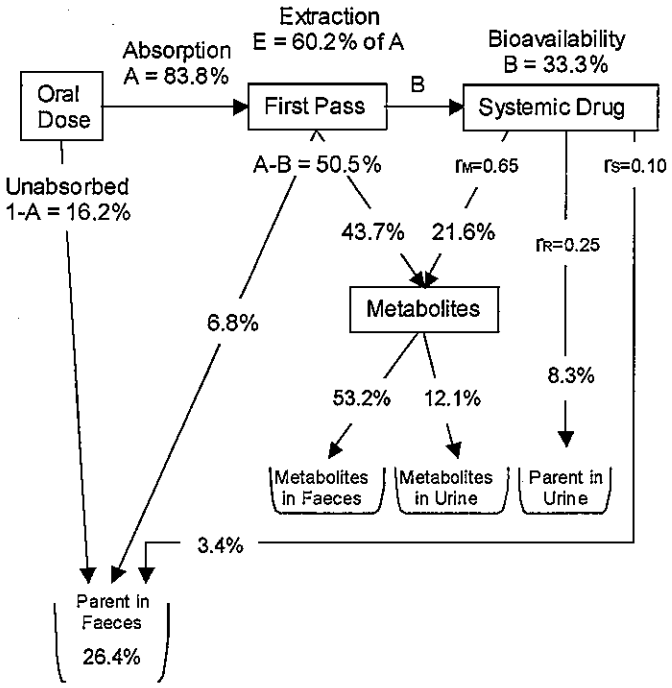
Pre-clinical evaluation has shown that maraviroc is a substrate of both CYP3A4 and P-glycoprotein (P-gp). Maraviroc was not shown to inhibit any of the 7 major cytochrome P450 enzymes at clinically relevant concentrations (IC50 > 30μM) in vitro. Protein binding in humans is estimated at 75%. In Phase 1 studies orally administered maraviroc demonstrates rapid absorption (Tmax 1-4h) and non proportional pharmacokinetics. Multiple dosing leads to limited accumulation at a 300 mg BID dose (the selected nominal dose, as discussed below) and steady state is observed within 7 days. Exposure increases supra-proportionately with increasing dose, and it is postulated that this may be due to saturation of Pgp with increasing maraviroc concentrations in the gut. Intravenous (IV) administration showed linear pharmacokinetics. Population pharmacokinetic modelling of oral tablet data across the Phase 1 programme estimated bioavailability in the typical

individual as 33% at a unit dose of 300 mg. The same model estimated bioavailability at a 100 mg unit dose to be 24% (the observed absolute bioavailability of a 100 mg dose from Study A4001009 was 23%). At unit doses of 600 mg and above, exposure was predicted to increase linearly with a bioavailability of 33% (Module 5.3.3.5; Population Pharmacokinetics of Maraviroc after Oral Tablet Administration – A Pooled Analysis of Phase 1/2a Data). The actual tissue distribution of maraviroc is not known in humans. In rats CNS penetration is modest (10%) but significant penetration is noted in gut associated lymphoid tissues (Section 2.4.3.3 Module 2.4 Non-Clinical Overview).

The population pharmacokinetic analysis for Phase 1/2a studies was also utilised to examine the effects of age, gender and race. Age and gender had no impact on exposure to maraviroc. However no volunteers were over the age of 65 and, as would be expected, few patients were over the age of 65 in the Phase 2b/3 trials. Therefore, presently it is unknown whether maraviroc pharmacokinetics would be different in elderly patients, but given its predominant hepatic metabolism, significant age effects would not be predicted. A number of the Phase 1 studies were conducted in Singapore, which therefore included a number of Asian subjects who received maraviroc. The pooled analysis predicted a slight increase in exposure in Asians (26.5%) (Module 5.3.3.5; Population Pharmacokinetics of Maraviroc after Oral Tablet Administration – A Pooled Analysis of Phase 1/2a Data). However a specific study conducted to evaluate the potential differences between studies conducted in Brussels (in Caucasians), versus Singapore studies showed no difference in pharmacokinetic parameters between Caucasians and Asians (Study A4001038 Module 5.3.3.3 Intrinsic Factor PK Study Reports). Pharmacokinetic data in black subjects in Phase 1 were limited but on inspection no differences were observed. Two Phase 2a studies demonstrated that the pharmacokinetics of maraviroc at a range of doses in HIV-1 infected patients not receiving highly active antiretroviral therapy (HAART) were similar to the pharmacokinetics in healthy volunteers (Module 5.3.3.5; Population Pharmacokinetics of Maraviroc after Oral Tablet Administration – A Pooled Analysis of Phase 1/2a Data).

Maraviroc metabolic fate has been evaluated in a mass balance Study A4001010 (Module 5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports). Unchanged maraviroc was the major plasma circulating component (42% of plasma radioactivity) and the metabolites UK-408,027 (22%), an amine analogue (11%) and UK-463,977 (5%) were also identified in the plasma. UK-408,027 and UK-463,977 have been evaluated in vitro against a range of 74 receptors, ion channels and enzymes and these metabolites are considered to be devoid of activity of any biological relevance. All human metabolites have been identified as circulating metabolites in one or more toxicology species tested (Sections 2.4.2.5.6 and 2.4.3.4.2, Module 2.4 Non clinical Overview). Figure 2 below utilises data from Study A4001010 and the IV bioavailability Study A4001009 (Module 5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports) to delineate relative importance of routes of excretion of maraviroc.

Figure 2. Routes of Excretion of Maraviroc (300 mg)



As renal clearance of maraviroc accounts for less than 25% of total clearance, a study of maraviroc pharmacokinetics in patients with renal impairment is not considered necessary. A study of maraviroc pharmacokinetics in patients with hepatic impairment is ongoing. Patients with liver enzyme elevations up to and including ACTG Grade 2 (up to 5 times the upper limit of normal for ALT and AST) have been enrolled in the Phase 2b/3 clinical programme, as have patients co-infected with hepatitis B and/or C. No safety issue has been noted in these patients, although numbers were limited (reviewed in Module 2.7.4 Summary of Clinical Safety). As the indication for maraviroc is for treatment experienced HIV-1 infected patients, who are in critical need of new therapies as they have few or no remaining treatment options left, the absence of data from a hepatic impairment study is not thought sufficient to preclude cautious administration of maraviroc to patients with known hepatic impairment in need of antiretroviral therapy.

The pharmacokinetic profile of maraviroc has been evaluated examining genetic polymorphisms in CYP3A4/5, CYP2B6 (reportedly associated with high plasma concentrations of efavirenz), MDR1 (P-gp) and BCRP1 (another efflux transporter). Overall, no clinically significant effects were found. Two MDR1 polymorphisms gave a trend to lower Cmax values (presented in the Pharmacogenomics Special Review Report, Module 5.3.5.3 Reports of Analyses of Data from More than One Study).

Dose escalation studies demonstrated that postural hypotension was the dose limiting adverse event (reviewed in detail in Section 2.7.4.2.1.5.1.2 Module 2.7.4 Summary of Clinical

Safety). This was seen at unit doses of 1200 mg in Study A4001001. The events were spontaneous, temporally associated with Cmax and resolved with supportive measures. Subsequent studies, including the Phase 2b/3 studies have included objective assessment of postural hypotension. These studies examined doses up to 300 mg BID for 28 days, 600 mg QD for 10 days and a dose titration study up to 14 days (7 days on a lower dose) to a maximum of 900 mg BID and 1200 mg QD. Single doses of 600 mg and 900 mg were also studied. At unit doses of 300 mg or less the incidence of postural hypotension was similar to placebo. Incidence rates at unit doses of 600 mg were approximately 10% and nearer 50% at 1200 mg. The event rates observed in Phase 1 studies conducted at the clinical pharmacology unit are likely to represent a worse case scenario. In almost all of these studies maraviroc was given in the fasted, caffeine-restricted state, with requirements to stand stationary for 2 minutes by a chair or bed prior to assessment of standing blood pressure. Only at 1200 mg unit doses were spontaneous cases of symptomatic postural hypotension usually observed and measured. It was concluded that the 300 mg unit dose was the maximum well tolerated dose and dose adjustments were planned to provide a 300 mg Cmax equivalent, as described below.

As maraviroc is a substrate for CYP3A4 and P-gp it is expected to be affected by drugs that inhibit or induce these pathways. Many drugs inhibit both, or induce both pathways, some drugs and some HAART combinations have both inhibitory and inducing characteristics on either or both pathways. Maraviroc pharmacokinetics in healthy volunteers were evaluated in combination with saquinavir +/- ritonavir, lopinavir/ritonavir*, atazanavir +/- ritonavir, tipranavir/ritonavir and ritonavir alone as a boosting dose. Ketoconazole was also studied as a reference CYP3A4 inhibitor. With the exception of tipranavir/ritonavir, which had no net effect, all other drugs caused an increase in maraviroc exposure with a range of AUC results increasing from 2.6 fold (ritonavir 100 mg BID) to 8.3-9.7 fold with saquinavir/ritonavir (2 studies). Atazanavir/ritonavir (4.9-fold), lopinavir/ritonavir* (3.8-4-fold in 2 studies) and atazanavir alone (3.6-fold) showed lesser effects than saquinavir/ritonavir. In all cases the Cmax increase was less notable, typical increases being less than half the increase seen in AUC. This is important as the dose limiting adverse events with maraviroc appear to be related to Cmax rather than AUC, and efficacy/potency appears to be driven by AUC/ average concentration (Cave), as described below. Dose adjustments of 0.5 (lopinavir/ritonavir*) and 0.25 (saquinavir/ritonavir) were explored and were found to under-correct for AUC (geometric mean ratios compared to unadjusted maraviroc 158% and 144% respectively) and over-correct for Cmax (geometric mean ratios compared to unadjusted maraviroc 53% and 61% respectively) (Study A4001013 Module 5.3.3.4 Extrinsic Factor PK Study Reports). The reason for saquinavir/ritonavir showing the greatest impact on maraviroc pharmacokinetics is unknown. The drug-drug interaction studies are described in detail in Section 2.7.2.2.6.2 Module 2.7.2 Summary of Clinical Pharmacology Studies.

Efavirenz and rifampicin are inducers of CYP3A4 and P-gp. The effect of both drugs on maraviroc pharmacokinetics was individually studied. They both reduced maraviroc exposure by 45% or more. Doubling the maraviroc dose restored exposure (AUC) to approximately 100%. Because of the prevalence of tuberculosis in HIV-1 infected patients rifampicin is often a desirable component of an anti- tuberculosis regimen, however its enzyme inducing effects make some concomitant HIV-1 medications difficult to use and not recommended (e.g., efavirenz). A simple doubling of maraviroc dosing corrects for the

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induction, therefore maraviroc may be particularly useful in HIV-1 patients co-infected with *Mycobacterium tuberculosis*.

The results of these drug-drug interaction studies in volunteers were then supported by single dose probe studies in patients receiving HAART regimens containing efavirenz, or certain PIs as anchor drugs, with NRTIs as backbone antiretroviral agents. Consistent results were seen compared with healthy volunteers. These single dose probe studies also evaluated maraviroc pharmacokinetics in patients receiving nevirapine, an NNRTI associated with hypersensitivity and hepatotoxicity, in subjects with higher CD4 counts and therefore not suitable to study in healthy volunteers. Unexpectedly, maraviroc pharmacokinetics were not affected by nevirapine (Study A4001017 Module 5.3.3.4 Extrinsic Factor PK Study Reports), which is reportedly an enzyme inducer and therefore expected to reduce maraviroc exposure. This is discussed further below.

Inducers and inhibitors are likely to be co-administered as part of HAART or other supporting treatments. The effect of efavirenz coadministered with saquinavir/ritonavir or lopinavir/ritonavir* on the pharmacokinetics of maraviroc was studied. Inhibition predominates with AUC of maraviroc still being 5 fold and 2.5 fold higher, respectively, than when maraviroc was dosed alone.

The NRTIs are predominantly excreted renally, however tenofovir has been shown to have the unexpected effect of reducing atazanavir exposure. A study evaluating tenofovir's impact on maraviroc pharmacokinetics showed no effect (Study A4001022 Module 5.3.3.4 Extrinsic Factor PK Study Reports). trimethoprim/sulfamethoxazole* affects renal tubular transport. As maraviroc is excreted to limited extent in the urine, a drug-drug interaction study was conducted which showed no significant effect (Study A4001018 Module 5.3.3.4 Extrinsic Factor PK Study Reports).

Maraviroc has also been evaluated for its effect on other drugs. As expected, it showed no effect on the oral contraceptive pill, no effect on zidovudine or lamivudine and no clinically relevant effect on midazolam which is a sensitive probe CYP3A4 substrate (geometric mean ratio of 118% for AUC).

The drug-drug interaction programme is comprehensive, covering most drug classes commonly used by HIV-1 infected patients, and facilitated dose adjustment strategies for the Phase 2b/3 studies utilising an optimised background design. The nominal unit dose was selected to be 300 mg QD or BID, adjusted downwards to 150 mg to correct for Cmax for all PIs (excepting tipranavir/ritonavir) and delavirdine, with efavirenz recommended to be given with a boosted PI. Within those studies sparse pharmacokinetic sampling was conducted and a population pharmacokinetic analysis was undertaken (with the first 500 patients recruited into Studies A4001027 and A400128 [398 received maraviroc] and all patients on maraviroc in Study A4001029 [124]). This analysis used a model originally developed to describe the rich pharmacokinetic maraviroc data in Phase 1/2a studies to estimate exposure in individuals. The impact of inducers and inhibitors of CYP3A4 (in the OBT or as additional concomitant medication) were examined for their influence on maraviroc exposure. Different PIs produced differential effects on maraviroc pharmacokinetics, the rank order of which is broadly consistent with the Phase 1 data. The rank order of median Cave from

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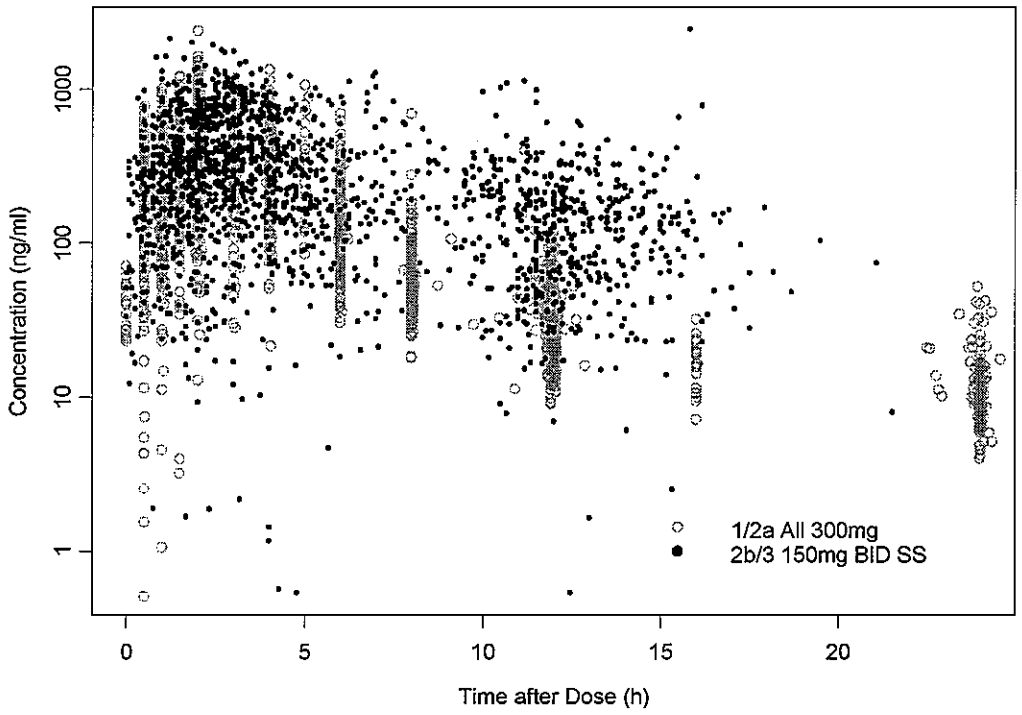
largest change (an approximate 6-fold increase relative to 150 mg maraviroc alone) to smallest (an approximate 2-fold increase relative to 150 mg maraviroc alone) was: saquinavir/ritonavir > lopinavir/ritonavir = indinavir/ritonavir > atazanavir/ritonavir > atazanavir > fosamprenavir. In this analysis atazanavir/ritonavir appeared to be no more than a moderate inhibitor of CYP3A4, as was fosamprenavir. This difference between patient data and the healthy volunteer study results is conjectured to be due to concomitant tenofovir use (due to its effects on atazanavir pharmacokinetics).

The most important aim of the dose adjustment of maraviroc in the presence of CYP3A4 inhibitors in the background OBT was to correct for Cmax. The figure below shows the observed plasma concentrations from the phase 2b/3 studies when maraviroc was given at 150 mg BID (with a CYP3A4 inhibitor) overlaid on the Phase 1/2a pharmacokinetic profiles following 300 mg single or multiple (QD or BID) maraviroc dosing (Figure 3). These data confirm the appropriateness of the dose correction in that there is just one observed concentration from the Phase 2b/3 studies above the range of the exposures seen in Phase 1/2a.

