PFIZER INC

MARAVIROC Tablets NDA 22-128

ANTIVIRAL DRUGS ADVISORY COMMITTEE (AVDAC) BRIEFING DOCUMENT

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACTG	AIDS Clinical Trials Group
AIDS	Acquired immune deficiency syndrome
AFSSAPS	Agence Francaise de Securite Sanitaire des Produits de Sante, the French regulatory agency
ALT	Alanine aminotransferase
ANCOVA	Analysis of co-variance
ARV	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUS	Australia
BID	Twice daily treatment regimen
CCR5	CC Chemokine Receptor 5
CCR5Δ32	CCR5 gene with 32 base pair deletion
CCR5-Tropic Viruses	Viruses may use CCR5 as their entry co-receptor
CD	Cluster of differentiation
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulation
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CNS	Central nervous system
CTD	Common Technical Document
CXCR4	CX Chemokine Receptor 4
CXCR4-Tropic Viruses	Viruses may use CXCR4 as their entry co-receptor
CXCR4-Using	Collective term for X4-tropic and D/M-tropic samples
CYP3A4	Cytochrome P450 Enzyme 3A4
D/M	Dual/mixed tropic virus
D/M-Tropic	Samples in which both CCR5-tropic and CXCR4-tropic virus is detected in the Trofile™ assay.
DSMB	Data safety monitoring board
Dual-Tropic Viruses	Viruses may use either CCR5 or CXCR4 as their entry co-receptor
EAP	Expanded access program
ECG	Electrocardiogram
EFV	Efavirenz
EU	Europe
FAS	Full analysis set
FDA	United States Food and Drug Administration
GALT	Gut-associated lymphoid tissue
GAM	Generalized additive model
GGT	Gamma glutamyltransferase
gp41	Glycoprotein 41
gp120	Glycoprotein 120
GSK	Glaxo SmithKline
GSS	Genotypic susceptibility score
HAART	Highly active antiretroviral therapy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High density lipoprotein cholesterol
hERG	Human ether a-go-go-related gene
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 Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
I_{KR}	hERG current
ISOD	In-Study-Off-Drug
KLH	Keyhole limpet hemocyanin
K_m	Michaelis-Menten constant: the concentration of substrate that permits half maximal rate of reaction
LA	Latin America
LDL	Low density lipoprotein cholesterol
LFT	Liver function test
LOCF	Last observation carried forward
LOQ	Limit of quantification
MedDRA	Medical Dictionary for Regulatory Activity
MIP	Macrophage inflammatory protein
MNU	N-methyl-N-nitrosourea
MPA	Medical Products Agency, the Swedish regulatory agency
MR	Mortality Ratio
MVC	Maraviroc
NA	North America
NDA	New Drug Application (United States)
NK	Natural killer cell
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NOAEL	No observed adverse effect level
NRTI	Nucleoside/nucleotide reverse transcriptase inhibitor
OBT	Optimised background therapy
OSS	Overall susceptibility score
PBL	Peripheral blood leucocytes
P-gp	P-glycoprotein
PHA	Phytohaemaglutinin
PI	Protease inhibitor
PID	Patient identification number
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
QT	Time from beginning of the QRS complex to the end of the T wave in the electrocardiogram
QTc	QT interval, corrected for heart rate
R5-Tropic	Samples in which only CCR5-tropic virus is detected in the Trofile™ assay
RANTES	Regulated on activation of normal T cell expressed and secreted
RNA	Ribonucleic acid
RSA	South Africa
RT-PCR	Reverse transcriptase polymerase chain reaction
SDM	Site directed mutagenesis
TAD	Time averaged difference
TdP	Torsade de pointes
TID	Three times a day treatment regimen
Tg	Transgenic
TSH	Thyroid stimulating hormone
UDPGT	Uridine 5-diphosphate glucuronyl transferase
ULN	Upper limit of normal
USPI	United States Package Insert
WT	Wild type
X4-Tropic	samples in which only CXCR4-tropic virus is detected in the Trofile™ assay

EXPLANATION OF TERMS USED TO DESCRIBE TROPISM IN THIS DOCUMENT

Viruses may use CCR5 as their entry co-receptor ('**CCR5-tropic' viruses**), CXCR4 as their entry co-receptor (**'CXCR4-tropic' viruses**) or either CCR5 or CXCR4 ('**dual-tropic' viruses**). A patient may harbor a mixture of viruses with different co-receptor usage. Viral tropism was determined throughout the maraviroc program using a phenotypic assay. Samples in which only CCR5-tropic virus is detected in the assay are classified as '**R5-tropic**'; samples in which only CXCR4-tropic virus is detected are classified as '**X4-tropic**' and samples in which both CCR5-tropic and CXCR4-tropic virus is detected are classified as '**D/M-tropic**'. In most cases, the detection of CXCR4-tropic virus in a pure or mixed population is considered collectively (i.e. X4-tropic and D/M-tropic samples are collectively referred to as "**CXCR4-using**"), in light of the fact that both contain viruses which are not inhibited by maraviroc.

1. SUMMARY

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 infection with viruses resistant to current antiretroviral drug classes.

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 activity 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. This translated to approximately 2x patients receiving maraviroc achieving a viral load less than 50 copies/mL than placebo treated patients. These studies also demonstrated an acceptable safety and tolerability profile with no significant effect on QTc interval nor an increase in the incidence of hepatoxicity, infections or malignancies, relative to placebo.

This briefing document provides a summary of the development of maraviroc, including pre-clinical data, as well as a discussion of the clinical data from the maraviroc development program, which supports the conclusions 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 having very few or no remaining treatment options available;
- Does not appear to result in harm when administered to patients infected with dual/mixed tropic HIV-1.

2. INTRODUCTION

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 utilized 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 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). 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