Figure 3. Maraviroc Concentrations of 150 mg BID Dose from Combined Phase 2b/3 Overlaid with all 300 mg Phase 1/2a Maraviroc Concentrations



Taken together, these data indicate that the maraviroc dose modification recommendations for the Phase 2b/3 clinical studies were successful in limiting Cmax so as not to significantly exceed a 300 mg dose equivalent (in the absence of metabolic inhibitors), while maintaining

an average plasma exposure that was at or above a 300 mg dose equivalent (median estimated increase over 300 mg of 1.56 fold for maraviroc QD and 1.73 for maraviroc BID).

In the same analysis a small number of patients were found to be receiving nevirapine in the absence of a boosted PI in combination with maraviroc 300 mg. These limited data suggest that nevirapine reduces maraviroc exposure, consistent with its reported induction effects. Given that the earlier results with nevirapine are only single dose maraviroc data in a small number of patients (n=8) and not consistent with expected outcome, it is considered that nevirapine should be considered an inducer of maraviroc metabolism and dose adjustments should follow those for efavirenz (see recommendations for dose selection in Section 2.5.5.5).

No drug-drug interaction programme can be exhaustive. During the Phase 2b/3 programme, 2 new HIV-1 drugs have been approved (tipranavir and darunavir) and 2 more drugs have entered expanded access programmes (MK 0518 and TMC-125). The drug-drug interaction programme with maraviroc is considered sufficient to develop appropriate labelling for use and has neglected no important areas. Maraviroc has no clinically relevant effect on a recognized sensitive CYP3A4 probe, midazolam, and therefore is considered very unlikely to affect the pharmacokinetics of other drugs metabolised via this route, including methadone. No pure P-gp inhibitor has been studied, but it is predicted that complete inhibition of P-gp alone could not increase maraviroc exposure by more than approximately 30% at 300 mg, which would be clinically irrelevant (based on the mass balance for 300 mg above (Figure 2) and assuming that P-gp is solely responsible for the incomplete absorption). Some studies utilised maraviroc 100 mg BID, as this was initially thought to be the appropriate dose, but later studies used 300 mg BID. The lopinavir/ritonavir* drug-drug interaction studies were conducted with both dose regimens and showed consistent results. Finally, it should be noted that no effect was seen on the urinary 6β-hydroxycortisol/cortisol ratio at doses up to and including 600 mg QD, suggesting no induction of CYP3A4 in vivo, and no effect on the debrisoquine metabolic ratio in vivo at doses up to and including 300 mg BID, suggesting no inhibition of CYP2D6.

In addition, the available drug-drug-interaction data from the maraviroc programme provide evidence that there is no rationale for an interaction between maraviroc and other commonly co-administered agents, such as HMG-CoA reductase inhibitors (statins) and PDE5 inhibitors.

Maraviroc exerts its anti-retroviral effects by binding to CCR5, leading to an allosteric change in the receptor such that CCR5 tropic HIV-1 cannot recognise and bind to the receptor and enter the cell. In the clinic, antiviral effects were studied in classic 10 day monotherapy designs (Studies A4001007, A4001015). Viral load decline should reflect receptor occupancy and the rate of infected cell turnover. In practice, an experimental ex vivo CCR5 receptor occupancy assay was uninformative probably due to the high affinity and slow offset of maraviroc, with the conjectured high efficiency of the HIV-1 CCR5 interaction, such that high receptor occupancy was seen at low doses of maraviroc but HIV-1 viral load declines were modest. The biological assay deployed has an inherent variability of 10-20%, but it is thought just a few percent of unoccupied receptors will allow viral entry. HIV-1 viral load decline did, however, correlate to maraviroc dose and exposure (Cmax was

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less relevant than AUC). All maraviroc doses of 200 mg/day or more to the maximum dose studied of 300 mg BID, showed a mean maximal viral load decline of ≥1.6 $\log_{10}$ copies/mL following 10 days of therapy. Dose interval (QD or BID), and food (high fat meal BID) had no significant impact on mean viral load on Day 11.

The presence of CCR5 polymorphisms and impact on maraviroc efficacy was evaluated in these trials. Numbers of patients were limited but no significant effect was observed at the planned doses.

Preclinical evaluations of maraviroc had shown limited binding to other receptors, and where binding occurred there was little evidence of functional activity. However hypotension was seen in the dog and in the macaque toxicology studies. Maraviroc was shown to be a weak inhibitor of agonist binding to the α2a adrenergic receptor, but appears to have no functional activity at recombinant human adrenergic receptors. In general it has not been possible to find convincing reproducible in vitro evidence of a blood pressure effect mediated by α-adrenergic blockade, despite the similarity of the symptoms to those seen in early treatment with alpha blockers for hypertension. An alternative explanation has been sought, evaluating the effects of MIP-1β binding to CCR5 in human saphenous vein explants. MIP1β leads to contraction, which is then inhibited by maraviroc (Section 2.4.5.2 Module 2.4 Non-Clinical Overview). This may provide an alternative explanation for the symptoms seen. To further explore the impact of maraviroc on the cardiovascular system a non-invasive placebo and active controlled (GTN) haemodynamic study of 900 mg of maraviroc was conducted in healthy volunteers (Study A4001033 Module 5.3.4.1 Healthy Subject PD and PK/PD Study Reports). This showed an increase in cardiac index with maraviroc and a reduction in systemic vascular resistance and stroke index in the supine position, though supine blood pressure was not affected. The data was consistent with those expected of a mild vasodilator with a fully compensated haemodynamic response maintaining supine blood pressure. However postural hypotension was still observed in 3 of 16 subjects.

Maraviroc inhibits dofetilide IKr binding (14% at 10 fold 300 mg Cmax, and 43% at 30 fold Cmax). Maraviroc was also shown to prolong QTc in the dog (6 fold) and the macaque (12 fold). A thorough QTc study (A4001016) evaluating single doses of maraviroc up to 900 mg showed no clinically relevant effect on QTcI compared to placebo (upper 90% CI <7 msec at 900 mg, equating to 2 fold 300 mg Cmax). A multiple dose study was not considered necessary because of the limited accumulation of maraviroc on multiple dosing. The effects of maraviroc on QTc interval is discussed further in Section 2.5.5.4.1.

As maraviroc binds to CCR5 and prevents ligand binding and signaling, there is a theoretical risk of an effect on immune function. A macaque immuno-toxicology study showed no effects of maraviroc at supra-therapeutic concentrations. Exploratory immunophenotyping was conducted in several Phase 1 studies and showed no adverse effects, neither was there any evidence of excess infections. An evaluation of these findings in relation to the Phase 2b/3 clinical programme is discussed in Section 2.5.5.4.3.

In conclusion, the clinical pharmacology of maraviroc has been studied to provide optimal information used for dosing guidance both in clinical studies and for HIV physicians. Theoretical and observed risks have been thoroughly explored and explanations sought. The

dose selected and the dose adjustment deployed in the Phase 2b/3 clinical trials achieved the intended maraviroc exposures and optimises efficacy and tolerability. The only revision to the intended dose regimens, based on pharmacokinetic data from the Phase 2b/3 studies, is to recommend that nevirapine (and efavirenz) should be considered an enzyme inducer. Hence, if either agent is coadministered with maraviroc in a regimen that does not include a potent CYP3A4 inhibitor (including PIs, except tipranavir/ritonavir) the dose of maraviroc should be doubled.

Table 2 summarises the strategy in the Phase 2b/3 clinical trials. The product labeling strategy considering the dose adjustments following evaluation of the data from the clinical trials is discussed in Section 2.5.5.5.

Table 2. Recommended Dose Used in the Maraviroc Phase 2b/3 Clinical Programme

Concomitant Antiretrovirals	Recommended Maraviroc Dose
≥1 PI (other than tipranavir) and/or delavirdine	150 mg
All other regimens[a]	300 mg

[a] including tipranavir/ritonavir.
Efavirenz recommended to be given with a boosting PI.

2.5.4. Overview of Efficacy

Two randomised, double-blind, placebo-controlled Phase 3 superiority studies (A4001027 and A4001028) were conducted to support this application for maraviroc in the management of treatment-experienced patients infected with CCR5 tropic HIV-1. The study designs were identical for both studies and the patient populations were similar (Section 2.7.3.1.4 Module 2.7.3 Summary of Clinical Efficacy). One additional Phase 2b supportive study (A4001029) was conducted to provide safety and efficacy data for the use of maraviroc in treatment-experienced patients infected with non-CCR5 (dual/mixed tropic, CXCR4-tropic or non-phenotypable) HIV-1. The majority of patients recruited into this study were infected with dual/mixed tropic HIV-1.

The results of these individual studies and the combined analysis of Studies A4001027 and A4001028 are presented in Sections 2.7.3.2 and 2.7.3.3 Module 2.7.3 Summary of Clinical Efficacy.

2.5.4.1. Primary Endpoint Analysis

The change from baseline to Week 24 in HIV-1 RNA was analysed for Studies A4001027 and A4001028 using analysis of covariance (ANCOVA), including treatment and adjusting for the two randomisation strata (screening HIV-1 RNA <100,000 or ≥100,000 copies/mL and enfuvirtide use in OBT). Comparisons were made between each maraviroc treatment group and placebo and 97.5% confidence intervals (CI) were presented. For patients who discontinued for any reason (including treatment failure), missing values were imputed as the baseline value, leading to a change from baseline of zero.

The results for the primary endpoint analysis of Studies A4001027 and A4001028 were almost identical and therefore only a combined analysis is discussed in this overview. For

both individual studies the 2-sided 97.5% CIs were completely to the left side of zero, excluding zero, indicating the superiority of both doses of maraviroc compared with placebo.

The primary efficacy endpoint analysis for the combined studies is presented in Table 3. The mean reduction in HIV-1 RNA from baseline to Week 24 was -1.876 and -1.960 for maraviroc QD and BID, respectively, versus -0.987 $\log_{10}$ copies/mL for placebo. In addition, the upper bound of the 97.5% confidence intervals was to the left of 0.5 $\log_{10}$ copies/mL. A reduction in viral load of $\geq$0.5 $\log_{10}$ copies is recognised as clinically significant demonstrating that both doses of maraviroc provided overwhelming efficacy over placebo (OBT alone).

Table 3. Statistical Analysis of Change from Baseline to Week 24 in $\log_{10}$ HIV-1 RNA (Combined Studies A4001027 and A4001028)

Treatment Group		Change from Baseline to Week 24 in HIV-1 RNA ($\log_{10}$ copies/mL)			Treatment difference Maraviroc-Placebo	
	N	Raw Median	Raw Mean (se)	Adjusted Mean (se)	Estimate (se)	97.5% CI
Maraviroc QD	414	-2.274	-1.868 (0.069)	-1.876 (0.069)	-0.888 (0.118)	(-1.153, -0.623)
Maraviroc BID	426	-2.424	-1.957 (0.069)	-1.960 (0.068)	-0.973 (0.118)	(-1.237, -0.709)
Placebo	209	0.000	-0.987 (0.091)	-0.987 (0.097)	N/C	N/C

Source: Table 13.4.6.1.2 Summary of Clinical Efficacy.
Missing values have been imputed as the baseline value for subjects who discontinued from blinded therapy.
CI = Confidence interval; N/C = Not calculated; se = Standard error.

While the individual studies were not designed to formally test a hypothesis of a treatment difference between maraviroc QD and maraviroc BID, a non-inferiority analysis was planned on the combined data from both studies. This analysis was conducted as planned. The treatment difference was -0.085 $\log_{10}$ copies/mL and the 95% CI included zero and the lower bound was above -0.3 $\log_{10}$ copies/mL (the pre-defined non-inferiority margin) suggesting non-inferiority of the QD maraviroc treatment group to BID.

2.5.4.2. Secondary Endpoint Analyses

A number of secondary endpoints were analysed for Studies A4001027 and A4001028, which were replicated for the combined analysis. As for the primary endpoint, for both studies and the combined analysis, both doses of maraviroc demonstrated clear superior efficacy over placebo. The results of secondary endpoints for the combined study analysis are presented in Table 4.

Table 4. Summary of Selected Secondary Endpoints at Week 24 (Combined Studies A4001027 and A4001028)

	Maraviroc QD (N= 414)	Maraviroc BID (N= 426)	Placebo (N= 209)
% Patients HIV-1 RNA <50 copies/mL	44.0	45.3	23.0
% Patients HIV-1 RNA <400 copies/mL	55.1	61.0	27.8
% Patients with ≥1.0 $\log_{10}$ Reduction in Viral Load	65.7	69.2.	35.9
% Patients with ≥0.5 $\log_{10}$ Reduction in Viral Load	69.3	71.1	41.6
Mean Δ in CD4 Cell Count from Baseline	+ 108.6	+ 106.3	+ 57.4

Source: Tables 13.4.6.5.1, 13.4.6.3.1, 13.4.6.7, 13.4.6.9, 13.4.6.11 Summary of Clinical Efficacy.
QD = Once daily dosing; BID = Twice daily daily dosing.

2.5.4.3. Subpopulation Analyses

For all the subpopulation analyses conducted on the primary and selected secondary endpoints for Studies A4001027 and A4001028, both doses of maraviroc demonstrated superiority over placebo. In addition, there was no impact on the magnitude of response of treatment for age, gender, geographic region, clade, CCR5 Δ32 genotype or CCR5 promoter haplotype even though numbers of patients in these subgroups were too small to draw any definite conclusions. These results are presented in the A4001027 and A4001028 Clinical Study Reports (Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication) and Section 2.7.3.4 Module 2.7.4 Summary of Clinical Efficacy. Other selected subgroup analyses are discussed below.

Screening HIV-1 RNA:

Screening HIV-1 RNA was incorporated as a stratification factor for randomisation to ensure the proportion of patients with high and low viral loads were the same in each treatment group, as it is accepted that patients with high viral loads are at greater risk of virologic failure as they may take longer to achieve virus suppression.

There was no apparent difference in the primary efficacy endpoint for patients receiving either dose of maraviroc who had high (≥100,000 copies/mL) and low (<100,000 copies/mL) viral loads and both doses of maraviroc demonstrated superiority over placebo and there was no apparent difference between treatment groups. Patients with a low viral load who received placebo treatment, however, appeared to have a small benefit over those with high viral loads (Table 5).

Table 5. Summary of selected virologic endpoints by HIV-1 RNA Level at Screening (Combined Studies A4001027 and A4001028)

HIV-1 RNA at Screening (copies/mL)	Virologic Endpoint	Maraviroc QD (N= 414)[a]	Maraviroc BID (N= 426)[a]	Placebo (N= 209)[a]
<100,000	N[b]	238	243	123
	Mean change from baseline in HIV-1 RNA (log_{10} copies/mL)	-2.067	-2.129	-1.247
	% Patients HIV-1 RNA <50 copies/mL	61.3	57.6	34.2
	% Patients HIV-1 RNA <400 copies/mL	72.3	74.9	40.7
	Mean Δ in CD4 Cell Count from Baseline (cells/μL)	94.8	99.8	58.6
≥100,000	N[b]	170	176	84
	Mean change from baseline in HIV-1 RNA ((log_{10} copies/mL))	-2.127	-2.197	-1.032
	% Patients HIV-1 RNA <50 copies/mL	28.2	34.7	10.7
	% Patients HIV-1 RNA <400 copies/mL	44.7	51.7	15.5
	Mean Δ in CD4 Cell Count from Baseline (cells/μL)	128.3	114.1	53.5

Source: Tables 13.4.9.1.1, 13.4.9.3.1, 13.4.9.2.1 and 13.4.9.4.1 Summary of Clinical Efficacy.
[a] Number of patients in the treatment group
[b] Number of patients contributing to the summary statistics for the primary endpoint.
Last Observation Carried Forward (LOCF) was used to impute missing values.
QD = Once daily dosing; BID = Twice daily dosing

As expected, for the secondary endpoints of proportion of patients achieving an HIV-1 RNA <50 and <400 copies/mL, there was a greater response in patients with a screening viral load of <100,000 copies/mL, irrespective of treatment group. For patients receiving maraviroc with a screening HIV-1 RNA of ≥100,000 copies/mL more of those in the maraviroc BID treatment group achieved an HIV-1 RNA of <50 copies/mL compared with maraviroc QD (34.7% versus 28.2%). A similar result was obtained for patients achieving an HIV-1 RNA <400 copies/ mL (51.7% versus 44.7%, respectively).

For both doses of maraviroc, patients with a screening HIV-1 RNA of ≥100,000 copies/mL receiving both doses of maraviroc had a greater increase from baseline in CD4 cell count than patients with a screening HIV-1 RNA of <100,000 copies/mL. This result is not unexpected, as patients with a high viral load are more likely to have a corresponding low CD4 cell count and the increase from baseline in response to treatment is proportionately greater in those patients. There was no difference in response between maraviroc treatment groups. Patients receiving placebo had a much lower increase in CD4 cell count, which was independent of screening viral load.