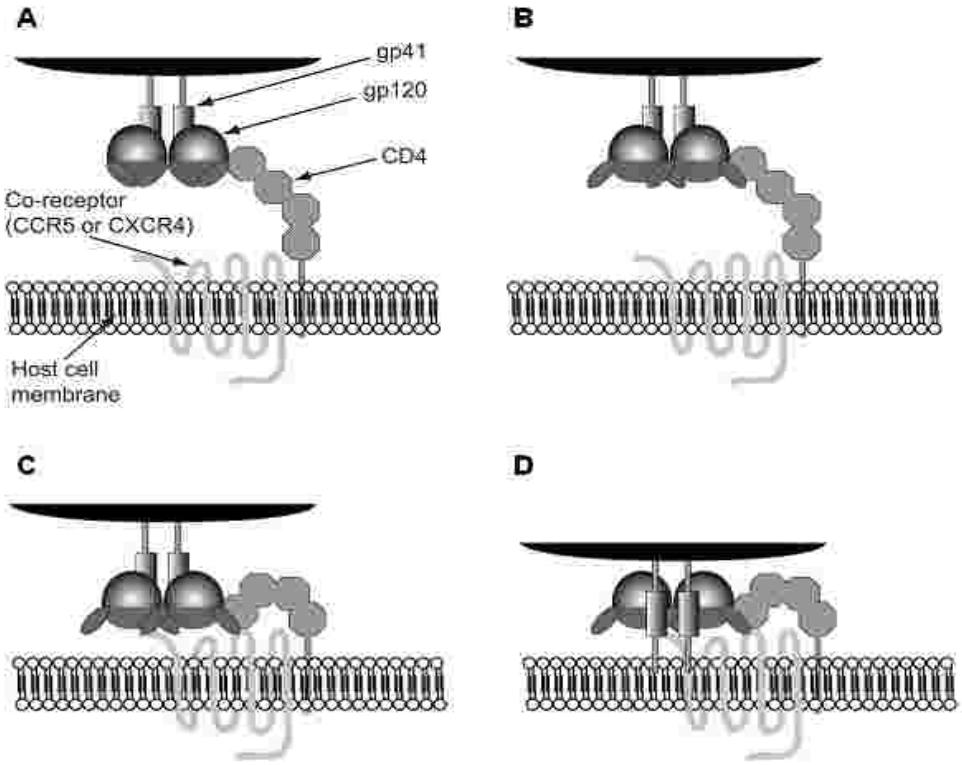


Figure legend. A model for HIV-1 entry. HIV-1 gp120 binds to CD4 (A). This induces conformational changes in gp120 and exposure of the co-receptor binding site (B), which is a complex domain that includes the V3 loop and is collectively termed the 'bridging sheet'. Exposure of the co-receptor binding 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 (rather than X4 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 subjects 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 following infection with HIV-1 compared to 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 strains resistant to any or several of the four existing drug classes. 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 program 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 Sponsor in the NDA 22-218 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 only. 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 only 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 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, are presented in this submission.

3. MICROBIOLOGY

Maraviroc has been developed as an HIV-1 entry inhibitor for chronic oral administration to prevent the development and progression of AIDS in individuals infected with HIV-1. Targeting a human cellular receptor in order to prevent viral entry is a new approach to HIV-1 therapy.

A number of primary pharmacodynamic studies were conducted to investigate the antiviral mode of action of maraviroc. The objectives of these in vitro studies were to characterize the binding of maraviroc to CCR5 and the consequent inhibition of virus entry. Cell based assays of acute viral infection were used to project an efficacious dose in order to guide subsequent non-clinical and clinical testing. The ability of maraviroc to inhibit viruses of wide geographical origin, diverse clade and with reduced susceptibility to existing drug classes was also investigated.

3.1. Mechanism of Action

This new chemical entity acts by selectively binding to the human chemokine receptor CCR5 and inhibiting the interaction of the envelope glycoprotein (gp120) from CCR5-tropic HIV-1 strains with CCR5. Binding of gp120 to CCR5 is an essential step in the HIV-1 entry process for CCR5-tropic strains.

Maraviroc binds to human CCR5 with a K_D of 0.86 nM and at room temperature has a dissociation half-life of approximately 16 hours. Site directed mutagenesis and computer modeling studies locate the likely binding site of maraviroc to a pocket within the transmembrane region of CCR5. As a consequence of this binding, maraviroc is thought to alter the three dimensional structure of CCR5 such that the viral envelope glycoprotein, gp120, is unable to recognize and bind to the co-receptor. Consistent with this, maraviroc blocks the soluble form of gp120 binding to CCR5 with an IC_{50} of 11 nM and inhibits gp120/CCR5-mediated membrane fusion with an IC_{50} of 0.22 nM.

3.2. Antiviral Activity In Vitro

Maraviroc selectively inhibits CCR5-tropic HIV-1 replication in vitro. The compound is active in antiviral assays using immortalized cell lines, peripheral blood lymphocytes (PBL) and monocyte-derived macrophages. Maraviroc also inhibits the infection by HIV-1 envelope pseudotyped viruses of a recombinant cell line transformed to express high levels of CCR5 and CD4. Maraviroc inhibits viral replication in vitro in a non-competitive manner with respect to virus input. This is consistent with the compound binding to a human drug target (CCR5) rather than a viral target. The antiviral activity of maraviroc occurs in the absence of any compound cytotoxicity in all these assay systems.

Maraviroc inhibited replication of 43 CCR5-tropic primary isolates in human peripheral blood lymphocytes with a geometric mean IC_{90} of 2.03 nM (1.04 ng/mL, N = 190, 4 replicate assays per isolate). This panel of isolates represented a wide geographical origin and diversity of viral clades. Peripheral blood lymphocytes contain primary CD4+ T-cells, which represent the major cellular reservoir for HIV-1 replication in vivo. The IC_{90} value obtained in these studies is therefore taken as the primary pharmacological value representing the antiviral activity of maraviroc. As the unbound concentration of maraviroc in these assays was determined to be 54.8%, the unbound in vitro antiviral IC_{90} for maraviroc is estimated to be approximately 1.0 nM (0.5 ng/mL).

The primary pharmacological value was used to plan and assess pre-clinical and clinical studies with the aim of targeting concentrations/doses where the free C_{min} exceeded this value. The rationale for selecting IC_{90} to derive this value is that this represents a clinically relevant 1 $\log_{10}$ drop in virus replication. When the lowest drug concentration (C_{min}) in patients treated with maraviroc is compared to the in vitro unbound drug IC_{90}, the patient exposure is 16-fold higher than the in vitro antiviral values. When consideration of the IC_{50} is made, the patient exposure is 60-fold higher than the in vitro antiviral value.

Maraviroc inhibits replication of viruses resistant to existing antiretroviral agents that target viral enzymes. This has been evaluated in vitro with a large panel of pseudotyped viruses (200 viruses of which 100 were derived from protease and reverse transcriptase inhibitor resistant viruses), containing envelope genes (gp120/gp41) derived from well-characterized clinical samples of Clade-B and non-B genetic background. The geometric IC_{50} *n*-fold change (defined as the clinical isolate IC_{50}/JRCSF reference virus IC_{50}) against this panel is 0.69-fold (95% CI, 0.64 to 0.73).

There is no difference in the susceptibilities of Clade B viruses and non-B viruses to maraviroc. There is a small but statistically significant difference between the drug-naïve and drug resistant groups, with geometric *n*-fold changes of 0.60 fold (95% CI, 0.55 to 0.65) and 0.79 fold (95% CI, 0.72 to 0.86) respectively ($p < 0.001$). Given the large window between in vitro efficacy and steady-state unbound C_{min} levels achieved in HIV-1 infected patients, this small difference is unlikely to be of clinical relevance, supporting the use of maraviroc in patients harboring virus strains resistant to existing antiretrovirals.

Maraviroc is also active in vitro against virus strains resistant to the fusion inhibitor, enfuvirtide. This was demonstrated during the clinical phase of the program, when 38 patient-derived viruses (half of which harbored resistance to enfuvirtide) were all shown to be susceptible to maraviroc.

Maraviroc-resistant (MVCres) virus has been selected by serial passage. The characteristics of these MVCres variants are that they remain CCR5-tropic, are sensitive to other entry inhibitors and the test PI (saquinavir) and contained amino acid substitutions/deletions in the gp120 V3 loop, which appeared to be strain specific. Currently there are no genotypic markers of resistance to maraviroc. This is discussed further in Section 8 of this briefing document.

4. NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY

4.1. Introduction

To investigate the effects of maraviroc on CCR5 that are not related to its antiviral activity, studies on chemokine binding and cellular signaling were conducted. Secondary pharmacodynamic studies were conducted to determine the effects of maraviroc unrelated to its therapeutic target. Safety pharmacology studies were conducted to investigate the potential undesirable pharmacodynamic effects of maraviroc on physiological functions in relation to exposure in the therapeutic range and above.

The nonclinical pharmacokinetic program for maraviroc comprised detailed single dose studies in mice, rats and dogs to define basic pharmacokinetic parameters. This program was supplemented by sampling during repeat dose toxicology studies in mice, rats, dogs and monkeys to confirm the pharmacokinetics of maraviroc under the actual conditions of safety evaluation. Tissue distribution, metabolism and excretion studies were conducted using three radiolabelled forms of maraviroc - tritium (3H) and both single and dual carbon-14 labeled material. In vitro metabolism studies were used to support in vivo studies, to characterize the enzymes involved in maraviroc metabolism and to determine the potential for interactions with co-administered drugs.

The nonclinical safety evaluation program was carried out predominantly in rats and macaque monkeys and included an assessment of carcinogenicity potential using a 6-month study in transgenic mice and a 24-month study in rats. Additional studies were conducted to assess the involvement of hepatic enzyme induction in thyroid changes observed in rats and to assess the effect of maraviroc on immune function in monkeys.

Exposure multiples have been calculated by comparing unbound plasma concentrations (C_{max} or AUC_{24}) in the toxicology species with those at the maximum therapeutic dose in humans (300 mg BID: C_{max} 155 ng/mL; AUC_{24} 1275 ng.h/mL; from the Clinical Study A4001007, A randomized, double-blind, placebo-controlled, multicentre study of UK-427,857 25 mg QD, 50 mg BID, 100 mg BID and 300 mg BID in asymptomatic HIV infected patients to investigate pharmacodynamics, pharmacokinetics, safety and toleration).

4.2. Non-Clinical Pharmacology

CCR5 Primary Pharmacodynamics Not Related to the Antiviral Mode of Action

As a consequence of binding to CCR5, maraviroc has pharmacological effects that are not related to its antiviral activity. Thus maraviroc blocks binding of endogenous human CCR5 chemokines and acts as an antagonist of subsequent signaling processes.

Human CCR5 interacts with three endogenous chemokines, MIP-1α, MIP-1β and RANTES (also known as CCL3, CCL4 and CCL5) all of which act as receptor agonists causing downstream cellular effects such as chemotaxis. Maraviroc inhibited binding of iodinated MIP-1α, MIP-1β and RANTES ligands to recombinant human CCR5 receptors expressed in whole HEK-293 cells and membrane homogenates with IC_{50} values in the single figure

nanomolar range. In addition, the IC_{50} for maraviroc was unaffected when the concentration of radiolabelled MIP-1β was increased from 0.005 to 100 nM (IC_{50} = 2.7 to 6.1 nM) suggesting that the inhibition of chemokine binding was insurmountable under these conditions and that circulating chemokines are unlikely to affect the binding of maraviroc to CCR5.

Maraviroc was shown to inhibit chemokine induced intracellular calcium release (IC_{50} range 7-30 nM). Specifically for MIP-1β-induced intracellular calcium release IC_{50} = 14 nM (95% CI 10 – 20 nM; 7 ng/mL (95% CI 5 to 10 ng/mL)) and for MIP-1β-induced changes in intracellular cAMP levels IC_{50} = 9.4 nM in human cells. In the latter assay maraviroc showed evidence of insurmountable MIP-1β antagonism. The most likely explanation for this insurmountable profile relates to the slow rate of maraviroc dissociation from the human CCR5 receptor and the state of hemi-equilibrium that results. The data for MIP-1β antagonism was therefore analyzed assuming hemi-equilibrium conditions, and a p*K*b value of 9.4 (95% CI 9.01 – 9.75) was calculated for maraviroc.

Secondary Pharmacology

Maraviroc has no significant inhibitory activity in a range of in vitro assays of immune function, including specific activities mediated by the chemokine receptors CCR1, 2, 2b, 3, 4, 7, 8, CXCR1 and 2, cytokines IL-2, IL-8 and IL-4 and non-specific activities such as antigen-stimulated lymphocyte proliferation.

Safety Pharmacology

Safety Pharmacology studies were conducted where possible using human recombinant proteins, cell lines or tissues. In addition, in vitro and in vivo studies used animal models where appropriate. It was demonstrated that the affinity and functional activity of maraviroc at the macaque CCR5 is similar to that of human CCR5, and the macaque is therefore likely to represent a non-rodent toxicology species with a mechanistically relevant interaction with the compound. However, sequence homology and maraviroc interaction studies with mouse, rat and dog CCR5, in comparison with human, indicate at least 1,400-fold lower affinity of maraviroc for CCR5 in the species used in safety pharmacology studies. The main outcomes in these species are therefore likely to be non-CCR5 driven, although there will be a degree of mechanistic interaction at high concentrations.

Maraviroc up to 10 μM did not display biologically relevant affinity for a range of physiologic receptors, ion channels, and enzymes. The exceptions to this were moderate inhibition in the human μ opioid, rat non-selective muscarinic receptor (but not human M1-M5 receptor), and the human α_{2A} adrenergic binding assays. Weak functional μ opioid agonist activity was observed at 10 μM (5137 ng/mL), which represents approximately 34-fold the mean unbound C_{max} in HIV-positive patients at a dose of 300 mg BID and is unlikely to be of biological significance. Although maraviroc was shown to be a functional antagonist at canine venous alpha adrenergic receptors (threshold effect level = 3 μM) there was no consistent adrenergic mediated activity in a variety of additional preparations,

including rat vas deferens, recombinant human adrenergic receptor cell lines and isolated human saphenous vein.