Baseline CD4 Cell Count:

Primary and selected secondary efficacy endpoints were analysed for the combined A4001027 and A4001028 results by CD4 cell count at baseline in order to assess any differences in the response to treatment, as lower CD4 cell counts are often associated with more advanced disease. Patients' CD4 cell counts were divided into strata of <50, 50-100,

101-200, 201-350 and >350 cells/μL. The superiority of both doses of maraviroc over placebo for the primary endpoint analysis, change in HIV-1 RNA from baseline, remained apparent across all baseline CD4 cell count strata. As expected, the reduction in viral load from baseline was less for patients with a baseline CD4 cell count of <50 cells/μL irrespective of treatment group. For these patients however, maraviroc still appeared to provide substantial benefit over placebo (mean reduction in viral load was -1.311 and -1.351 $\log_{10}$ copies/mL for maraviroc QD and BID versus -0.632 $\log_{10}$ copies/mL for placebo). For all other patient subgroups with baseline CD4 cell count >50 cells/μL the reduction in viral load from baseline was consistently better than for placebo. There was no clinically relevant difference between maraviroc QD and BID treatment groups.

This pattern was repeated for each of the secondary endpoints analysed. However, for patients with a baseline CD4 cell count <50 cells/μL there were approximately twice as many patients achieving an HIV-1 RNA <50 and <400 copies/mL in the maraviroc BID treatment group compared with patients receiving maraviroc QD (for HIV-1 RNA <50 copies/mL 20.0% versus 10.6% and for HIV-1 RNA <400 copies/mL 30.6% versus 20.0% in the maraviroc BID and QD groups, respectively). Evaluation of endpoints for all other baseline CD4 cell count strata demonstrated no difference between the maraviroc treatment groups.

Overall Sensitivity Score:

Phenotypic and genotypic resistance to PIs, NRTIs and NNRTIs were evaluated using the Monogram Biosciences PhenoSense™ GT (PSGT) assay at screening. Genotypic resistance to enfuvirtide was determined using gp41 sequencing and identification of specific mutations in the HR1 domain at screening. These results were used to calculate the genotypic, phenotypic and overall susceptibility scores (GSS, PSS and OSS) for each patient in order to estimate the activity of OBT in each patient. OSS is a composite score that takes into account both genotypic and in vitro phenotypic susceptibility of the virus to each component of the OBT regimen. OSS uses a proprietary algorithm to assess the likely susceptibility of the virus to any component of the OBT where the phenotypic and genotypic test results are discordant (shown on the PhenoSense™ GT test report as the "Net Assessment"). Details of these scores are presented in Section 2.7.3.1.5.3 Module 2.7.3 Summary of Clinical Efficacy. More than two thirds of the patients enrolled into Studies A4001027 and A4001028 had an OSS of ≤2, which is consistent with the study design and enrollment criteria and confirms that these were treatment-experienced patients with few remaining treatment options.

Primary and secondary endpoints were evaluated split by GSS, PSS and OSS of 0, 1, 2, and ≥3 at baseline. A treatment benefit for maraviroc for all endpoints was observed for each OSS group. In patients with an OSS of ≥3, the mean reduction in HIV-1 RNA from baseline to Week 24 was -2.594, -2.592 and -2.307 $\log_{10}$ copies/mL for maraviroc QD, BID and placebo respectively, suggesting a dilution of treatment effect due to susceptibility to multiple drugs in the OBT. This is not an unexpected result as studies of three versus four antiretroviral drug regimens in treatment naïve patients have shown no apparent benefit by adding a fourth drug (Gulick RM, 2006), while studies in treatment-experienced patients have shown inconsistent results (Fischl MA, 2003). Patients with an OSS of 0 appeared to respond better to treatment with maraviroc BID than QD as demonstrated by a greater proportion of patients achieving an HIV-1 RNA of <50 and <400 copies/mL (for HIV-1

RNA <50 copies/mL 28.6% versus 17.7% and for HIV-1 RNA <400 copies/mL 41.1% versus 25.5% in the maraviroc BID and QD groups, respectively). No apparent difference between the maraviroc treatment arms was seen for any of the other OSS strata.

Similar results were obtained when assessing the individual GSS and PSS. As GSS not OSS are more commonly used in the European Union, the EU Summary of Product Characteristics (SPC) reflects the GSS values rather than OSS. The analyses of GSS and PSS are presented in detail in Section 2.7.3.4.10 Module 2.7.3 Summary of Clinical Efficacy.

Enfuvirtide Use in OBT:

Enfuvirtide use in OBT was one of the stratification factors incorporated into randomisation. The rationale for this was to ensure a balance of enfuvirtide use between treatment groups given the demonstrated efficacy of enfuvirtide in this treatment-experienced patient population (Lalezari JP, 2003, Lazzarin A, 2003).

Just over 40% of the patients in the Full Analysis Set for Studies A4001027 and A4001028 received enfuvirtide as part of their OBT. Response to treatment in each of the treatment groups was consistent irrespective of enfuvirtide usage. In addition, both maraviroc treatment groups maintained superiority over placebo with and without concomitant enfuvirtide treatment.

The data have not revealed any evidence of an in vivo synergy between two different HIV-1 entry inhibitors, as has been reported in vitro with another CCR5 antagonist (Tremblay CL, 2002). This analysis did not take into account previous use of enfuvirtide or baseline resistance to enfuvirtide in patients using enfuvirtide as part of their OBT, therefore synergy, in a subset of these patients, cannot be completely excluded by this analysis. Importantly, the results of these two placebo-controlled studies in which enfuvirtide treatment was incorporated as a stratification factor for randomization confirm that maraviroc has clinical efficacy, both in patients who receive enfuvirtide as part of their OBT and those that do not.

Protease Inhibitors and/or Delavirdine Use in OBT:

Approximately 80% of patients enrolled into Studies A4001027 and A4001028 were receiving a PI and/or delavirdine in their OBT and therefore received a dose adjustment of maraviroc to 150 mg QD or BID (except for those on tipranavir/ritonavir who received 300mg QD or BID). There was no difference in reduction in viral load from baseline for patients receiving a 150 mg dose of maraviroc for any of the treatment groups, compared with those receiving a 300 mg dose, and both doses of maraviroc demonstrated superior efficacy over placebo.

Subgroup analyses examining the efficacy of maraviroc in the presence or absence of any PI, and the presence or absence of tipranavir/ritonavir (a late introduction to OBT), demonstrated a consistent treatment benefit for maraviroc over placebo in subgroups. The magnitude of treatment differences from placebo was consistent and no notable differences were observed between maraviroc QD or BID (Table 6).

Table 6. Summary of Change in HIV-1 RNA from Baseline to Week 24 Split by Protease Inhibitor, Tipranavir and Delavirdine use in OBT (Combined Studies A4001027 and A4001028)

		Change in HIV-1 RNA from Baseline (log_{10} copies/mL)		
		Maraviroc QD (N= 414)[a]	Maraviroc BID (N= 426)[a]	Placebo (N= 209)[a]
PI[b] and/or Delavirdine in OBT				
Yes	N[c]	316	329	169
	Mean	-2.100	-2.169	-1.191
No	N[c]	92	90	38
	Mean	-2.065	-2.118	-1.021
PI[d] in OBT				
Yes	N[c]	373	385	193
	Mean	-2.102	-2.163	-1.174
No	N[c]	35	34	14
	Mean	-1.988	-2.098	-0.959
Tipranavir in OBT				
Yes	N[c]	65	62	29
	Mean	-2.137	-2.143	-0.985
No	N[c]	343	357	178
	Mean	-2.084	-2.160	-1.188

Source: Tables 13.4.9.1.11, 15.1.3 and 15.1.4 Summary of Clinical Efficacy.
[a] Number of patients in treatment group.
[b] Any protease inhibitor except for tipranavir/ritonavir.
[c] Number of patients contributing to summary statistics.
[d] Includes Tipranavir/ritonavir
Last Observation Carried Forward (LOCF) was used to impute missing values.
QD = Once daily dosing; BID = Twice daily dosing

Efficacy in Subgroups Based on Race:

The majority of patients participating in Studies A4001027 and A4001028 were white (83.6%); 14.0% were black, 0.9% Asian and 1.4% were designated other (one patient was unspecified). The summary of change from baseline in viral load at Week 24 by race indicated that the black placebo subgroup had an unusually high mean change from baseline (-1.515 log_{10} copies/mL) compared with the white placebo subgroup (-1.132 log_{10} copies/mL). This may be explained by the small number of patients in the black placebo subgroup (N= 25) and also by the skewed nature of the data in the black placebo treatment group towards higher decreases in viral load (10 of the 25 subjects in the placebo treatment group had a decrease in viral load >2.0 log_{10} copies/mL).

Table 7 presents the mean and median change from baseline to Week 24 in HIV-1 RNA for white and black patients in Studies A4001027 and A4001028.

Table 7. Summary of Change from Baseline to Week 24 in HIV-1 RNA for White and Black Patients (Combined Studies A4001027 and A4001028)

Patient Population		Change in HIV-1 RNA from Baseline to Week 24 (log_{10} copies/mL) Maraviroc QD (N= 414)[a]	Maraviroc BID (N= 426)[a]	Placebo (N= 209)[a]
Total	N[b]	408	419	207
Population	Mean (SD)	-2.092 (1.272)	-2.158 (1.279)	-1.160 (1.293)
	Median (Range)	-2.385 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
White	N[b]	333	357	178
	Mean (SD)	-2.137 (1.249)	-2.212 (1.286)	-1.132 (1.283)
	Median (Range)	-2.437 (-4.492, 1.080)	-2.571 (-4.547, 1.317)	-0.537 (-4.148, 0.965)
Black	N[b]	67	50	25
	Mean (SD)	-1.799 (1.373)	-1.704 (1.193)	-1.515 (1.377)
	Median (Range)	-2.170 (-4.231, 2.039)	-1.858 (-3.890, 0.532)	-.801 (-3.519, 0.512)

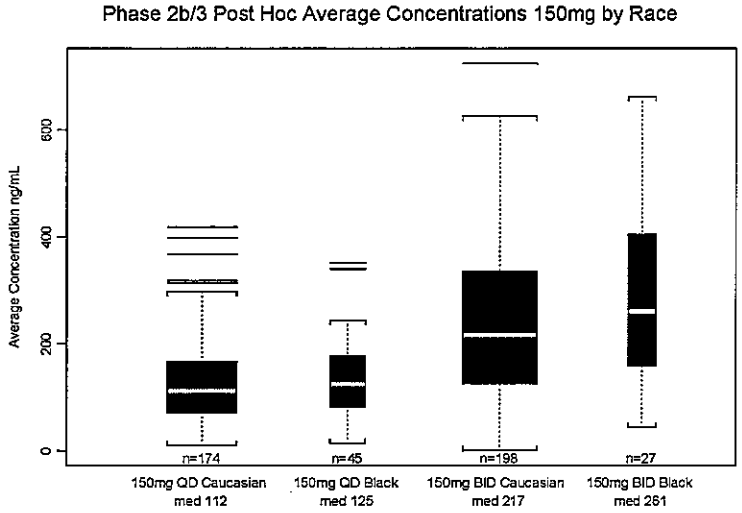
Source: Table 13.4.9.1.6 Summary of Clinical Efficacy.
[a] Number of patients in treatment group.
[b] Number of patients contributing to summary statistics, which includes patients with a valid baseline and Week 24 value.
Last Observation Carried Forward (LOCF) was used to impute missing values.
QD = Once daily dosing; BID – Twice daily dosing; SD = Standard deviation.

The difference in the mean and median results for the placebo treatment group at Week 24 in the black subgroup highlight the effect of the 10 patients with large decreases in viral load on the mean viral load reduction in this group.

For patients receiving maraviroc QD the mean viral load change from baseline to Week 24 for white patients was -2.137 log_{10} copies/mL compared with -1.799 log_{10} copies/mL for black patients. For patients receiving maraviroc BID the mean viral load change from baseline for white patients was -2.212 log_{10} copies/mL and -1.704 log_{10} copies/mL for black patients. The range of change from baseline to Week 24 for all 4 racial designation groups (white, black, Asian and other) was similar.

There was a potential concern that black patients may have a lower exposure to maraviroc than other racial designations. Although numbers of black patients in Studies A4001027, A4001028 and A4001029 were small, an exploratory post-hoc analysis of the population pharmacokinetic data of black versus white patients demonstrated that exposure to maraviroc was similar for each of the maraviroc treatment groups. Figure 4 presents the average concentrations of maraviroc by race for those patients who received a dose adjustment of maraviroc to 150 mg. The same pattern is observed for those patients who received maraviroc at doses of 300 mg, although the numbers are smaller.

Figure 4. Analysis of Average Concentration of Maraviroc in Black and White Patients by Dose Regimen (Combined Studies A4001027, A4001028 and A4001029)



Black patients still derive a significant benefit from treatment with maraviroc in combination with OBT (mean change from baseline -1.799 and -1.704 $\log_{10}$ copies/mL for maraviroc QD and BID respectively), however, and as the numbers of black patients enrolled in these studies are very small no firm conclusions can be drawn from these results. Having excluded a pharmacokinetic reason for the limited response the Applicant concludes that the most likely rationale for these differences in response in black patients is due to small patient numbers with chance imbalances. The Applicant does not intend to provide specific dosing advice for black patients.

2.5.4.4. Treatment Failure and Discontinuations from Treatment

Time to Treatment Discontinuation and Failure:

There were approximately twice as many patients discontinuing blinded study drug in the placebo treatment group compared with both maraviroc treatment groups and the majority of these were due to treatment failure (Table 8).

Table 8. Patient Evaluation Groups (Combined Studies A4001027 and A4001028)

	Maraviroc QD	Maraviroc BID	Placebo
Number of Patients Treated, n (%)	414	426	209
Discontinuations (Total), n (%)	143 (34.5)	138 (32.4)	133 (63.6)
Discontinuations Due to Lack of Efficacy, n (%)	81 (19.6)	91 (21.4)	106 (50.7)
Ongoing at Date of Cut Off[a], n (%)	271 (65.5)	288 (67.6)	76 (36.4)

Source: Tables 3.1.2 and 3.1.4.1 Summary of Clinical Safety.
[a] Date of data cut off for this submission = 15th September 2[redacted]
QD = Once daily dosing; BID = Twice daily dosing.

The time to treatment discontinuation and failure were longer in the maraviroc QD and BID treatment groups compared with the placebo treatment group. There was no apparent difference between the maraviroc treatment groups. These results of these analyses are presented in Section 2.7.3.3.2.1 Module 2.7.3 Summary of Clinical Efficacy.

2.5.4.5. Impact of Changes in Tropism Result from CCR5 Tropic to CXCR4-Using or Dual/Mixed Tropic

As previously noted, HIV-1 strains are categorized as R5 (CCR5-tropic), X4 (CXCR4-tropic) or R5X4 (strains using both CCR5 and CXCR4; also referred to as 'dual-tropic') (Berger EA, 1998). A patient plasma sample may also contain a heterogeneous population of viruses with different tropism termed 'mixed tropism' (Figure 5 Panel A). CCR5 antagonists inhibit only strains which are obligate users of CCR5, while X4 and R5X4 strains ("CXCR4-using") can infect cells in the presence or absence of a CCR5-specific antagonist.

There is a complex association between HIV-1 co-receptor tropism, transmission and pathogenesis which is not yet fully understood (Moore JP, 2004, Philpott, 2003). Throughout infection, the detection of R5 virus only is most common; dual/mixed-tropic virus is more likely to be detected in advanced patients than early asymptomatic patients, and the detection of X4 virus only is rare (Moyle GJ, 2005, Whitcomb JM, 2003). Although increasing prevalence of X4 virus and decreasing prevalence of R5 virus have been associated with increasing viral load and decreasing CD4 cell counts (Brumme ZL, 2005, Moyle GJ, 2005), the emergence of CXCR4-using virus is not a prerequisite for the development of AIDS. Whether emergence of CXCR4-using strains is a marker for disease progression rather than the cause is not known (Moore JP, 2004). It also remains to be determined whether the emergence of CXCR4-using strains during treatment with a CCR5 antagonist is associated with the same clinical outcome as when they emerge during the natural course of HIV-1 infection.

There are two possible mechanisms by which maraviroc could select for CXCR4-using virus. The first is by selection of a virus containing amino acid mutation(s) in the envelope glycoprotein, which confers a switch from CCR5 to CXCR4 usage. The second possible mechanism is by the relative expansion of a pre-existing, but previously undetectable, reservoir of CXCR4-using virus. Regarding this second mechanism, it is expected that

maraviroc will selectively suppress R5 variants in a mixed virus population. This will result in a relative increase in the proportion of CXCR4-using virus (Figure 5, Panel B).