Maraviroc was shown to be active at the human cardiac hERG channel with an in vitro threshold for inhibition of [^{3}H]dofetilide binding and the I_Kr current and prolongation of the Purkinje fibre action potential duration and an effect on cardiac repolarization in vivo at unbound plasma concentrations greater than 3 μM, which is approximately 10-fold higher than the mean unbound C_{max} in HIV-positive patients at a dose of 300 mg BID. The integrated IC_{50} for these effects is >10 μM. From these observations a value for the ratio hERG IC_{50}/free C_{max} of at least 33 can be calculated. Therefore, whilst at high concentrations (>10 μM) maraviroc will interact with hERG and prolong the QT interval, in vitro data predict an adequate exposure multiple.

Maraviroc was well tolerated in in vivo tests, with no effects seen in the rat respiratory and renal systems and no effect on motor coordination or sodium pentobarbitone induced sleeping times in mice. The maximum tolerated dose, at which there were no marked effects on appearance and behavior in rats, was 1000 mg/Kg achieving a peak unbound C_{max} of 5 μM (2543 ng/mL, approximately 17-fold the mean unbound C_{max} in HIV-1-positive patients at a dose of 300 mg BID).

Maraviroc, at an unbound C_{max} of 168 nM (86 ng/mL) caused no biologically relevant, or statistically significant, haemodynamic or ECG changes when orally administered to conscious freely moving dogs. In conscious, restrained dogs intravenous administration of maraviroc did not cause any meaningful effects upon basal haemodynamic parameters at concentrations of approximately 3-6-fold the mean unbound C_{max} in HIV-positive patients at a dose of 300 mg BID. In this study, modest prolongation (mean 14.5 msec, maximum 23.1 msec) of the QT interval was observed in the absence of an effect on heart rate. This finding is consistent with toxicology studies in which maraviroc induced increases in the QTc interval in dogs and monkeys. Thus non-clinical data indicate that QT prolongation in humans is not anticipated at concentrations expected in clinical use (clinical data are included in Section 9.7.1).

Of the maraviroc metabolites observed in human plasma two structurally diverse products, a secondary amine and a carboxylic acid (comprising approximately 22% and 5% respectively of total administered compound compared with a parent level of 42%) were profiled against a panel of pharmacologically relevant receptors, enzymes and ion channels. No activities of biological relevance were observed at the concentrations observed in humans.

4.3. Pharmacokinetics

The results of preclinical in vitro studies and in vivo pharmacokinetic/toxicokinetic studies in animals are summarized below, with reference to appropriate human data:

Absorption

Oral bioavailability following single oral administration of Maraviroc in rats and dogs was generally low to moderate (5 to 42%). Systemic exposure in toxicology studies increased in a

supra-proportional manner in rat and greater than the increment in dose in cynomolgus monkey. Exposure in the remaining species was approximately proportional with dose following repeated daily oral administration of maraviroc.

Distribution

Plasma protein binding was moderate in animal and human plasma. In human plasma the unbound fraction was 0.245. Fraction unbound in animal species ranged from 0.34 to 0.516.

Following oral administration to pigmented rats, drug-related radioactivity was primarily associated with the liver, kidney, small intestine, bladder, seminal vesicles and prostate gland. In separate studies radioactivity did not readily cross the blood brain barrier with cerebrospinal fluid (CSF) concentrations approximately 10% of free plasma concentration. Radioactivity was slowly eliminated from the eye (elimination half life 7 days), suggesting an affinity for melanin, as commonly observed with basic compounds. Maraviroc shows some partitioning into red blood cells in rat, dog and human with ratios of 1.1, 0.9 and 0.7, respectively. In rats, the distribution of radioactivity to gut-associated lymphoid tissue (GALT) showed penetration into all lymph nodes regardless of anatomical location.

Maraviroc has been shown to be a substrate for the efflux transporter P-glycoprotein, with a Km of 37μM.

Metabolism

Maraviroc was the major component present in human urine, feces and plasma, accounting for 33% of excreted radioactivity and 42% of plasma radioactivity. Significant metabolites detected in human plasma were a secondary amine product of N-dealkylation (UK-408,027, 22%) and an hydroxylated analogue (11%). These metabolites were also present in excreta together with several oxidized products involving hydroxylation in the difluorocyclohexane, phenyl or substituted triazole functions. All of the human metabolites are observed in the toxicology species. Maraviroc was the major component in the excreta and plasma of all animal species, ranging from 39% to 79% of excreted radioactivity (male CD1 mouse and rat (mean of both sexes), respectively) and 40% to 79% of plasma radioactivity (female rabbit and female rat, respectively).

Metabolism of Maraviroc to the plasma metabolite, UK-408,027 has been shown to be mediated by CYP3A4 in man.

Elimination

In mouse, rat, rabbit, dog, monkey and human the main route of excretion of drug-related radioactivity following oral administration of radiolabelled maraviroc was via the feces (≥76%).

Drug-related radioactivity was secreted in milk of lactating rats following oral administration of maraviroc.

Toxicokinetics

In mice, the increase in exposure was approximately proportional with the increment in dose over the 200 to 750 mg/Kg dose range. In rats, C_{max} increased approximately proportionally with dose whereas AUC increased super-proportionally and plasma concentrations were approximately 1.4 to 2.2-fold higher on Day 181 compared with Day 0 (first day of dosing). There was a proportional increase in C_{max} and AUC in dogs with increasing dose although systemic exposure was similar on Days 1 and 176. In cynomolgus monkeys, the increase in mean AUC and C_{max} values was greater than the increment in dose over the 30 to 400 mg/Kg/day dose range (as twice daily doses). Systemic exposure was similar over the duration of treatment except for the highest dose group in which the AUC values were 1.5-fold higher from Day 133 and Day 270 compared with Day 0.

4.4. Toxicology

The full toxicology profile of maraviroc has been assessed by evaluating high daily doses in several animal species (up to 2000 mg/Kg in mice, 1500 mg/Kg in rats, 250 mg/Kg in dogs and 800 mg/Kg in monkeys). The dose range studied provided plasma exposures many times higher than found at the maximum therapeutic dose in humans, 300 mg BID (or 8.6 mg/Kg/day, assuming a 70 Kg subject); the unbound C_{max} and AUC values represented exposure multiples of up to 45 and 68 in mice, 30 and 51 in rats, 23 and 28 in dogs and 43 and 37 in monkeys.

In mice, mortality at 1000 mg/Kg, associated with local gastrointestinal pathology rather than systemic toxicity, gave a NOAEL of 750 mg/Kg, with an exposure multiple of 45 (C_{max}) or 68 (AUC).