The emergence of CXCR4-using variants has been described in patients responding to HAART (Delobel P, 2005). In a further study, Hunt and colleagues (Hunt PW, 2006) demonstrated a high prevalence of CXCR4-using virus among treated patients with detectable viremia. Hence, emergence of CXCR4-using variants is likely to occur over time in some patients receiving HAART regimens. It is, therefore, important to understand the net effect of maraviroc added to, or as part of a HAART regimen, on the emergence of CXCR4-using variants.

Figure 5. Relationship Between Viral Composition of Pure/Mixed Virus Populations

Panel A **Panel B**

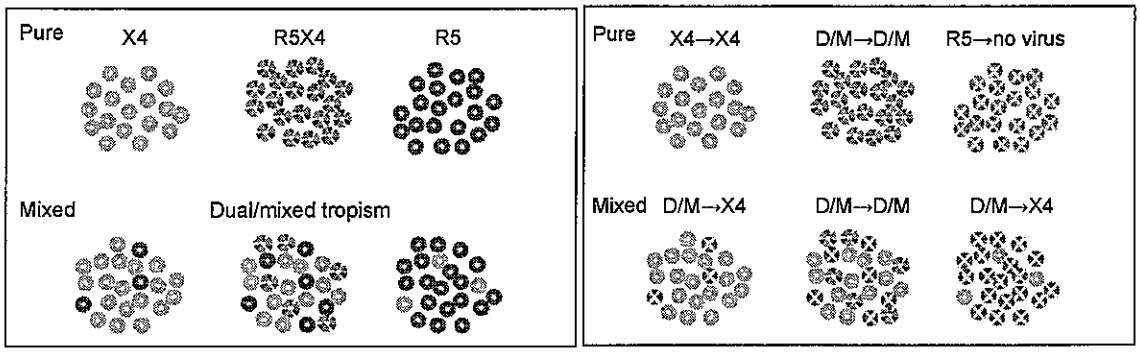


Figure legend. Within a patient, the circulating virus population is composed of various mixtures of closely related but genetically distinct viruses ("quasispecies"). These quasispecies may comprise a pure population that all share the same tropism (panel A, upper line). Alternatively, quasispecies with different tropisms may co-exist in a mixed population (panel A, lower line). Maraviroc selectively inhibits R5 viruses (shown as blue crosses in Panel B). Tropism assays that measure relative proportions of CXCR4-using and CCR5-using viruses may then report a different result in patients infected with mixed populations who are treated with maraviroc (Panel B).

Viral tropism was assessed in Studies A4001027 and A4001028 at screening, baseline and subsequent protocol-defined study visits when viral load was >500 copies/ml. Across the two studies, 7.6% of patients with a CCR5 tropism result at screening had a different tropism result at baseline, illustrating the background rate of change in tropism result over a 4 to 6 week period in this population, prior to a change in antiretroviral regimen or administration of a CCR5 antagonist. Analysis of the change from baseline in viral load at Week 24 in these patients demonstrated no treatment benefit for maraviroc compared to placebo. There was a higher mean change in CD4 cell count for patients with non-CCR5 tropic virus at baseline and who failed therapy with maraviroc (+53.8 and +25.6 cells/μL for maraviroc QD and BID, respectively), compared to placebo (+14.5 cells/μL) (Section 2.7.3.4.15.2.1 Module 2.7.3 Summary of Clinical Efficacy). This is consistent with the findings in Study A4001029 conducted in treatment-experienced patient with non-CCR5 tropic HIV-1, which demonstrated a beneficial impact of maraviroc treatment in patients infected with dual/mixed tropic HIV-1 on CD4 cell count, even in the absence of a demonstrable effect on viral load (A4001029 Clinical Study Report Module 5.3.5.1 Study Reports of Controlled Clinical

Studies Pertinent to the Claimed Indication and the Post Hoc Analysis Report: Protocol A4001029, Module 5.3.4.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication).

Of the 204 patients with a CCR5 tropism result at baseline, and who experienced treatment failure, 32.8% had a change in tropism result to CXCR4 or dual/mixed at time of treatment failure. More of these subjects were in the maraviroc treatment groups compared with the placebo treatment group. Of patients with a CCR5 tropism result at baseline and who failed on maraviroc + OBT, 54.8% had a change in tropism result to dual/mixed or CXCR4 tropic, compared to 4.5% of those who failed on placebo + OBT. Overall, there was a higher mean change in CD4 cell count for patients who failed therapy with maraviroc, compared to placebo (+49.4 and +71.1 cells/μL for maraviroc QD and BID, respectively, compared to +13.8 cells/μL for patients receiving placebo). The mean increase in CD4 cell count from baseline in patients who failed with a change in tropism result to dual/mixed tropic or CXCR4, in both the maraviroc QD (+37 cells/μL) and BID (+56 cells/μL) groups was greater than that seen in patients failing placebo (+13.8 cells/μL) regardless of tropism result (Section 2.7.3.4.15.2.1 Module 2.7.3 Summary of Clinical Efficacy).

In summary, these results demonstrate that patients failing on maraviroc had higher mean increases in CD4 count, even when failing in the context of a change in tropism result from CCR5 tropic to dual/mixed or CXCR4-tropic at time of failure, indicating no adverse effect on CD4 cell count resulting from a change in tropism result to dual/mixed or CXCR4-tropic. Collectively these data are consistent with the data obtained from the post-hoc analysis performed on patients in Study A4001029 (Post Hoc Analysis Report: Protocol A4001029, Module 5.3.4.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication). The origin of the emerging CXCR4 virus in a representative subset of these patients is discussed in the microbiology review of the mechanisms of resistance/shifts in tropism in the maraviroc programme (Module 5.3.5.3 Reports of Analysis of Data from more than one Study).

2.5.4.6. Efficacy Results from Study A4001029

Study A4001029 had a similar study design to the Phase 3 studies A4001027 and A4001028, but was a smaller Phase 2b safety study conducted in treatment-experienced patients infected with non-CCR5 (dual/mixed tropic, CXCR4-tropic or non-phenotypable) HIV-1. The primary reason for conducting this study was to determine whether it was safe to add maraviroc to OBT in patients with documented dual/mixed tropic HIV-1. Of particular concern was the possibility that the selective suppression of CCR5 variants by maraviroc, when given as part of a failing regimen, in this patient population would result in a shift towards a predominantly CXCR4 phenotype resulting in an adverse outcome. The majority of patients enrolled were infected with dual/mixed tropic virus and the same primary and secondary efficacy endpoints were analysed as for Studies A4001027 and A4001028 discussed above.

As maraviroc selectively suppresses CCR5 tropic HIV-1, a significant treatment response in patients infected with dual/mixed tropic HIV-1 was not expected, and the results of this study reflected this. For the primary and secondary virologic endpoints, neither dose of maraviroc

was superior to the placebo treatment group. However, there was no evidence of an adverse outcome with regards to viral load response compared with placebo, and there was a trend towards a larger viral load reduction in both maraviroc treatment groups compared with placebo for patients with an OSS of 0-1.

Furthermore, unadjusted for multiple comparisons, there was a greater increase in CD4 cell count from baseline for the maraviroc BID treatment group compared with placebo, which was particularly notable for patients with an OSS of 0-1. Similarly, there was an increase in CD4 cell count in the maraviroc QD treatment group, although this was less than maraviroc BID. The increase in CD8 cell count was higher for both doses of maraviroc compared with placebo.

The primary analysis of results of Study A4001029 has demonstrated that there is a beneficial impact of maraviroc treatment in patients infected with dual/mixed tropic HIV-1 in terms of CD4 cell count, even in the absence of a demonstrable effect on viral load. The results of this study are presented in the A4001029 Clinical Study Report (Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication) and in Section 2.7.3.2.2 Module 2.7.3 Summary of Clinical Efficacy.

A post hoc analysis to investigate changes in viral tropism assignment in patients receiving maraviroc in Study A4001029 and the effect on clinical outcome was performed (Post Hoc Analysis Report: Protocol A4001029, Module 5.3.4.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication). The findings from this analysis demonstrated that both maraviroc treatment groups had a higher CD4 cell increase compared with placebo, irrespective of virologic response, indicating that CD4 increases observed in the maraviroc + OBT treatment groups were not restricted to subjects that were on study drug at Week 24. As expected, more subjects had a CXCR4 tropism result at Week 24 (or time of failure) in the maraviroc groups compared with placebo, consistent with selective suppression by maraviroc of CCR5 virus strains in these subjects. However, the CD4 count increases in the maraviroc groups did not differ by tropism result at time of failure, confirming that a CXCR4 tropism result was not associated with an adverse CD4 outcome in this patient population.

2.5.4.7. Overview of the Mechanisms of Resistance and Changes in Tropism Result in the Maraviroc Clinical Programme

In vitro antiviral studies demonstrated that maraviroc is only active against CCR5-tropic viral strains (Module 2.6.2.2.1.5 Pharmacology Written Summary: Maraviroc Antiviral Activity). There are two possible ways for a virus to develop resistance to maraviroc. The first of these is through selection of variants that can use the alternative co-receptor, CXCR4. The second is through becoming resistant to maraviroc with continued CCR5 usage for entry.

There are two possible mechanisms by which CXCR4-using virus may be selected during maraviroc treatment. The first is by selection of a virus containing amino acid mutation(s) in the envelope glycoprotein, which confers a switch from CCR5 to CXCR4 usage. The second possible mechanism is by the relative expansion of a pre-existing, but previously undetectable, reservoir of CXCR4-using virus. The relative importance of these two mechanisms (i.e. co-receptor switch versus detection of a pre-existing CXCR4-using virus)

in the emergence of CXCR4-using virus during maraviroc treatment was investigated during the clinical testing phase of the resistance program.

Again, two mechanisms of maraviroc resistance can be envisaged for CCR5-tropic viruses. Viruses encoding gp120 with an increased affinity for CCR5 may be selected. The consequence of this would be that the mutant virus infects cells at lower concentrations of free CCR5 molecules than the wild type virus; this would be characterized in antiviral assays as a shift in IC_{50} to maraviroc. Alternatively, virus may be selected that has acquired the ability to use CCR5 even when maraviroc is bound to the receptor; this would be characterized in antiviral assays as a plateau in maximal percentage inhibition (Petropoulos CJ, 2004). In either case, resistance will be associated with the selection of viruses with mutant viral envelopes, which recognize the receptor differently compared to the wild type virus. The pre-clinical resistance program investigated these mechanisms of maraviroc resistance.

A summary of the findings from exploratory analyses performed during the pre-clinical and clinical phases of the maraviroc development programme designed to characterise the phenotypic and genotypic correlates of viral resistance is given below (Microbiology Review of the Mechanisms of Resistance/Shifts in Tropism in Maraviroc Programme, Module 5.3.5.3 Reports of Analysis of Data from more than one Study).

In order to be able to conduct the exploratory analyses in time for inclusion in the primary submission, a subgroup of 267 patients was selected on a blinded basis from clinical Studies A4001027 and A4001028. This subgroup was studied blinded but was estimated to comprise of approximately 213 patients who were randomised to receive maraviroc and OBT and 54 patients who received placebo and OBT, since both clinical studies included a 2:2:1 randomisation (maraviroc BID + OBT: maraviroc QD + OBT: placebo + OBT). Therefore, conclusions made on these 267 patients should be representative of the whole study population (1049 patients) at Week 24.

Both in vitro serial passage experiments and exploratory in vitro analyses conducted on samples from this subgroup found no evidence for tropism switch on maraviroc caused by mutation of a CCR5-tropic virus. Instead, the extensive cloning of envelope genes and subsequent phylogenetic analyses conducted on representative patients indicates that these changes in tropism are a result of the detection, on-treatment, of CXCR4-using virus that pre-existed the active treatment phase. This is consistent with tropism data presented for a patient receiving another CCR5 antagonist, aplaviroc, as monotherapy (Kitrinos K, 2005) and is supported by previous analyses of 2 maraviroc monotherapy patients (Westby M, 2006).

The pre-clinical studies of maraviroc resistance (with continued CCR5-tropism) were predictive of what was seen in clinical trials. Dose response inhibition curves with plateaus in MPI are predictive of resistance to maraviroc, consistent with its mechanism of action as a non-competitive allosteric inhibitor of viral entry. No 'signature' mutations for maraviroc resistance (with continued CCR5 use) were identified in gp120 during the course of this programme, either from in vitro selected virus or resistant clinical isolates. This is perhaps not surprising given the highly variable primary amino acid sequence of the HIV-1 envelope, and the V3 loop in particular, between different strains. It is likely that the viral envelope's

three dimensional structure influences which mutations will be required for the virus to recognise compound-occupied receptors. Therefore it is not possible to propose a genotypic (sequence) algorithm to identify maraviroc resistance.

The low incidence of maraviroc resistance detected in the clinical programme is consistent with the pre-clinical findings that resistance was slow to emerge or could not be selected under the conditions used. In the blinded cohort of 267 patients (with approximately 213 being randomised to receive maraviroc) only 13 patients failed blinded therapy on maraviroc with a CCR5-tropic virus (Section 4.6.3 Microbiology Review of the Mechanisms of Resistance/Shifts in Tropism in Maraviroc Programme, Module 5.3.5.3 Reports of Analysis of Data from more than one Study). Of these, only 4 were identified as having resistance to maraviroc characterised by a plateau in inhibition <95%, with a further patient showing a small shift in IC_{50} between baseline and failure. The impact of resistance to other components of the OBT regimen in these patients has not yet been fully evaluated but may explain why some of the patients on the maraviroc treatment arms failed therapy without detectable resistance to maraviroc or a change in tropism phenotype to dual/mixed or CXCR4-tropic virus.

Representative patients whose virus is exclusively CCR5-tropic and who failed a maraviroc-containing regimen harboured virus that was susceptible to enfuvirtide. Exceptions to this were only seen when enfuvirtide was a component of the failing regimen itself or the baseline sample contained enfuvirtide resistant virus (presumably from prior exposure of the patient to an enfuvirtide regimen). Similarly, viruses with reduced in vitro susceptibility to enfuvirtide were sensitive in vitro to maraviroc. These findings are consistent with genotype information that points to different regions of the gp160 envelope as being important for conferring resistance to maraviroc and enfuvirtide. Key determinants of enfuvirtide susceptibility are localized in the gp41 fusion protein, notably the HR1 domain (Greenberg ML, 2004). On the other hand, the pre-clinical and clinical findings summarised in the microbiology review of the mechanisms of resistance/shifts in tropism in maraviroc programme point to the HIV-1 gp120 V3 loop as playing an important role in maraviroc susceptibility. There is therefore no evidence to suggest that resistance to maraviroc will result in cross-resistance to enfuvirtide from these pre-clinical and clinical studies, and no rationale for why resistance to a CCR5-antagonist will result in cross-resistance to any of the other drug classes. There is also no evidence to suggest that CCR5-tropic viruses from enfuvirtide-experienced patients have reduced susceptibility to maraviroc.

2.5.4.8. Efficacy Conclusions

Maraviroc demonstrated overwhelming efficacy compared with placebo (OBT alone) as indicated by the estimates of the treatment difference for maraviroc QD, which were -0.888 $\log_{10}$ copies/mL (97.5% CI: -1.153, -0.623) and for maraviroc BID was -0.973 $\log_{10}$ copies/mL (97.5% CI: -1.237, -0.709), both relative to placebo. The 2-sided 97.5% confidence intervals were completely to the left side of zero, excluding zero, indicating the superiority of maraviroc QD and maraviroc BID compared with placebo. In addition, the upper bounds of the 97.5% confidence intervals were to the left of 0.5 $\log_{10}$ copies/mL. A reduction in viral load of $\geq$0.5 log10 copies is recognized as clinically significant. In addition, all the secondary endpoint results at Week 24 were

consistent with the primary endpoint and support the superior efficacy of both maraviroc treatment groups over placebo. Per protocol analyses and sensitivity analyses (last observation carried forward [LOCF], setting missing data to failure, setting patients who met protocol failure criteria but did not discontinue to failure) confirmed the results of the pre-specified primary and secondary analyses.

The high placebo response of >1.0 $\log_{10}$ copies/mL, provides evidence that the OBT selections for these studies were appropriate, providing these patients with a clinically relevant reduction in HIV-1 RNA from baseline, which was comparable or greater than previous registrational trials for approved antiretroviral agents (Cahn P, 2006, Gathe J, 2006, Lalezari JP, 2003, Lazzarin A, 2003). The addition of maraviroc to this OBT, however, resulted in approximately 1.0 $\log_{10}$ copies/mL reduction in HIV-1 RNA above that of the placebo response.

Overall, 73%, 62% and 67% of subjects had GSS, PSS and OSS of ≤2, respectively, consistent with a heavily treatment experienced population. A treatment effect was seen between the maraviroc treatment groups and placebo over the range of susceptibility scores from 0 to ≥3. The treatment effect was greatest in subjects with 2 or less potentially active drugs in their OBT.

Most patients who responded had no tropism assignment at Week 24, and many had no on-treatment tropism result as they had a viral load of <500 copies/mL at all visits from Week 4 onwards. Of the 1049 patients in the studies only a few had treatment failure due to insufficient clinical response and had a change in tropism result, more of these subjects were in the maraviroc treatment groups compared with the placebo treatment group. However, patients failing on maraviroc had higher mean increases in CD4 count, even when failing in the context of a change in tropism result from CCR5 tropic to dual/mixed or CXCR4 tropic at time of failure, indicating no adverse effect on CD4 cell count resulting from a change in tropism result to dual/mixed or CXCR4 tropic.

There was no indication of a clinically meaningful difference between maraviroc QD and BID across the whole population studied, based on the primary and key secondary efficacy endpoints measured following 24 weeks of therapy. However, certain subgroups, notably patients with lower CD4 count, higher viral loads and fewer potentially active drugs in their OBT, seem to receive greater benefit from maraviroc BID. This appears to be consistent with the finding from the interim analysis of Study A4001026 that higher viral loads and lower CD4 counts were associated with differences from the 2 ongoing arms of that trial in treatment naïve patients infected with CCR5 tropic HIV-1 (Section 2.7.3.1.3 Module 2.7.3 Summary of Clinical Efficacy).

2.5.5. Overview of Safety

2.5.5.1. Overview of Safety Database

The maraviroc clinical safety database consists of 674 subjects participating in Phase 1 single and multiple dose studies (including 37 HIV-1 infected patients) and 66 asymptomatic HIV-1 infected patients participating in Phase 2a 10-day monotherapy dose-ranging studies. There

were a total of 1049 patients infected with CCR5 tropic HIV-1 participating in the Phase 3 treatment-experienced studies. The median exposure in each treatment group was 235.5 days (range 2-381) for maraviroc QD, 238.5 days (range 1-366) for maraviroc BID and 145 days (range 7-427) for placebo. The total exposure in patient-years were 258.7, 266.8 and 99.3 for maraviroc QD, BID and placebo respectively. The exposure for 186 patients infected with non-CCR5 tropic HIV-1 was much less (26.4, 27.9 and 25.0 patient-years for maraviroc QD, BID and placebo respectively). The patients contributing to the overall safety database for maraviroc are mostly Caucasian males aged <65 years. There were few females recruited into the Phase 3 registrational studies and a limited number of patients from non-white racial groups, which is typical of studies of this type (Lazzarin A, 2003, Lalezari JP, 2003). This is, however, reflective of the epidemiology of HIV-1 disease for treatment-experienced patients, which is the indication being sought by the Applicant. The epidemiology of this patient population is discussed in the Risk Management Plan. Further populations assessed included 109 patients who went onto open label maraviroc BID therapy after treatment failure in Studies A4001027 and A4001028, and the unblinded maraviroc QD to open label maraviroc BID arm from Study A4001026 in treatment naïve patients (174-129 patients).

Integrated safety information for patients included in the Phase 3 registrational studies was reported up to 48 weeks for each patient where available. Serious adverse events are reported up to September 15th 2006 and include reports from all patients to a maximum of 22 months follow-up. Safety data for the submission have been pooled by Phase and also by treatment populations to provide an indication of the safety profile for the target indication population (treatment-experienced patients infected with CCR5 tropic HIV-1) and also the wider treatment-experienced population (irrespective of virus tropism assignment) to provide a larger population in which to assess potential safety issues. Integrated analyses primarily focus on double blind randomised patients from the studies in treatment-experienced patients infected with CCR5 HIV-1, with appropriate merging of the database from patients infected with non-CCR5 tropic HIV-1 to address specific issues. Treatment naïve patients and open label data are not merged except to evaluate important rare events, such as deaths and lymphomas. A summary of all the safety data available from the maraviroc clinical programme is provided in Module 2.7.4 Summary of Clinical Safety.

Maraviroc belongs to a new class of antiretroviral agents known as CCR5 antagonists, as such there are no established adverse events associated with this drug class. Two other CCR5 antagonists have been in development in parallel with maraviroc. One agent, aplaviroc, was discontinued from clinical development due to severe hepatotoxicity. The second agent, vicriviroc, was associated with an increased number of malignancies in a Phase 2b study (4 lymphomas and an adenocarcinoma), which all occurred in vicriviroc treated patients. There was no clear evidence that these cases were linked to study drug and this observation did not lead to discontinuation of development, but studies were unblinded and continued as open label therapy.

Potential safety issues raised during the pre-clinical stages of the development of maraviroc were postural hypotension and the potential for QTc prolongation. In addition, as maraviroc belongs to a new class of therapeutic agents, theoretical concerns based on the mechanism of action were also considered; including an increased risk for infection and development of malignancies. These issues, together with the potential for hepatotoxicity and laboratory

abnormalities have been thoroughly reviewed during the maraviroc clinical development programme and are presented in detail in Sections 2.7.4.2.1.5.3 and 2.7.4.3 Module 2.7.4 Summary of Clinical Safety and the conclusions are discussed below in Sections 2.5.5.4.2, 2.5.5.4.1, 2.5.5.4.3, 2.5.5.4.4.

Although the clinical development studies for maraviroc were conducted in a double-blind manner to limit bias, attention is focused on the all-causality adverse event assessments for this submission, as it is recognised that there is difficulty in distinction between treatments for the Phase 3 studies in which all patients were receiving concomitant OBT regimens. The baseline demographic characteristics, medical histories (including duration of HIV-1 disease) and previous use of antiretroviral agents were largely similar between treatment groups and studies and with few exceptions are unlikely to have affected interpretation of the study results.

2.5.5.2. Overall Adverse Event Profile

The adverse event profile for maraviroc unit doses ≤300 mg in the Phase 1 development programme was consistent with that of the placebo treated subjects. The dose limiting adverse event was postural hypotension, which occurred at a dose of 1200 mg in the first-in-human study. Subsequently, a review across the Phase 1 studies showed that postural hypotension was observed at a greater incidence than placebo at unit doses >300 mg (Section 2.7.2.3.2, Module 2.7.2 Summary of Clinical Pharmacology Studies).

The most commonly reported all-causality adverse events during the Phase 3 registrational studies (A4001027 and A4001028), occurring ≥2% in the maraviroc treatment groups, and at a higher incidence than placebo (by at least 3% or 3 times as often), were pyrexia, cough, upper respiratory tract infection, rash, herpes simplex, myalgia, dysuria, dyspnoea, ALT increased, AST increased, blood creatine phosphokinase increased and influenza. The majority of treatment-related adverse events reported at an incidence of ≥2% in either of the maraviroc treatment groups were reported at similar incidences to placebo (Section 2.7.4.2 Module 2.7.4 Summary of Clinical Safety).

In Study A4001029, in patients infected with non-CCR5 tropic (dual/mixed tropic, CXCR4-using or non-phenotypable) HIV-1, adverse events reported were comparable to the Phase 3 studies conducted in patients infected with CCR5 tropic HIV-1. The detailed safety information for this study is presented in A4001029 Clinical Study Report (Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication).

The following safety sections focus on the results obtained for Studies A4001027 and A4001028, from the patient population for the target indication. As appropriate, safety data are presented from the additional Studies A4001029 in treatment-experienced patients infected with non-CCR5 tropic (dual/mixed, CXCR4-tropic or non-phenotypable) HIV-1 and Study A4001026 in treatment-naïve patients infected with CCR5 tropic HIV-1 to aid interpretation.

2.5.5.3. Discontinuations, Serious Adverse Events and Deaths

Discontinuations due to Adverse Events:

A similar number of patients in each treatment group permanently discontinued from blinded study drug due to adverse events, irrespective of relationship to study drug; 16 (3.9%), 16 (3.8%) and 8 (3.8%) for maraviroc QD, BID and placebo respectively). Similar results were observed for discontinuations due to treatment-related adverse events (2.9%, 2.3% and 2.4% for maraviroc QD, BID and placebo respectively).

There were slightly more patients who temporarily discontinued or underwent a reduction in dosage from study due to adverse events in the maraviroc BID and placebo treatment groups compared with maraviroc QD (20 [4.8%], 28 [6.6%] and 13 [6.2%] for maraviroc QD, BID and placebo respectively). In addition, 6 patients (2 maraviroc QD, 3 maraviroc BID, 1 placebo) temporarily discontinued and later permanently discontinued. More patients experienced adverse events that were ascribed as treatment-related by the Investigator in the maraviroc BID treatment group (7 [1.7%], 16 [3.8%] and 2 [1.0%] for maraviroc QD, BID and placebo respectively). For the majority of patients who temporarily discontinued due to adverse events related to rash, dizziness and laboratory abnormalities, drug was re-introduced and the event resolved or stabilized and the patient either continued treatment until the data cut off date or discontinued for another reason.

The details of these events are presented in Section 2.7.4.2.1.4.1 Module 2.7.4 Summary of Clinical Safety.

Serious Adverse Events:

In Studies A4001027 and A4001028, a similar number of patients reported serious adverse events in the maraviroc BID and placebo treatment groups, which was slightly higher than the number reported in the maraviroc QD treatment group; 56 (13.5%) in the maraviroc QD treatment group, 70 (16.4%) in the maraviroc BID treatment group and 36 (17.2%) in the placebo treatment group. Of these, only 2.7% (maraviroc QD), 2.8% (maraviroc BID) and 1.0% (placebo) were considered possibly treatment related by the Investigator.

As the number of serious adverse events reported for the Phase 2b/3 clinical programme is very small and the number of all-causality events was similar between treatment groups, no conclusions can be drawn as to the nature and likelihood of serious adverse events reported with maraviroc treatment compared with placebo. The details of these events are presented in Section 2.7.4.2.1.3 Module 2.7.4 Summary of Clinical Safety.

Deaths:

During the maraviroc Phase 2b/3 clinical development programme (including Studies A4001026, A4001027, A4001028 and A4001029) there have been a total of 42 deaths reported up to the date of data cut off of 15th September 2006. Of these, 12 were reported during the 4-6 weeks period between the screening and randomisation visits and included a variety of causalities associated with HIV disease progression, which indicates the advanced nature of HIV disease in patients recruited into these studies. Thirty deaths have been

reported in patients who had received at least one dose of blinded study drug; 11 have occurred in the maraviroc QD treatment group, 9 in the maraviroc BID treatment group, 5 in the placebo treatment group, 2 in the efavirenz treatment group (in Study A4001026 only), 2 patients receiving open label maraviroc BID and 1 patient who was in-study-off-drug (ISOD) previously randomised to maraviroc BID. Five deaths occurred in treatment naïve patients in Study A4001026 (maraviroc QD 2, maraviroc BID 1, efavirenz 2), 25 patients died in the treatment experienced studies as discussed below.

There were a total of 25 (2.0%) deaths in all treatment-experienced studies (A4001027, A4001028 and A4001029), including 2 patients receiving maraviroc BID open label and 1 patient in-study-off-drug. Of these, 17 (1.4%) deaths occurred in patients who were still on treatment or who had discontinued study drug, but died within the standard 28-day post-treatment capture period for serious adverse events and deaths. The proportion of deaths, irrespective of whether patients were on or off study drug was similar between treatment groups; all deaths were 9 (1.9%) in the maraviroc QD group, 8 (1.6%) in the maraviroc BID group and 5 (1.8%) in the placebo group and for deaths occurring within 28 days of stopping study drug there were 8 (1.7%) in the maraviroc QD treatment group, 6 (1.2%) in the maraviroc BID treatment group and 3 (1.1%) in the placebo treatment group.

Of the 25 deaths occurring on study drug (including placebo and open label maraviroc) in the maraviroc Phase 2b/3 treatment-experienced studies 8 occurred in Study A4001027, 10 occurred in Study A4001028 and 7 occurred in Study A4001029, as presented in Table 9 below.

Table 9.Summary of All Deaths, As Treated, Occurring in the Phase 2b/3 Treatment Experienced Studies (A4001027, A4001028 and A4001029)

Study	Maraviroc QD (N= 477)	Maraviroc BID (N= 487)	Placebo (N= 271)	Maraviroc BID Open Label	ISOD[a]
A4001027	2	1	2	2	1
A4001028	5	5	0	0	0
A4001029	2	2	3	0	0
Total	**9 (1.9%)**	**8 (1.6%)**	**5 (1.8%)**	**2**	**1**

[a] Patients in-study-off-drug.

Table 10 presents these deaths according to the patients' original randomised treatment.

Table 10. Summary of Deaths, As Randomised, Occurring in the Phase 2b/3 Treatment Experienced Studies (A4001027, A4001028 and A4001029)

Study	Maraviroc QD (N= 477)	Maraviroc BID (N= 487)	Placebo (N= 271)
A4001027	2	3	3
A4001028	5	5	0
A4001029	2	2	3
Total	**9 (1.9%)**	**10 (2.1%)**	**6 (2.2%)**

The rates of deaths in each treatment group were similar for the as-treated and as-randomised populations. Only one death, occurring on open label therapy in Study A4001027, was considered treatment-related by the Investigator. This patient, after discontinuing placebo as blinded therapy, had received 143 days of maraviroc BID and was diagnosed with a B cell lymphoma (confirmed) 9 days after discontinuing treatment. There have been five deaths reported in Study A4001026 in treatment-naïve patients receiving maraviroc QD (suicide and lymphoma), maraviroc BID (liver failure/pneumonia) and efavirenz (Castleman's disease and non-Hodgkin's lymphoma) none of which was considered related to study drug.

The Phase 2b/3 treatment-experienced studies (A4001027, A4001028 and A4001029) reflect a clinically advanced HIV-1 infected patient population, and, as such, there were a total of 12 deaths during the 5-6 week period between screening and randomisation for a variety of HIV-1 disease related causes, which are presented in Table 11.

Table 11. Causality of Deaths for Patients During the Pre-Randomisation Period[a] (Studies A4001027, A4001028 and A4001029)

Study	PID	Cause of Death
A4001027	1[redacted]70011	Pneumonia/respiratory failure
	1[redacted]00018	Pulmonary tuberculosis
	1[redacted]20019	Nocardia infection
	1[redacted]40005	Death – unspecified
A4001028	1[redacted]30004	Progressive multifocal leucoencephalopathy
	1[redacted]00003	Respiratory failure
	1[redacted]30003	Asthenia/anorexia/dehydration/left hemiplegia
	1[redacted]70008	Pneumonia
	1[redacted]50007	Renal insufficiency
	1[redacted]50008	Haematemesis/respiratory arrest
	1[redacted]20001	Disease progression
A4001029	1[redacted]30004	Coma

Source: Table 3.8.4.3 Summary of Clinical Safety.
[a] 5-6 week period in between screening and randomisation visits.

There were 17 deaths recorded on treatment or within 28 days of study drug discontinuation; 14 in the maraviroc groups and 3 in the placebo group. This imbalance was driven by the findings in Study A4001028, where there were 8 deaths in the maraviroc treatment groups and none in the placebo group.

Table 12. Summary of Deaths for the Pre-Randomisation Period and Deaths Occurring on Treatment (Studies A4001027, A4001028 and A4001029)

Study	Pre-Randomisation Period[a] (N= 3244)[b]	On Treatment or Within 28 Days of Discontinuation of Treatment		
		Maraviroc QD (N= 477)	Maraviroc BID (N= 487)	Placebo (N= 271)
A4001027	4	2	1	1
A4001028	7	4	4	0
A4001029	1	2	1	2
Total	**12 (0.4%)**	**8 (1.7%)**	**6 (1.2%)**	**3 (1.1)**

Source: Table 3.8.4.3 Summary of Clinical Safety.
[a] 5-6 week period in between screening and randomisation visit. The same population was screened for all treatment-experienced studies.
[b] Number of patients screened for randomisation into Studies A4001027, A4001028 and A4001029 (includes subjects who were re-screened).

Imbalances in mortality have been observed in other individual trials in similar populations, including TORO-2 (Lazzarin A, 2003), and in the controlled portions of the darunavir (TMC-114/ritonavir) studies TMC-C202 and TMC-C213, in which 18 deaths occurred in the darunavir treatment groups with none on the control PI treatment group (NDA 21-976 [redacted]™ [darunavir] Medical Review). Of these 18 deaths, 1 was due to an AIDS-related lymphoma of the lung and 1 due to acute myeloid leukaemia. In the safety update of these studies there were 3 additional lymphomas; 2 non-Hodgkin's lymphomas and 1 B-cell lymphoma. Finally, the deaths occurring in the maraviroc treatment-experienced studies were from a variety of causes, many of which occur commonly in HIV-infected individuals, including cerebrovascular disease, cardiovascular disease, respiratory illnesses, infections, anorexia and HIV disease progression (Section 2.7.4.2.1.2 Module 2.7.4 Summary of Clinical Safety).

The finding for the maraviroc Phase 2b/3 clinical programme should be seen in the context of a 2:2:1 randomisation schedule and a much higher discontinuation rate in the placebo arm, resulting in a shorter duration of exposure on placebo relative to both maraviroc groups. As such, mortality rates (number of deaths/100 patient-years of exposure) have been calculated, as presented in Table 13 below, as per patients' last recorded treatment for deaths irrespective of time in study and for those occurring on treatment or within 28 days of discontinuing study drug.