In rats, the dose of 900 mg/Kg, with exposure multiples of 30 (C_{max}) or 51 (AUC), was found to be the maximum tolerated dose and was used as the high dose in the 24-month carcinogenicity study. Reductions in body weight were noted at 900 mg/Kg. The liver has been identified as a target organ in rats. There was a weak signal of adverse liver findings at high doses, characterized by slight increases in plasma transaminases and bile duct hyperplasia, at 34-fold and 25-fold, respectively, the AUC exposure at 300 mg BID. No adverse liver effects were observed in rats at 8x the AUC exposure at 300 mg BID.

In dogs, there were multiple bouts of emesis from relatively low doses (15 mg/Kg), accompanied by body weight loss and frequent reductions or absence of food intake at the dose of 150 mg/Kg. This was considered to be the maximum tolerated dose in dogs, with an exposure multiple of 23 (C_{max}) or 28 (AUC). In the 1- and 6-month studies, the NOAEL was 5 mg/Kg, with an exposure multiple of 2 (C_{max}), based on increases in QTc interval at higher doses.

In monkeys, the daily dose of 800 mg/Kg was not well-tolerated, being associated with cardiovascular changes (reduced blood pressure and heart rate) and treatment reactions (reduced activity, prostration, loss of balance). The dose of 400 mg/Kg produced similar, though less severe findings, as well as an increase in QTc interval, in the 9 month study at

exposure multiples of 14 (C_{max}) and 23 (AUC). The NOAEL, established from the 9-month study, was 120 mg/Kg in monkeys, with a C_{max} exposure multiple of 5. There was no evidence of cardiac arrhythmias in dogs or monkeys over the dose range studied.

The assessment of maraviroc in repeat-dose studies in rats, dogs and monkeys using daily dosing for up to 6 or 9 months of treatment demonstrated no histopathological evidence of toxicity on the male or female reproductive systems of these species.

Reproductive toxicology studies in male and female rats indicate no effects on fertility at 1000 mg/Kg, corresponding to an AUC exposure multiple of 39. In addition, there was no effect on reproduction parameters or embryo-fetal development at 1000 mg/Kg in rats (AUC exposure multiple of 39) and 200 mg/Kg in rabbits (AUC exposure multiple of 34). In the pre-and postnatal study in rats, there was no effect on the reproductive function of treated females up to the dose of 1000 mg/Kg, producing an AUC exposure multiple of 27-fold. This dose produced a slight increase in motor activity in male F1 offspring. Based on this finding, the NOAEL for development toxicity in the offspring of maraviroc-treated female rats was 300 mg/Kg, corresponding to an AUC exposure multiple of 9. A study in lactating female rats has shown that maraviroc is extensively secreted into milk, and this is also likely to occur in humans.

Maraviroc binds to the CCR5 receptor in rats with a significantly reduced affinity compared with that in humans. The high concentrations used in the rat and rabbit embryofetal development studies are in the range producing approximately 30% inhibition of the recombinant rat CCR5 receptor. In neither of these studies was there evidence of adverse effects of the treatment on embryo or fetal development. A higher dose (300 mg/Kg) was administered to pregnant rabbits in the range-finding study and produced severe maternal toxicity (including mortality) but no evidence of embryofetal toxicity. However plasma drug exposure levels were not measured in this study.

Maraviroc was shown not to be mutagenic or clastogenic in appropriate genetic toxicology assays. Carcinogenicity studies in rats (24 months duration) and Tg mice (6 months duration) at plasma AUC exposures 21- and 39-times higher than those found in humans at the maximum therapeutic dose, indicate no carcinogenic potential for humans.

4.5. Specific Areas of Interest Arising from the Nonclinical Safety Program

Blood pressure and Heart rate

Studies in dogs indicated no significant changes in blood pressure at plasma concentrations 3-6-fold that of the maximum therapeutic dose and only inconsistent reductions in blood pressure in individual animals at concentrations 5 and 9-fold that at the maximum therapeutic dose. Maraviroc produced a slight impairment of normal reflex control of blood pressure in the dog during the change to the upright position at plasma concentrations 3-6 fold the concentrations at the maximum therapeutic dose in humans. However, once the upright position had been established, blood pressure control was maintained at a normal level.

Toxicology studies in monkeys indicated reductions in blood pressure at daily doses of 200 and 400 mg/Kg, accompanied at 400 mg/Kg by lower heart rates. The doses of 200 mg/Kg (1-month study) and 400 mg/Kg (9-month study) were associated with similar unbound plasma concentrations (1815 ng/mL and 1718 ng/mL, respectively) and were approximately 11-fold higher than that at the maximum therapeutic dose. No effects on blood pressure or heart rate were observed at 120 mg/Kg in the 9-month study, with a plasma concentration 5-fold that of the maximum therapeutic dose in man. The reduction in heart rate seen in monkeys has not been observed in humans throughout the clinical program and is unlikely to represent a risk for patients.

Although the mechanism responsible for postural hypotension in humans is unclear, in vitro studies suggest effects of maraviroc on alpha adrenoceptors or vascular CCR5 receptors.

QT interval prolongation

At therapeutic concentrations, maraviroc had no effect on cardiac repolarization in either in vitro or in vivo assays. This is consistent with the lack of effect of maraviroc on QT interval in humans at therapeutic doses. However at supra-therapeutic concentrations, or in the event of an overdose, maraviroc could block the hERG potassium channel. 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 1541 ng/mL. These results indicate that maraviroc has the potential to block the I_{Kr} current and affect cardiac repolarization in vivo at unbound plasma concentrations greater than 3 μM, which is approximately 10-fold the C_{max} at the maximum therapeutic dose.

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, doses of 5 mg/Kg and 120 mg/Kg, respectively, had no effect on QTc interval at plasma concentrations 2 and 5-fold the maximum therapeutic concentration. The blockade of cardiac potassium channels can cause prolongation of action potential duration, thereby delaying ventricular repolarization, lengthening QT interval and increasing the risk of serious arrhythmias, such as torsade de pointes. This activity of maraviroc is considered to represent a low risk to humans given that the ion channel effects occur at a plasma concentration that was 10-fold the maximum therapeutic concentration (155 ng/mL). Furthermore 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.

In vitro studies and animal data from dogs and monkeys indicated the potential for QT interval prolongation in human patients which led to the conduct of a thorough QT study in humans and QT monitoring in the Phase 2b/3 clinical program. The range of in vitro, animal and clinical data has served to characterize the action of maraviroc on cardiac repolarization and to provide reassurance that maraviroc does not increase the arrhythmogenic risk for humans, even when taking concomitant medication that would increase exposure.