Table 13. Summary of Incidence of Deaths and Mortality Rates Occurring in the Maraviroc Phase 2b/3 Studies (A4001027, A4001028 and A4001029)

Treatment Group	N	Exposure Pt-yrs	All Deaths		Deaths on Study Drug or Within 28 Days[a]	
			n (%)	MR[b]	n (%)	MR
Maraviroc QD	477	285.1	8 (1.7)	2.8	8 (1.7)	2.8
Maraviroc BID[c]	487	294.7	11 (2.3)	3.7	6 (1.2)	2.0
All Maraviroc[d]	964	579.8	19 (2.0)	3.3	14 (1.5)	2.4
Placebo	271	124.3	5 (1.8)	4.0	3 (1.1)	2.4

[a] Standard 28-day post-treatment capture period for serious adverse events and deaths.
[b] Mortality rate corrected only for exposure during double blind therapy and excludes duration of subsequent open label or in study off drug follow up.
[c] Includes an additional 2 patients who received maraviroc BID open label (1 was originally randomised to maraviroc BID and 1 to placebo) and 1 patient who was in-study-off-drug who had previously discontinued from maraviroc BID treatment.
[d] Combined maraviroc QD and BID treatment groups.
Pt-yrs = Exposure by patient-years; MR = Mortality rate (number of deaths/exposure in patient-years).

As demonstrated, the mortality rates (adjusted for exposure to study drug) for all deaths and for deaths occurring on treatment or within 28 days of discontinuing study drug, were similar between all treatment groups. Furthermore, the mortality rate for the placebo treatment group was slightly higher than the mortality rate for the maraviroc treatment groups. This pattern of results was similar for the Phase 3 treatment-experienced studies in patients infected with CCR5 tropic HIV-1 (Table 14).

Table 14. Summary of Incidence of Deaths and Mortality Rates Occurring in the Maraviroc Phase 3 Studies (A4001027 and A4001028)

Treatment Group	N	Exposure Pt-yrs	All Deaths		Deaths on Study Drug or Within 28 Days[a]	
			n (%)	MR[b]	n (%)	MR
Maraviroc QD	414	258.7	6 (1.4)	2.3	6 (1.4)	2.3
Maraviroc BID[c]	426	266.8	8 (1.9)	3.0	5 (1.2)	1.9
All Maraviroc[d]	840	525.5	14 (1.7)	2.6	11 (1.3)	2.1
Placebo	209	99.3	3 (1.4)	3.0	1 (0.5)	1.0

[a] Standard 28-day post-treatment capture period for serious adverse events and deaths.
[b] Mortality rate corrected only for exposure during double blind therapy and excludes duration of subsequent open label or in study off drug follow up.
[c] Includes an additional 2 patients who received maraviroc BID open label (1 was originally randomised to maraviroc BID and 1 to placebo) and 1 patient who was in-study-off-drug who had previously discontinued from maraviroc BID treatment.
[d] Combined maraviroc QD and BID treatment groups.
Pt-yrs = Exposure by patient-years; MR = Mortality rate (number of deaths/exposure in patient-years).

These results are consistent with mortality rates published on the CDER website for other treatment-experienced antiretroviral studies at the Week 24 endpoint; the frequency and mortality rates for tipranavir/ritonavir compared with comparator PI treatment group was 2%

(MR 4.5) versus 1.2% (MR 2.6), enfuvirtide compared with placebo was 1.5% (MR 3.3) versus 1.5% (MR 3.3) and for duranavir 1.2% (MR 2.6) versus 0% (MR 0).

Overall, the mortality data for the maraviroc Phase 2b/3 clinical programme do not indicate that maraviroc is associated with an increase number of deaths compared with placebo (Studies A4001027, A4001028 and A4001029) or efavirenz (Study A4001026) and are similar to other published registrational trials for antiretroviral agents. The details of these events are presented in Section 2.7.4.2.1.2 Module 2.7.4 Summary of Clinical Safety.

2.5.5.4. Special Safety Considerations

The following sections discuss the safety considerations reviewed throughout the maraviroc clinical programme and which were raised from pre-clinical findings, Phase 1-3 clinical data or a theoretical concern based on the mechanism of action of maraviroc.

2.5.5.4.1. Cardiovascular Safety

Postural Hypotension:

Postural hypotension was identified as the dose limiting adverse event in Phase 1 as described in the clinical pharmacology Section 2.5.3 above. The mechanism remains unknown, and it rarely seems to occur at unit doses less than 600 mg). Therefore, when the Phase 2b/3 studies were started some exclusion criteria were in place to exclude patients with significant cardiovascular disease or pre-existing postural hypotension (A4001027 and A4001028 Clinical Study Reports, Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication). During the conduct of the Phase 2b/3 programme an additional study was performed to assess heamodynamic parameters at 3 times the clinical dose of maraviroc (Study A4001033 described above in Section 2.5.3). The results from this study and an interim evaluation of cardiovascular events and blood pressure data from the Phase 2b/3 programme by the DSMB led to the removal of these restrictions.

Postural blood pressure was systematically measured at Weeks 2, 24 and 48 in Phase 2b/3 studies. The incidence of postural hypotension in the Phase 3 registrational studies was slightly higher in the maraviroc treatment groups compared with placebo, but no dose relationship was observed. The magnitude of this finding, relative to placebo, was unaffected by whether patients were receiving concomitant medications known to lower blood pressure. In patients receiving concomitant saquinavir/ritonavir, who might potentially have had the highest exposures of maraviroc, dizziness was observed at a greater percentage of patients in the maraviroc treatment groups compared with placebo. No dose response was observed, however, and the numbers of patients in this subgroup analysis was small.

In conclusion, therefore, postural hypotensive events are rare with therapeutic doses of maraviroc and appeared at a similar frequency across treatment groups. However, in cases of inadvertent (e.g., if patients fail to receive the correct dose adjustment for background treatments) or intentional overdose, it would be expected that dizziness and/or postural events may occur at a higher rate than have been observed during the clinical trials reported in this submission.

The Potential to Prolong QTc Interval:

QTc prolongation is of particular interest in drug development as it has the potential to cause a very rare, but potentially life threatening condition known as torsade de pointes (TdP). However, the QTc interval duration exhibits a high degree of spontaneous intra-subject variability and is not necessarily a direct predictor of the risk of TdP (Morganroth J, 1993). This observation holds implications for the assessment of the potential proarrhythmic effects of noncardiac pharmacologic agents. In addition, the upper limit for QT interval that results in clinically significant consequences has not been identified. However, until more reliable methods of assessing the risk of TdP are established in clinical practice the measurement of QTc interval remains the standard tool for predicting risk and the recently published ICH E14 provides guidance on conducting a thorough QT study during clinical drug development (Guidance for Industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, October 2005).

Non-clinical studies indicated that at therapeutic concentrations, maraviroc had no effect on cardiac repolarisation in either in vitro or in vivo assays. However at supra-therapeutic concentrations, maraviroc can block the hERG potassium channel, which may lead to QTc prolongation. In vitro studies show that maraviroc inhibits dofetilide binding, is active at the human cardiac hERG channel and prolongs the action potential of the dog Purkinje fibre at concentrations ≥3 μM or 155 ng/mL, which is approximately 10-fold the Cmax at the therapeutic dose (155 ng/mL free Cmax at steady state given at a dose of 300 mg BID; study A4001007). These changes were consistent with findings from toxicology studies in which maraviroc increased QTc interval at doses of ≥15 mg/Kg in dogs and ≥200 mg/Kg in monkeys. The unbound plasma concentrations at these lowest effect doses (899 and 1815 ng/mL) represent exposure multiples of 6- and 12-fold, respectively. In these two species maraviroc had no effect on QTc interval at plasma concentrations 2 and 5-fold the maximum therapeutic concentration. Concentrations in dogs and monkeys have been explored up to 23- and 43-fold, respectively, those seen at the therapeutic dose, with no evidence of cardiac arrhythmias. Details of these findings are discussed in Section 2.4.5.3 Module 2.4 Non-Clinical Overview.

Due to these pre-clinical findings there was detailed monitoring of ECG parameters during early clinical studies with maraviroc, and a Phase 1 thorough QTc study was performed. This was a single dose study, at doses of 100-900 mg maraviroc with moxifloxacin 400 mg as an active control agent known to prolong QTc. Single doses were regarded as adequate because of limited, if any, accumulation observed with multiple dosing at 300 mg BID in Phase 1 and Phase 2a studies (accumulation with maraviroc dosing is presented in Module 2.7.2 Clinical Pharmacology Studies) Due to the severe cases of postural hypotension observed in the A4001001 at doses of 1200 mg, the upper limit of 900 mg was chosen to limit confounding postural effects. The results of this study indicated no clinically meaningful differences from placebo treatment at any tested dose of maraviroc; the 90% CI for the difference between maraviroc 900 mg and placebo was less than 7 msec, excluding a clinically meaningful effect at a supratherapeutic dose (details provided in A4001016 Clinical Study Report, Module 5.3.4.1 Healthy Subject PD and PK/PK Study Reports). An exposure-response analysis indicated that an increase in maraviroc concentration of 1000 ng/mL might be expected to be associated with an increase in QTc interval duration of

0.97 msec (Exposure-Response Modelling Report for UK427,857 Exposure on QT interval corrected for heart rate. Phase 1 Data (Protocol A4001016) Module 5.3.4.1. Healthy Subject PD and PK/PK Study Reports).

ECG measurements from the Phase 2b/3 studies in treatment-experienced patients demonstrated a mean change in QTc interval duration from baseline that was similar for all treatment groups at each study visit (+1.7, +1.3 and +2.2 msec at Week 24 for maraviroc QD, BID and placebo respectively, and -0.5, +0.6 and +5.2 msec at Week 48 for maraviroc QD, BID and placebo respectively). Three patients, all receiving maraviroc BID, experienced a change in QTc interval ≥60 msec. However, the number of these outliers is too small to draw conclusions and results are also confounded by the multiple background therapies, many of which (including protease inhibitors [approximately 90% of patients were receiving a PI in the maraviroc Phase 2b/3 clinical programme] and NNRTIs) have been shown to prolong the QTc interval (Anson BD, 2005, Castillo R, 2002).

No events of TdP have been reported during the maraviroc clinical programme. A review of adverse events that may reflect the potential for arrhythmias was conducted for the Phase 2b/3 studies and events were infrequent and evenly distributed between treatment groups (Section 2.7.4.2.1.5.1 Module 2.7.4 Summary of Clinical Safety).

In conclusion, therefore, although pre-clinical studies suggested the potential for maraviroc to prolong the QTc interval at high plasma concentrations, at therapeutic concentrations in the Phase 2b/3 clinical programme no clinically relevant effect was observed.

Cardiovascular Events Associated with Ischaemia:

The Phase 3 studies were reviewed for the incidence of cardiovascular-related adverse events (Section 2.7.4.2.1.5.1 Module 2.7.4 Summary of Clinical Safety and the Risk Management Plan). In Studies A4001027 and A4001028 the number of patients experiencing all causality cardiac-related adverse events were evenly distributed between treatment groups; 12 (2.5%), 8 (1.9%) and 3 (1.4%) reported in patients receiving maraviroc QD, BID and placebo respectively.

Of these cardiovascular-related adverse events there were more events that were possibly related to coronary heart disease occurring in patients receiving maraviroc compared with those receiving placebo, however, none led to temporary or permanent discontinuation from blinded study drug. There were 5 (1.2%) patients in maraviroc QD treatment group and 5 (1.2%) patients in the maraviroc BID treatment group versus 0 (0%) in the placebo treatment group.

Assessing the frequency of events per patient years and comparing to established cohorts showed that myocardial infarction event rate was consistent in this treatment-experienced population with overall event rates from the HIV-1 population as a whole. The rates were compared with published studies of coronary events in HIV-1 infected patient populations, including the Kaiser Permanente cohort (Klein D, 2003) and the D.A.D study (Friis-Møller N, 2006). Adjusted rates of MI in these populations were 3.6/1000 patient-years and 3.5/1000 patient-years respectively. The observed rate of myocardial infarction in the

combined maraviroc QD and BID treated patients was 3.8/1000 patient-years (2 events) [5.7/1000 patient-years (3 events including a presumptive myocardial infarction death)], with a p-value of 0.56 [0.29 –for 3 events including the myocardial infarction death] compared to expected from published data under a Poisson distribution assumption. The event rate of zero in placebo compared with the expected rate from published data of 0.35 had a p-value of 0.70. Despite the advanced nature of the HIV-1 infection in this study population, the myocardial infarction event rate was in keeping with that observed in all HIV-1 infected patients (Risk Management Plan).

As would be expected for the patient population studied in the maraviroc Phase 2b/3 clinical programme (i.e., a mainly white male population with approximately 50% aged over 45 years, all heavily pre-treated with HAART), all cases had more than one known risk factor. A detailed assessment of the eight subjects who developed adverse events linked to coronary heart disease in the maraviroc treatment group (QD and BID) has shown that they all had several pre-existing risk, including diabetes mellitus, hypertension, previous myocardial infarction, known coronary artery disease, hyperlipidaemia and smoking. This is discussed further in the Risk Management Plan.

In conclusion, the adverse event profile in the treatment experienced population demonstrated a possible imbalance in cardiac events related to coronary heart disease in the maraviroc treatment groups compared with placebo, which did not appear to be dose-related. However, the numbers of patients experiencing such events were small and the event rate is consistent with published data from the overall HIV-1 population. It is most likely that this is a reflection of the pre-existing cardiac morbidity of this heavily treatment-experienced patient population coupled with the low exposure in the placebo arm.

2.5.5.4.2. Hepatic Safety

There were liver function test abnormalities observed during 4 of the Phase 1 maraviroc studies. These abnormalities were sporadic in nature, did not appear to be treatment-related and the transaminase elevations were not associated with hyperbilirubinaemia (Section 2.7.4.2.1.5.3 Module 2.7.4 Summary of Clinical Safety).

The registrational Phase 3 studies were designed to allow patients with limited treatment options and a degree of hepatic compromise access to novel therapy, and to assess the hepatic safety of maraviroc in the context of co-morbidities (e.g., co-infection with hepatitis B and C).

For Studies A4001027 and A4001028, Grade 3/4 hepatic-related adverse events were reported at an incidence of 28 (5.8%), 39 (8.0%) and 14 (5.1%) in the maraviroc QD, BID and placebo treatment groups respectively. However, when adjusted for exposure, the incidence was reported as 1.2, 3.5 and 5.3 events per 100 patient years for maraviroc QD, BID and placebo respectively. Of the unadjusted events occurring, 9 (1.9%), 19 (3.9%) and 5 (1.8%) in the maraviroc QD, BID and placebo treatment groups were considered treatment-related by the Investigator. The incidence therefore remains higher in patients receiving maraviroc BID, which is mainly driven by an imbalance in liver function test abnormalities reported as adverse events.

A review of the serious adverse event database, from Studies A4001027 and A4001028, also revealed that cases related to hepatobiliary system abnormalities were reported more in the maraviroc BID treatment groups compared with maraviroc QD and placebo; 3 were possibly treatment-related but occurred a long time after commencement of study drug (127, 150 and 187 days), which is not completely consistent with a drug-induced hepatotoxicity (typically 1-8 weeks after starting therapy) (Durand D, 1996). This led to permanent discontinuation in 2 patients and temporary discontinuation in the third patient. For these cases initially attributed to study treatment, an alternative non-study-drug cause has been identified following thorough review of the details. One case of hepatic failure was reported in a patient receiving maraviroc QD in Study A4001027, but was unrelated to study drug and more likely due to recreational drug use interacting with background antiretroviral medication and concomitant *Campylobacter jejuni* septicaemia.

Overall, 9 patients discontinued from study drug due to hepatic-related adverse events in the Phase 3 registrational studies; 4 in the maraviroc QD treatment group, 5 in the maraviroc BID treatment group and 2 in the placebo treatment group. When corrected for exposure the discontinuation rate was evenly distributed between treatment groups. Of 11 patients who temporarily discontinued study drug, 6 were rechallenged. The liver function test abnormalities resolved and did not re-occur on rechallenge in 3 patients, the other 3 patients did not have resolution of the liver function test abnormalities but continued study drug to the time of data cut or time of permanent discontinuation. Two patients currently remain in study and 1 patient later discontinued therapy as a result of the need for intubation and subsequently died due to another cause.

For Study A4001029, the incidence of liver function test result abnormalities was low and similar between groups.

The most severe case of hepatotoxicity in the maraviroc clinical programme has occurred in Study A4001026 in a treatment-naïve patient randomised to receive maraviroc QD. This was a complicated case, which resulted in a liver transplant, for which a contributory role of maraviroc could not be excluded. However, following a thorough review of the case, including a full independent assessment by two external experts (one from the USA and one from France), it was thought that the case was most likely due to isoniazid and/or trimethoprim-sulphamethoxazole toxicity, compounded by ongoing therapy with other known hepatotoxic drugs. Details of this case report are provided in Module 2.7.4 Summary of Clinical Safety.

There have been no deaths reported due to hepatic adverse events in the Phase 2b/3 maraviroc clinical programme.

The overall incidence of Grade 3/4 transaminase abnormalities, irrespective of abnormality at baseline, was low in all treatment groups. Although cumulatively, Grade 3/4 abnormalities were balanced between groups, there were slightly more Grade 4 transaminase abnormalities in the maraviroc BID treatment group than in the maraviroc QD and placebo treatment groups. However, a review of the shift in liver function test parameters from baseline indicated that there was no evidence of a greater shift in the maraviroc treatment groups compared with placebo and there was no dose relationship for maraviroc. Patients

potentially meeting the criteria for Hy's Law whilst on study drug in the Phase 3 studies were few and evenly distributed between treatment groups: 3 (0.7%) maraviroc QD, 4 (1.0%) maraviroc BID, 1 (0.5%) placebo. However, all the cases with a ≥3 ULN for ALT or AST and simultaneous ≥3 mg/dl of total bilirubin noted in these studies had an identifiable cause for these abnormalities apart from study drug. Therefore no subjects met the criteria for Hy's Law.

The numbers of patients co-infected with hepatitis B and/or C were small in these studies and the results did not indicate that these patients had an increased risk of hepatotoxicity (Risk Management Plan).

In conclusion, although there was a higher number of patients in the maraviroc BID treatment group, compared with maraviroc QD and placebo, who experienced a hepatic-related serious adverse event, only 3 were possibly related to maraviroc therapy. Of these, 2 had an alternative pathology, which could explain the observations and the third had a negative rechallenge with study drug. Grade 3 and 4 hepatobiliary adverse events were infrequent but also occurred more frequently on maraviroc BID than the other 2 treatment groups. The numbers of discontinuations were evenly distributed between treatment groups. Grade 3 and 4 liver function test abnormalities were evenly distributed between treatment groups, except for a slightly higher incidence of Grade 3 and 4 AST abnormalities in the maraviroc BID treatment group. However, numbers are small and results are heavily confounded by the use of multiple concomitant antiretroviral medications, many of which have previously been shown to cause liver function test abnormalities. Overall, the clinical and laboratory data for the maraviroc clinical development programme does not indicate an adverse effect on hepatic function.

2.5.5.4.3. The Potential for Immunotoxicity

Due to the theoretical risk for CCR5 antagonists to cause an adverse effect on immune function and an altered risk of malignancy, a detailed review of these factors was undertaken for the maraviroc clinical development programme. This Special Safety Review of the Immunotoxic Potential of Maraviroc is provided in Module 5.3.5.3 Reports of Analyses of Data from More than One Study.

Overall, there was no clinical or laboratory evidence suggesting an increased susceptibility to infection or malignancy in either healthy or HIV-infected subjects.

Category C Events:

In Studies A4001027 and A4001028, there were 47 subjects reporting Category C infections, with a similar incidence in the 3 treatment groups 23 (5.3%), 16 (3.8%) and 9 (4.3%) in maraviroc QD, BID and placebo groups. Herpes simplex and oesophageal candidiasis were the most commonly reported, with slightly higher rate of herpes simplex in the maraviroc treatment groups; 7 (1.7%) in the QD, 6(1.4%) in the BID and 1 (0.5%) in the placebo group.

A total of 24 subjects (12 [2.8%] subjects receiving maraviroc QD, 8 [1.8%] subjects receiving maraviroc BID and 4 [1.9 %] subjects receiving placebo) experienced a Category C

infection during the first 4 weeks of treatment in comparison to 3 (0.7%), 2 (0.5%) and 4 (1.9%) respectively at ≥6 months on treatment. The reduced rate of events on maraviroc after 6 months of treatment is evidence of the lack of a negative effect on immune function by maraviroc or that any potential negative effect is outweighed by overwhelming efficacy compared to placebo. As expected, patients who experienced Category C AIDS defining infections had a lower median baseline CD4 cell count than those who did not experience such events.

In conclusion, for Studies A4001027 and A4001028, the results indicated that the rates of infection were similar between both maraviroc treatment groups and placebo. Similar results were obtained for Study A4001029. There were no unusual or unexpected infections reported. The incidence rate of category C infections in patients receiving maraviroc were similar to that seen in the placebo group. A slightly higher frequency of cases of herpes simplex was observed in the maraviroc treatment groups, but the herpes simplex infections are common in this population and difference in exposure may explain the difference in frequency (Section 2.7.4.2.1.5.4.1 Module 2.7.4 Summary of Clinical Safety).

Malignancies:

Thirty one patients reported all-causality adverse events of neoplasm (neoplasms benign, malignant and unspecified) in the treatment-experienced Studies A4001027, A4001028 and A4001029. There was no difference in the incidence between treatment groups; 12 (2.9%) in the maraviroc QD group, 10 (2.3%) in the maraviroc BID group and 9 (4.3%) in the placebo group. Two patients in the maraviroc BID treatment group permanently discontinued due to a malignancy (one due to anal carcinoma; one due to squamous cell tongue carcinoma of the tongue). Both events were considered to be a serious adverse event and neither was attributed to study drug.

None of the deaths that occurred within 28 days of study therapy during Studies A4001027 and A4001028 were as a result of malignancy. However, deaths as a result of malignancy did occur more than 28 days after the end of treatment in both studies.

The lymphoma rates during the randomised period of the trials in the treatment-experienced patient population infected with CCR5 tropic HIV-1 at the date of database cut-off were 2/259 (0.8 per 100 patient-years) on maraviroc QD, 2/269 (0.8 per 100 patient-years) on maraviroc BID respectively and 2/99 (2.0 per 100 patient-years) on placebo. To provide the most conservative assessment this includes Patient 12[redacted]0011 (in Study A4001028) receiving maraviroc BID, with the presumptive central nervous system lymphoma. When Patient 10[redacted]0002 (in Study A4001027) who, following treatment failure on placebo, developed a large B cell lymphoma after >4 months of open label maraviroc BID is included this provides an overall lymphoma rate. The overall numbers of lymphoma cases reported in treatment-experienced patients, regardless of time post therapy, are 2 cases on maraviroc QD, 3 on maraviroc BID (including Patient 10[redacted]0002 * on open label) and 2 on placebo. When the randomisation schedule of approximately 2:2:1 is considered this also demonstrates no difference in frequency between maraviroc and placebo, despite the extended treatment duration on maraviroc.

*：新薬承認情報提供時に追加した。
51頁下から4行目 10[redacted]10002*の症例は，下から8行目
10[redacted]10002 (in Study A4001027) の症例と同じ。

In conclusion, the incidence and severity of malignancies was similar between the maraviroc treatment groups and slightly higher in the placebo treatment group, although the numbers reported across the clinical programme were small. There were no unusual or unexpected malignancies and no evidence of any increased risk of malignancy has emerged from the data generated in the Phase 3 clinical programme. However, the rates of lymphoma are lower in the maraviroc treatment groups compared with placebo, as are the rates of Kaposi's sarcoma and anal cell carcinoma, and are in keeping with what would be expected from this population (Section 2.7.4.2.1.6.5.3 Module 2.7.4 Summary of Clinical Safety). This is discussed in more detail in the Risk Management Plan.

2.5.5.4.4. Laboratory Abnormalities

Median changes from baseline in laboratory parameters for patients receiving maraviroc QD, BID or placebo in Studies A4001027 and A4001028 demonstrated similar changes across the three treatment groups, apart from lymphocytes (absolute and percentages), cholesterol (HDL, LDL and total), triglycerides and creatine kinase, where larger mean increases were observed in the maraviroc treatment arms compared with the placebo group. The results are presented in detail in Section 2.7.4.3 Module 2.7.4 Summary of Clinical Safety.

Lymphocytes:

The median change from baseline for total lymphocyte count was greater for patients receiving maraviroc compared with placebo in studies A4001027 and A4001028. This was expected as patients receiving maraviroc had significantly higher increases in CD4 and CD8 lymphocyte counts compared with placebo. Patients receiving maraviroc were less likely to have lymphocytopenia (<0.8 X lower limit of normal) compared with placebo; 11% each for patients receiving maraviroc QD or BID, compared with 17% for patients receiving placebo. Increases in lymphocyte count (>1.2 X upper limit of normal) were observed in 4 and 6% of patients receiving maraviroc QD and BID, respectively, compared with 2% in patients receiving placebo. Similarly, increases in lymphocyte percentage were noted for 15 and 16% of patients receiving maraviroc QD and BID, respectively, compared with 7% in subjects receiving placebo.

Lipids:

In studies A4001027 and A4001028 a slightly higher proportion of subjects in the maraviroc QD and maraviroc BID treatment groups had maximum increases in cholesterol, LDL cholesterol, and triglycerides of ≥20% than in the placebo treatment group. The vast majority of patients received protease inhibitors as part of their OBT, which are associated with lipid abnormalities (Friis-Møller N, 2003). Therefore, the most likely explanation for the higher rates of increased cholesterol, LDL cholesterol and triglyceride concentrations in the maraviroc treatment arms is the longer duration of exposure for the maraviroc treatment arms compared to placebo, as patients in the maraviroc treatment arms also had a longer duration of exposure to protease inhibitors. A slightly higher proportion of patients, 33.2 and 34.9% of patients in the maraviroc QD and BID treatment groups respectively, had maximum increases in HDL cholesterol of ≥20% than in the placebo treatment group (28.0%). Similarly, a slightly higher proportion of patients receiving maraviroc had an

increase in HDL/LDL ratio of more than ≥20% compared with the placebo treatment group. These potentially beneficial effects on lipid parameters were also observed in Study A4001029 (summarised in Section 2.7.4.3 Module 2.7.4 Summary of Clinical Safety).

Creatine Phosphokinase:

Patients receiving maraviroc had a higher median change from baseline in creatine phosphokinase compared with placebo. There was also a higher incidence of creatine phosphokinase abnormalities (>2 X ULN) in subjects receiving maraviroc; 30% and 29% on maraviroc QD and BID, respectively, compared with 20% on placebo. Creatine phosphokinase abnormalities are very common in this population, as is evidenced by the fact that 258 patients (115 (28%) on maraviroc QD, 103 (24%) on maraviroc BID and 40 (19%) on placebo) had abnormal creatine phosphokinase values at baseline. The slight excess of creatine phosphokinase increases in the maraviroc treatment arms may be explained by the longer duration of exposure compared with placebo.

Conclusion:

In conclusion, maraviroc treatment was associated with a slightly greater increase in lipid parameters compared with placebo in this patient population. In Study A4001029 there was also an increase in HDL cholesterol and HDL/LDL ratio, which may have a beneficial cardiovascular effect. However, these changes are difficult to interpret as they are heavily confounded by the frequent use of PIs in the OBT, which are known to affect lipid measurements. Similarly, the increase in creatine phosphokinase in patients receiving maraviroc is of uncertain clinical significance and the imbalance is most likely due to the longer exposure to drug in patients receiving maraviroc compared with placebo in a patient population with pre-exiting co-morbidities, which may predispose to fluctuating creatine kinase measurements. The changes observed in lymphocyte count were expected given the nature of the CD4 and CD8 cell count increases on maraviroc therapy.

2.5.5.4.5. Safety Conclusions

In Phase 1 clinical studies postural hypotension was the dose limiting adverse effect, such that 300 mg was chosen as the well tolerated dose, and dosing adjustments for PI-containing regimens were made to control for Cmax. Maraviroc given as either a QD or BID regimen, dose adjusted for OBT, was well tolerated compared with placebo, and dizziness and postural hypotension were not observed with significantly greater frequency than placebo. A slight excess of adverse events was noted compared with placebo for both maraviroc QD and BID regimens, but much of the difference is likely explained by the increase in duration of follow up for the maraviroc treatment groups compared with the placebo group. Discontinuations due to adverse events were similar in all 3 treatment groups suggesting that most adverse events were either tolerated or attributable to other causes. There was a slight difference in adverse event reporting rates between maraviroc QD and BID regimens, but again differences were neither marked nor consistent. Deaths, serious adverse events and Grade 3 and 4 laboratory abnormalities were similar between groups. A slight excess in the maraviroc BID group of elevated creatine phosphokinase and Grade 3 and 4 AST increases was noted, however numbers were small in each treatment group and no firm relationship

could be established. There was no evidence of a clear dose related trend in any other adverse events. Systematic measurement of QTc and postural blood pressure showed no differences between treatment groups. Category C events were reported with similar frequency in the placebo and maraviroc QD groups, and slightly less frequently in the maraviroc BID groups. Importantly, there was no evidence of a trend towards greater numbers of treatment discontinuations due to adverse events for either of the maraviroc treatment groups.

In conclusion, maraviroc as a 300 mg QD or BID dosing regimen, adjusted to 150 mg in the presence of CYP3A4 inhibitors, showed an acceptable toleration profile with no important differences compared with placebo. There were no important differences between QD and BID dosing with respect to adverse findings. Appropriate information about the safety of maraviroc, including an precautions for use in clinical practice an adverse effects of potential overdose.

2.5.5.5. Dose Selection for Marketing and Recommendations for Label

Studies A4001027 and A4001028 were designed to test the hypothesis that maraviroc (QD or BID) added to OBT provided an additional reduction in plasma HIV-1 RNA level compared with OBT alone, based on the mean changes from baseline in plasma HIV-1 RNA level at Week 48. In two independent studies, differing only by the range of geographic regions represented, the superiority of both maraviroc doses was confirmed, based on the primary efficacy endpoint, as well as all of the secondary virologic and immunologic endpoints. These studies also demonstrated that maraviroc (QD or BID) has an acceptable safety and tolerability profile, with no increased risk of hepatotoxicity, secondary infection, malignancy or QTc interval prolongation, relative to placebo.

These two studies were not designed to formally test the differences in efficacy between the QD and BID doses of maraviroc. However, one benefit from the merged Phase 2b/3 approach is the greater potential for any trends to become evident in a relatively large, adequately powered, long-term study of two individual dosing regimens. Although an unplanned analysis of the primary endpoint, conducted based on the pooled maraviroc data from the two studies, demonstrated a treatment difference between the maraviroc BID and maraviroc QD arms of only -0.085 $\log_{10}$ copies/mL (CI: -0.274, 0.104), there are several trends or factors which suggest that based on the 24-week interim analyses of these studies, maraviroc dosed twice-daily is the preferred option:

1. In the combined analysis of Studies A4001027 and A4001028 there were numerical trends in favour of maraviroc BID for all of the key secondary virologic endpoints (e.g., proportion of patients at Week 24 with HIV-1 RNA <400 copies/mL, < 50 copies/mL and >1 log reduction from baseline).

2. In the combined analysis of Studies A4001027 and A4001028, for patients with HIV-1 RNA ≥100,000 copies/mL, there was a greater proportion of patients at Week 24 with HIV-1 RNA <400 copies/mL (51.7% versus 44.7%) and with HIV-1 RNA <50 copies/mL (34.7% versus 28.2%) in the maraviroc BID treatment group compared with the maraviroc QD treatment group. This has actually been the case at the Week 24

timepoint (Week 16 for Study A4001026) for all the Phase 2b/3 studies in patients infected with CCR5 tropic HIV-1 that have been conducted in this programme, as demonstrated in the following table:

HIV-1 RNA (copies/mL)	Maraviroc QD		Maraviroc BID[b]		Placebo	
	N[a]	n (%)	N[a]	n (%)	N[a]	n (%)
A4001026 (ARV-Naïve) % < 400 copies/mL						
<100,000	34	30 (88.2)	71	63 (88.7)	NA	NA
≥100,000	34	23 (67.7)	66	57 (86.4)	NA	NA
A4001026 (ARV-Naïve) % < 50 copies/mL						
<100,000	34	30 (88.2)	71	59 (83.1)	NA	NA
≥100,000	34	15 (44.1)	66	38 (57.6)	NA	NA
A4001027 (ARV-Experienced) % < 400 copies/mL						
<100,000	135	95 (70.4)	139	101 (72.7)	70	33 (47.1)
≥100,000	93	41 (44.1)	95	48 (50.5)	46	6 (13.0)
A4001027 (ARV-Experienced) % < 50 copies/mL						
<100,000	135	77 (57.0)	139	83 (59.7)	70	26 (37.1)
≥100,000	93	26 (28.0)	95	35 (36.8)	46	4 (8.7)
A4001028 (ARV-Experienced) % < 400 copies/mL						
<100,000	103	77 (74.8)	104	81 (77.9)	53	17 (32.1)
≥100,000	77	35 (45.5)	81	43 (53.1)	38	7 (18.4)
A4001028 (ARV-Experienced) % < 50 copies/mL						
<100,000	103	69 (67.0)	104	57 (54.8)	53	16 (30.2)
≥100,000	77	22 (28.6)	81	26 (32.1)	38	5 (13.2)

[a] Number of patients in treatment group.
[b] Pooled Maraviroc BID + Efavirenz groups (blinded) for A4001026 analysis only.
Last Observation Carried Forward (LOCF) was used to impute missing values.
QD = Once daily dosing; BID = Twice daily dosing; ARV = Antiretroviral Therapy.