Hepatic Findings

Repeat-dose toxicology studies in mice, rats, dogs and monkeys identified the liver as a target organ in rats only; in mice, dogs and monkeys, no signals of adverse liver findings were seen at 68x, 28x and 37x the AUC exposure at 300 mg BID in humans, respectively. In rats, bile duct vacuolation was present from 100 mg/Kg and was associated with minimal bile duct hyperplasia from 300 mg/Kg. At higher dose levels, while the incidence of bile duct changes increased, there was no increase in the severity. In male rats, bile duct hyperplasia was still present 3 months after withdrawing the treatment, but was fully reversed in female rats. Bile duct hyperplasia appears morphologically similar to spontaneous changes known to occur in rats (Greaves, 2000). These changes are possibly a mild response to the biliary excretion of maraviroc or its metabolite, but were subsequently not seen in 2 year studies at similar exposures in rats during carcinogenicity testing.

At 900 mg/Kg, additional findings in the liver were altered cell foci and multinucleated hepatocytes. Although altered cell foci occur spontaneously in older rats, they are seen infrequently in rats aged 8 months. Multinucleated hepatocytes were not associated with concurrent evidence of liver damage or hepatocyte proliferation in this study. The presence of multinucleated hepatocytes after withdrawing the treatment for 3-month recovery period is consistent with a long recovery period for this finding (Brughera et al, 1995). At the dose of 1500 mg/Kg, there were increases in plasma transaminases, accompanied in one animal by hepatocellular necrosis.

In the 24-month study in rats, bile duct hyperplasia was noted in all groups (including controls) with a similar incidence and severity; although bile duct vacuolation was not observed. As in the 6-month study, there were no indications of atypia, mitosis or pleomorphism of bile duct epithelium. While biliary neoplasms (cholangiocarcinoma and cholangioma) were found only in rats receiving maraviroc, the lack of an indication of pre-neoplastic changes, the low incidence of tumors in this study, along with similar incidences in reported control data and in a control group in a concurrent study at the same laboratory, support the conclusion that these neoplasms are of spontaneous origin and unrelated to treatment. In the 6-month carcinogenic study in transgenic (rasH2) mice, there were no noteworthy findings in the liver.

In summary, the liver has been identified as a target organ in rats. There was a weak signal of adverse liver findings at high doses, characterized by slight increases in plasma transaminases and bile duct hyperplasia, at 34-fold and 25-fold, respectively, the AUC exposure at 300 mg BID. No adverse liver effects were observed in rats at 8x the AUC exposure at 300 mg BID. Given the high first pass extraction in this species, the systemic exposure (used to calculate exposure multiples), is likely to under-represent the chemical stress imposed on the liver (Walker, 2004). In mice, dogs and monkeys, no signals of adverse liver findings were seen at 68x, 28x and 37x the AUC exposure at 300 mg BID in humans, respectively. Carcinogenicity studies in rats and transgenic mice at plasma AUC exposures 21- and 39-times higher than those found in humans at the maximum therapeutic dose, indicate no carcinogenic potential for the human liver.

Carcinogenicity studies

Carcinogenicity studies have been conducted in rats for 24 months (50, 100, 500 and 900 mg/Kg) and in ras H2 transgenic mice for 6 months (200, 800 and 1500 mg/Kg). In both studies, treatment with maraviroc had no effect on survival.

In rats, there was an increased incidence of follicular cell adenoma of the thyroid at 900 mg/Kg. These thyroid changes are considered to be indirect effects of hepatic enzyme induction and are not interpreted to be a risk for human patients. Other tumours in this study were not considered treatment-related. At plasma AUC exposures 21-fold higher than those found in humans at the maximum therapeutic dose, there was no indication of carcinogenic potential for humans.

In transgenic mice, there were no significant differences in the nature or incidence of hyperplastic or neoplastic microscopic findings in any tissue/organ in maraviroc treated mice compared to control animals. All animals of the MNU-treated positive control group had microscopic findings indicative of neoplastic changes. The high dose corresponds to plasma AUC exposures at least 39-times higher than found in humans at the maximum therapeutic dose.

Immunological Considerations

Owing to its targeted patient population and mechanism of action, maraviroc was evaluated for effects on immune function. Maraviroc has no activity against a number of in vitro human immune function assays, including activity against a number of related chemokine receptor assays. In repeat-dose toxicology studies in mice, rats, dogs (up to 6 months duration) or monkeys (up to 9 months duration), maraviroc produced no alterations in circulating white blood cell parameters, serum globulins, or noteworthy changes to organ weights or histology of the bone marrow, lymph nodes, spleen or thymus. Similarly there was no increase in the incidence of infections during these studies to suggest impairment of the immune system.

A specific study to investigate the potential of maraviroc to impair the immune system in monkeys showed that treatment for 1-month at daily doses of up to 300 mg/Kg induced no changes in lymphocyte subset distribution, NK cell activity, phagocytosis activity or oxidative burst. All animals were able to mount a humoral primary (IgM) and secondary (IgG) immune response against KLH. The daily dose of 300 mg/Kg was shown to achieve 100% occupancy of CCR5 receptors over 24 hours. There was no adverse effect of maraviroc on the immune system in monkeys at plasma exposures (AUC_{24}) producing complete and continuous blockade of CCR5 receptors and with an exposure multiple 16-fold greater than observed at 300 mg BID.

There was no suggestion that maraviroc stimulated the immune system. In chronic (6 months or longer) studies in mice, rats, dogs and monkeys there was no evidence of lymphoid hyperplasia in the spleen or lymph nodes, which may be expected upon stimulation of the

immune system. Furthermore in the immunotoxicology study in monkeys, there was no potentiation of the antibody response to KLH.

Carcinogenicity studies in rats and transgenic mice indicate no carcinogenic potential for humans at plasma AUC exposures 21- and 39-times, respectively, higher than those found in humans at the maximum therapeutic dose. The CCR5 receptor binding at the high doses was estimated to be 10% in rats and 20% in the transgenic mice.

The results of these nonclinical studies with maraviroc provide no evidence for a risk to the human immune system.

5. CLINICAL PHARMACOLOGY

Polarized transport of maraviroc across Caco-2 cell monolayers, and three-fold higher systemic exposure in wild-type mice compared to double P-glycoprotein (P-gp) knockout mice, have indicated a potential role for the transport protein P-gp in limiting oral absorption of maraviroc. In the rat model, maraviroc shows wide tissue distribution, except for lower penetration into the central nervous system, possibly due to P-gp mediated efflux. Maraviroc is moderately protein bound (75% in man) and is eliminated predominantly by metabolism, primarily by CYP3A4, and does not inhibit major drug metabolizing cytochrome P450s in vitro, including CYP3A4 (IC_{50}'s > 30μM).