Interestingly, within the individual trials in treatment-experienced patients with CCR5-tropic HIV-1, the only secondary virologic endpoint which was numerically in favour of maraviroc QD (proportion <50 copies/mL at Week 24 in Study A4001028) was predominantly driven by the response in those patients with viral loads of <100,000 copies/mL. In patients with viral loads ≥100,000 copies/mL, the maraviroc BID arm is numerically superior, as it is for all the other trials.

Although the effect is somewhat more subtle in this comparison of maraviroc QD versus BID, other clinical trials, such as with abacavir/lamivudine/zidovudine (Staszewski S, 2001) and with nelfinavir (King MS, 2004), have highlighted important treatment differences when the efficacy of two different treatment regimens is assessed by the magnitude of the screening viral load.

3. In the combined analysis of Studies A4001027 and A4001028, for patients with CD4 count <50 cells/μL, there were approximately twice as many patients who achieved an HIV-1 RNA <50 copies/mL in the maraviroc BID group than in the maraviroc QD group (20.0% versus 10.6%) and a similar trend for the endpoint of <400 copies/mL (30.6% versus 20.0%, respectively). Reduced efficacy rates in patients with lower versus CD4 cell counts were also observed in the discontinued maraviroc QD arm of Study A4001026.

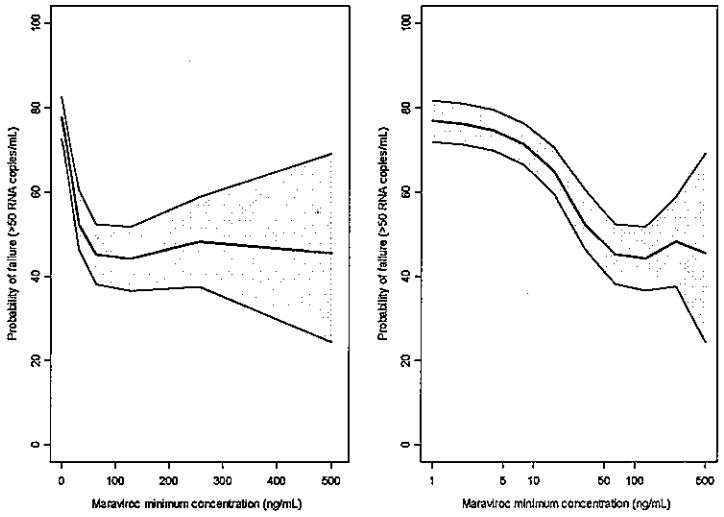
4. In the combined analysis of Studies A4001027 and A4001028, for patients with an OSS of 0, there was a greater proportion of patients at Week 24 with HIV-1 RNA

<400 copies/mL (41.1% versus 25.5%) and with HIV-1 RNA <50 copies/mL (28.6% versus 17.7%) in the maraviroc BID treatment group compared with the maraviroc QD treatment group. These patients represented approximately 20% of the population with an OSS ≤2 population. Similar trends were also observed for patients with GSS of 0 and PSS of 0.

5. Study A4001027, which was the larger of the two studies and recruited a more homogeneous population geographically, more clearly suggested trends in favour of the maraviroc BID treatment group.

6. The failure of the maraviroc 300 mg QD arm to meet pre-specified non-inferiority criteria to efavirenz in Study A4001026, which, while in a different patient population, argues against recommending a once-daily dose in the absence of a CYP3A4 inhibitor. The similarity of the maraviroc QD and BID arms of Studies A4001027 and A4001028 (versus A4001026) is probably the result of pharmacoenhancement with boosted and unboosted PIs, leading to adequate correction of maraviroc Cmax and under-correction of maraviroc AUC (resulting in maraviroc AUCs that in many cases greatly exceed that observed with a 300 mg dose in the absence of CYP3A4 inhibition). While there were no obvious differences in efficacy, between patients on PI and non-PI containing regimens (both within and across treatment groups), the numbers of patients on no PI were relatively small. A preliminary population pharmacokinetic-pharmacodynamic analysis has been performed evaluating maraviroc concentrations versus likelihood of a patient achieving a viral load of <50 copies/mL from the first 500 patients in Studies A4001027 and A4001028. Using a generalized additive model approach to try to adjust for a number of variables, including OBT, a concentration effect curve could be modelled (Figure 6). There are many assumptions and confounders, and interactions between covariates have not been modelled. However, concentration appears more informative than dose alone and a sigmoid concentration effect relationship could be derived from the clinical trials, suggesting that dosing strategies deployed should aim for maraviroc exposures equivalent to 300 mg BID for optimal efficacy in the largest number of patients.

Figure 6. Median (95% CI) Prediction of Likelihood of Failure (>50 copies/mL) at Week 24 as a Function of the Maraviroc Minimum Concentration



These graphs are based on the final GAM model fitted to 300 bootstrap samples of the original data set.
Left hand graph: linear-linear scale. Right hand graph: log-linear scale.

Other considerations, which should be considered given that only interim 24 week data are currently available include:

7. The fewer number of category C events in the maraviroc BID treatment group (19) compared with the maraviroc QD group (29). While these were primarily the result of an increase in the number of cases of mucocutaneous herpes simplex virus infection and esophageal candidiasis, rather than for severe or life threatening category C events and are most likely due to chance (particularly as the increase in CD4 cell counts from baseline were similar for the two groups) it nonetheless suggests that maraviroc BID may be preferable. Interestingly, there were also more category C events in the maraviroc QD arm (7) of Study A4001029 than in the maraviroc BID arm (3).

8. The trend in favour of maraviroc BID in Study A4001029 for the primary and key secondary endpoints. While treatment-experienced patients with dual/mixed-tropic virus are not the target population being sought in this application, for patients who receive maraviroc inadvertently, without laboratory evidence of CCR5-tropic virus, or who have circulating CXCR4-variants below the limit of assay detection, selection of the optimal dose for this population is prudent.

Finally, and as will be described in more detail in the following "Benefits and Risks Conclusions" Section 2.5.6, overall and for the dose-limiting adverse event of postural hypotension, as well as for hepatotoxicity, secondary infection and malignancy, there is no evidence of a dose response with respect to safety which would argue against the use of the

maximally efficacious dose in this highly treatment-experienced patient population with few or no remaining treatment options.

In summary, the efficacy and safety data for Studies A4001027 and A4001028, supported by safety data in patients with non CCR5-tropic HIV-1 in Study A4001029 suggest that maraviroc should be indicated for use in combination with other antiretroviral agents, in treatment-experienced adult patients infected with CCR5-tropic HIV-1. For the reasons stated above, a twice-daily dose is preferred.

With respect to dosing recommendations, the maraviroc dose modification recommendations for the Phase 2b/3 clinical studies were successful in limiting Cmax so as not to significantly exceed that seen with 300 mg in the absence of interacting agents, while maintaining an average plasma exposure (Cave) that was at or above a that seen with 300 mg in the absence of interacting agents (median estimated increase in Cave over a 300 mg reference concentration of 1.56 fold for maraviroc QD and 1.73 for maraviroc BID). Therefore, the recommended initial dose is 300 mg BID but a dose increase to 600 mg BID or decrease to 150 mg BID may be necessary based on the potential for drug interactions (

Table 15).

Table 15. Dosing Recommendations for Use of Maraviroc in Clinical Practice

Concomitant Medications	Maraviroc BID
CYP3A4 inhibitors including: • protease inhibitors (except tipranavir/ritonavir) • delavirdine • ketoconazole, itraconazole, clarithromycin, nefazadone, telithromycin	150mg BID
CYP3A4 inducers (without a CYP3A4 inhibitor) including: • efavirenz and nevirapine • rifampin and rifabutin,	600mg BID
Other concomitant medications, including all other antiretrovirals including tipranavir/ritonavir	300mg BID

2.5.6. Benefits and Risks Conclusions

The efficacy of maraviroc for the treatment of treatment-experienced patients infected with CCR5 tropic HIV-1 was established in two independent, randomised, double-blind, placebo-controlled, adequately powered Phase 3 studies, with supportive safety data from a Phase 2b exploratory study in treatment-experienced patients infected with non-CCR5 (dual/mixed tropic, CXCR4-tropic or non-phenotypable) HIV-1. The Phase 3 studies (A4001027 and A4001028) were designed and conducted in accordance with published guidance from the FDA and CHMP. For both studies and for the combined analysis of the studies, the prospectively defined endpoint was achieved for both doses of maraviroc with a wide superiority margin against placebo, when all therapies were administered in combination with OBT. Statistical superiority of both doses of maraviroc over placebo was also demonstrated for every one of the virologic and immunologic secondary endpoints.

Maraviroc also demonstrated superior efficacy and comparable safety in each of the subgroup populations studied. The patient demographics for the 2 Phase 3 studies adequately

reflected the epidemiology of treatment experienced patients globally. However, the maraviroc clinical programme was limited in terms of the epidemiology of some of the patient population targeted for treatment. Specifically, there were relatively few women randomised, very few patients >65 years of age and limited numbers in each of the racial non-white groups studied.

There appeared to be a smaller mean change from baseline for the subgroup of black patients (compared to the overall, predominantly white population) receiving maraviroc QD and BID compared with placebo. However, this may be explained by the black placebo subgroup having an unusually high mean change from baseline compared with the white placebo subgroup, by the small number of patients in the black placebo subgroup and also by the skewed nature of the data in the black placebo treatment group towards higher decreases in viral load. Despite this, the black subgroup population still derived significant clinical benefit from receiving maraviroc.

With respect to the other demographic subgroups, although there were few females included in these studies, the results demonstrated no effect of gender on reduction in HIV-1 RNA from baseline. Similarly, although there were very few patients aged ≥65 years, the results demonstrated that there was no pattern of effect of age on response to therapy in any of the treatment groups. Maraviroc has not been studied in children <16 years of age. A pediatric study of maraviroc in patients aged 2 to 16 years is planned to commence in the latter half of 2[redacted]

Consistent with the activity of maraviroc being limited to CCR5-tropic HIV-1, patients with evidence of dual/mixed-tropic or CXCR4-tropic HIV-1 (or whose virus could not be phenotyped to establish a tropism assignment) were excluded from these registrational studies. Of the 1042 patients with a CCR5 tropism result at screening, 79 (7.6%) patients had a different tropism result at baseline and all of these were assigned as dual/mixed-tropism result. This illustrates the background change in tropism result over a 4 to 6 week period in this treatment-experienced population, prior to a change in antiretroviral regimen or administration of a CCR5 antagonist. As shown in study A4001029, which specifically targeted patients with dual/mixed-tropic HIV-1, patients in the A4001027 and A4001028 with dual/mixed-tropic HIV-1 at baseline received no significant antiviral benefit from maraviroc (dosed either QD or BID) added on to OBT. However, as in A4001029, there was also no evidence of harm, with comparable mean changes in HIV-1 RNA from baseline to week 24 in the maraviroc QD, maraviroc BID and placebo groups. Reassuringly, the mean change from baseline in $\log_{10}$ HIV-1 RNA for patients with dual/mixed virus receiving maraviroc was comparable or better than that observed for the total placebo population. Similar to the results of Study A4001029, mean increases in absolute CD4 cell counts were observed for both the maraviroc QD and maraviroc BID treatment groups with a non-CCR5 tropism result at baseline.

The maraviroc dose modification recommendations for the Phase 2b/3 clinical studies were meant to limit Cmax so as not to significantly exceed that seen with 300 mg in the absence of interacting agents, while maintaining an average plasma exposure (Cave) that was at or above that seen with 300 mg in the absence of interacting agents. There was no difference in reduction in viral load from baseline for patients receiving a dose adjustment to 150 mg

maraviroc compared with those who were not, for any of the treatment groups, and both doses of maraviroc continued to demonstrate superior efficacy over placebo. These results indicate that the dose adjustment for concomitant antiretroviral agents that are known to inhibit CYP3A4 was adequate and provided similar efficacy to unadjusted doses in the absence of a PI (except for tipranavir/ritonavir) and/or delavirdine.

With respect to safety, both doses of maraviroc appeared to be comparable to the placebo treatment group. Postural hypotension was the dose-limiting adverse event observed in the Phase 1/2a clinical program primarily occurring at unit doses greater than 300 mg. As expected, postural hypotension events were rare during the Phase 2b/3 clinical studies. The dose adjustments (i.e., a 50% reduction to maraviroc 150 mg QD or BID in the presence of CYP 3A4 inhibitors) used to correct Cmax were therefore adequate, in that the event rate in Phase 2b/3 trials for this adverse event is similar to placebo, reproducing the Phase 1/2a observations.

Cardiovascular events possibly related to coronary heart disease were noted at a greater frequency in the maraviroc treatment groups than on placebo, although the event rate itself was very low and comparable to the broad HIV-1 population cohorts. However, considering the high cardiovascular morbidity of these patients and the longer duration of treatment for patients on maraviroc these results are most likely due to chance.

There was no indication of in an increased risk for hepatotoxicity (which has been reported with another CCR5 antagonist previously in development) with maraviroc treatment even in patients coinfected with hepatitis B and C. Likewise, there did not appear to be any adverse effect of treatment on immune function, and in fact, maraviroc treatment was associated with a lower incidence of lymphomas than would be expected from the patient population studied.

In conclusion, based on the efficacy data from two registrational trials in highly treatment-experienced patients with CCR5-tropic HIV-1, maraviroc has the potential to meet an urgent unmet medical need for novel antiretroviral agents without cross-resistance to other classes, in patients who have few or no remaining options. The increased efficacy of maraviroc, dosed either once-daily or twice-daily, versus patients receiving OBT alone, is comparable or better than what has been shown with the fusion inhibitor enfuvirtide (despite the availability of new potent agents, leading to a relatively inflated placebo response). It is also comparable to more recently approved agents such as darunavir (TMC-114), which like maraviroc, also has the potential when added to background therapy, to achieve suppression of viral replication in a substantial number of patients who are heavily pre-treated with advanced HIV infection. Finally, the results in treatment-experienced patients with CCR5-tropic versus non CCR5-tropic HIV-1 provide long term clinical data validating the Monogram Biosciences (Trofile™) HIV Entry Tropism assay as an effective and appropriate means to identify patients with CCR5-tropic HIV-1 and who are therefore likely to respond to maraviroc. The Applicant has taken steps to ensure that at least this assay is available worldwide if maraviroc is approved for use.

A careful and comprehensive review of the maraviroc safety database has shown that a) the dose limiting adverse event identified in early clinical development of maraviroc (i.e. postural hypotension) does not occur to significant degree and is not different to placebo at

doses equivalent to 300mg QD and BID and b) there is no evidence of a "class effect" in terms of the safety concerns that have emerged due to other CCR5 antagonists (e.g. hepatotoxicity, malignancy). Maraviroc has therefore clearly demonstrated a positive benefit-risk for treatment-experienced patients infected with CCR5 tropic HIV-1. In addition, maraviroc does not appear to cause any untoward effects in patients with dual/mixed tropic HIV-1 and may provide an immunologic benefit (CD4 cell count increase) in these patients. These data, therefore also indicate that maraviroc is safe if inadvertently administered to a patient without laboratory evidence of CCR5-tropic virus, or who has circulating CXCR4-using variants below the limit of assay detection.

Maraviroc has met the regulatory definition for accelerated review; (i) the disease studied is serious or life-threatening, (ii) plasma viral load measurements are an acceptable surrogate marker for demonstrating clinical benefit, and (iii) all patients were treated with a patient-specific OBT chosen on the basis of virus susceptibility testing, irrespective of treatment group and (iv) maraviroc demonstrated statistically superior efficacy over placebo at 24 weeks in treatment-experienced patients with few or no remaining treatment options. These data support the use of maraviroc, in combination with other antiretroviral agents, for use in treatment-experienced patients infected with CCR5 tropic HIV-1.

In the European Union, the European Guideline on the Procedure for accelerated assessment (EMEA/419127/05) adopted by CHMP July 2006 sets out the criteria for accelerated assessment. Maraviroc is a novel potentially first in class orally administered agent that has been shown to be safe and highly effective in a treatment-experienced patient population (as demonstrated by viral loads of approximately 4.86 $\log_{10}$ copies/mL, mean baseline CD4 cell count approximately 170 cells/μL and more than 70% of patients with an Genotypic Susceptibility Score of ≤ 2). Importantly, approximately 45% of patients receiving maraviroc were found to have a viral load <50 copies/ml (i.e., considered maximally suppressed), compared with just 23% on placebo (OBT alone), thus reducing the risk of resistance emergence and the risk of transmission of a multidrug resistant virus. Based on the novel therapeutic mechanism, the in vitro resistance profile and safety and efficacy data presented in this submission, the Applicant has provided justification for accelerated review.

The recommended dosing regimen is for maraviroc to be administered twice-daily (with unit doses to be adjusted based on concomitant medications, as outlined in the previous table).

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