Maraviroc (up to 10μM) had little interaction with physiologically important receptors, binding sites, enzymes or ion channels apart from weak functional activity at the human μ opioid receptor and a moderate affinity for the human α_{2A} adrenergic receptor. In vitro studies have shown the primary metabolite, UK-408,027 (up to 10μM), to be inactive in viral protein mediated cell fusion assays and devoid of any relevant pharmacological activity against physiological receptors ions and enzymes tested.

Pre-clinical studies indicated that maraviroc has the potential to block the I_{Kr} current and affect cardiac repolarization in vivo at approximately 10-fold the C_{max} at the maximum therapeutic dose. A clinical study specifically designed to evaluate the potential for QTc prolongation was conducted and demonstrated that at maraviroc doses up to and including 900 mg there was no clinically meaningful effect on QTc interval.

Maraviroc will be administered with multiple drugs, including other antiretroviral agents, (NRTIs, NNRTIs, PIs and fusion inhibitors) and drugs to treat other medical conditions including opportunistic infections. Many of these drugs are known to modulate the activity of CYP3A4 and/or P-gp and hence could be expected to affect maraviroc pharmacokinetics. Given the potential for a complex dosing environment, an extensive clinical drug interaction program has been performed to elucidate any significant effect of maraviroc on representative drugs and also the effect of other representative drugs on maraviroc.

This section summarizes the results from clinical pharmacology studies conducted with maraviroc during its development. Data from clinical pharmacology studies indicate that:

- The clinical pharmacology profile supports therapeutic dosing at 300 mg QD and 300 mg BID.

- Maraviroc does not affect the pharmacokinetics of other drugs.

- Maraviroc dose should be halved when co-administered with CYP3A4 and/or P-gp inhibitors, and doubled when co-administered with CYP3A4 and/or P-gp inducers (in the absence of potent CYP3A4 inhibitors).

5.1. Clinical Pharmacology Program Overview

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 the NDA 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, one study evaluated bioequivalence, 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 (details of these endpoints are presented in Section 6.2).

5.2. Clinical Pharmacokinetics

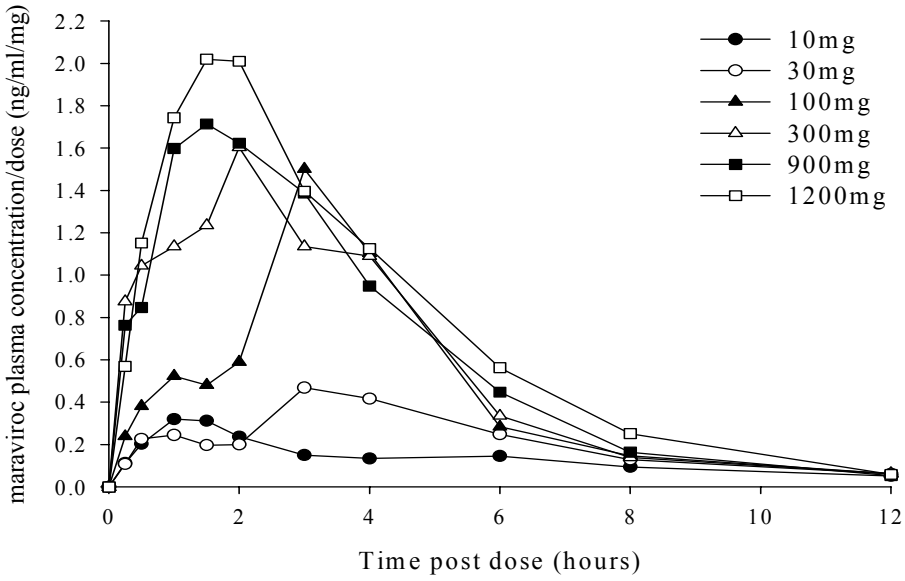
Healthy subjects have received single doses of maraviroc ranging from 1 to 1200 mg and multiple doses of maraviroc ranging from 3 to 900 mg BID, and 1200 mg QD for periods ranging from 7 to 28 days in clinical pharmacology studies.

Absorption

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).

In Phase 1 single and multiple dose studies orally administered maraviroc demonstrates rapid absorption (Tmax 1-4h, C_{max} 0.5-4h) and non proportional pharmacokinetics (Figure 2) at doses below 300 mg. Multiple dosing leads to limited accumulation at a 300 mg BID dose and steady state is observed within 7 days.

Figure 2. Mean Dose-Normalized Maraviroc Plasma Concentration versus Time Profiles (A4001001)



Exposure increases supra-proportionately with increasing dose, and it is postulated that this may be due to saturation of P-gp with increasing maraviroc concentrations in the gut. Intravenous (IV) administration showed linear pharmacokinetics. Population pharmacokinetic modeling of oral tablet data across the Phase 1 program 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%.

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%, primarily by reduction of C_{max}. 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. 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 BID 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 5.5.2 below), the effect of food on exposure of maraviroc was believed to be negligible. No recommendation for food restriction was therefore made in the Phase 2b/3 clinical program.

Distribution

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. In humans CNS penetration is likely to be modified by concomitant drugs that either inhibit (many PIs) or induce (efavirenz) P-gp. The steady state volume of distribution of maraviroc is approximately 194 L (Study A4001009). Maraviroc is bound (approximately 75%) to human plasma proteins, and shows moderate affinity for albumin and alpha-1 acid glycoprotein. Red blood cell partitioning was indirectly measured using whole blood and plasma radioactivity from a mass balance study when [^{14}C]-labeled maraviroc was administered to healthy subjects. Blood to plasma ratio was 0.6; suggesting maraviroc is predominantly confined to plasma with negligible distribution into red blood cells.

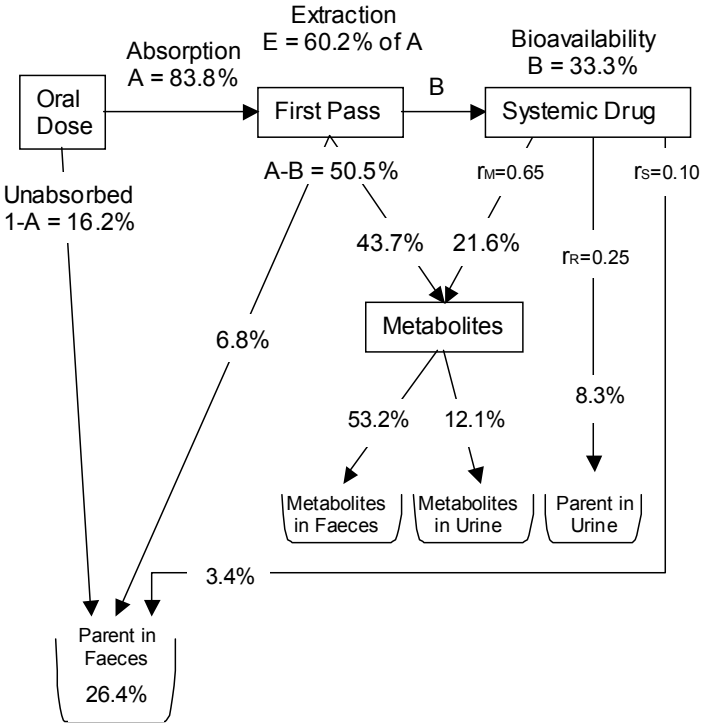
Metabolism and Excretion

Maraviroc metabolic fate has been evaluated in a mass balance Study (A4001010). 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.

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.

Figure 3 below utilizes data from Study A4001010 and the IV bioavailability Study A4001009 to delineate relative importance of routes of excretion of maraviroc.

Figure 3. 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. 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 program, as have patients co-infected with hepatitis B and/or C. No safety issue has been noted in these patients, although numbers were limited. A single dose study (A4001023) in subjects with mild to moderate hepatic impairment has shown little impact on maraviroc pharmacokinetics, with less than a 50% increase in exposure to maraviroc. Maraviroc has not been studied in subjects with severe hepatic impairment.

5.3. Effects of Age, Gender, Race and HIV-1 Status on Pharmacokinetics

Phase 1/2a population pharmacokinetic analysis indicated that 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%). However a specific study designed 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. 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.

5.4. Safety Considerations

Dose escalation studies demonstrated that postural hypotension was the dose limiting adverse event. This was seen at unit doses of 1200 mg in Study A4001001. The events were spontaneous, temporally associated with C_{max} and resolved with supportive measures. Due to small changes in standing blood pressure observed in Study A4001002, an exploratory analysis of the relationship between maraviroc plasma concentrations and standing systolic and diastolic blood pressure data from two healthy volunteer studies (A4001002 and A4001006) was conducted. A population analysis using nonlinear mixed effects modeling was employed. No significant placebo effect was identified and a linear concentration effect relationship was found to describe adequately the standing blood pressure changes on active treatment. The estimate of the slopes describing the standing systolic and diastolic blood pressure: concentration relationships were –0.00387 and -0.00179 respectively (equivalent to a decrease of 3.87 mmHg (systolic) or 1.79 mmHg (diastolic) per 1000 ng/mL within the maraviroc concentration range studied (0-2000 ng/mL).

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 (as per pre-defined by blood pressure changes rather than symptoms) was similar to placebo (1-3%). Incidence rates at unit doses of 600 mg were approximately 13% 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 C_{max} equivalent. Postural hypotension is discussed in further detail in Section 9.7.1.

To further explore the impact of maraviroc on the cardiovascular system a non-invasive placebo and active controlled (glyceryl trinitrate, GTN) haemodynamic study of 900 mg of maraviroc was conducted in healthy volunteers. 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 were 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 C_{max}, and 43% at 30 fold C_{max}). 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 and including 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 C_{max}). A multiple dose study was not considered necessary because of the limited accumulation of maraviroc on multiple dosing.

A population analysis using mixed effects modeling was employed to explore and characterize the plasma concentration-QTc response relationship. A direct, linear relationship was assumed i.e. that plasma concentrations are in equilibrium with any effect on the ECG. This analysis showed that there was a small mean increase in individually corrected QTcI (less than 3 msec) at 1 and 2 hours post-dose in subjects who received 900 mg maraviroc but not in those who received 100 mg and 300 mg. The estimate of the slope describing the QT-concentration relationship within the concentration range studied (up to 2360 ng/mL) was 0.00097; thus, an increase of 1000 ng/mL in maraviroc concentration might be expected to be associated with an increase in QTc interval duration of 0.97 msec. The QT:RR relationship was similar pre- and post-dose and was not related to maraviroc concentration.

The effects of maraviroc on QTc interval is discussed further in Section 9.7.1.

5.5. Drug Interactions

5.5.1. Maraviroc Effects on Other Drugs

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) (Table 1).

Table 1. Summary of the Effect of Maraviroc on Other Drugs

Co-administered drug (dose)	N	Maraviroc Dose	Ratio (90% CI) of 'Other Drug' Pharmacokinetic Parameters With/Without Co-administered Maraviroc (No Effect = 1.00)	
			AUC_{tau}	C_{max}
Ethinylestradiol (30 μg QD)	15	100 mg BID	1.00 (0.95, 1.05)	0.98 (0.91, 1.06)
Levonorgestrel (150 μg QD)	15	100 mg BID	0.98 (0.92, 1.04)	1.00 (0.93, 1.08)
Midazolam (7.5 mg SD)	12	300 mg BID	1.18 (1.04, 1.34)	1.21 (0.92, 1.60)
Zidovudine (300 mg BID)	11	300 mg BID	0.98 (0.79, 1.22)	0.92 (0.68, 1.24)
Lamivudine (150 mg BID)	11	300 mg BID	1.14 (0.98, 1.32)	1.16 (0.88, 1.54)

5.5.2. Effects of Other Drugs on Maraviroc

As maraviroc is a substrate for CYP3A4 and P-gp, its pharmacokinetics are likely to be affected by co-administration of inhibitors and inducers of these enzymes/transporters. In addition, in clinical practice, maraviroc will be co-administered with other antiretroviral drugs, many of which are known to affect CYP3A4 and/or P-gp activity. Hence, the main focus of the drug interaction studies has been to understand the impact of CYP3A4 and P-gp modulation in the complex dosing environment of OBT to be used in Phase 2b/3 studies, with the aim of guiding dose adjustment recommendations for maraviroc. As maraviroc is also renally cleared (20.3% of total clearance), with a significant contribution of active processes, the effect of substrates and inhibitors of renal clearance (tenofovir and co-trimoxazole) on the pharmacokinetics of maraviroc have also been investigated.

A summary of the effect of drugs on maraviroc pharmacokinetics (geometric mean ratios) from clinical studies (excluding patient probe studies) is shown in Table 2.

Table 2. Summary of the Effect of Other Drugs on Maraviroc

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

Interactions with CYP3A4 Inhibitors

Maraviroc pharmacokinetics in healthy volunteers were evaluated in combination with saquinavir +/- ritonavir, Kaletra™, 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), Kaletra™ (3.8-4-fold in 2 studies) and atazanavir alone (3.6-fold) showed lesser effects than saquinavir/ritonavir. In all cases the C_{max} increase was less notable, typical increases being half the increase seen in AUC. This is important as the dose limiting adverse events with maraviroc appear to be related to C_{max} rather than AUC, and efficacy/potency appears to be driven by AUC/ average concentration (Cave), as described below. Dose adjustments of 0.5 (Kaletra™) 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 C_{max} (geometric mean ratios compared to unadjusted maraviroc 53% and 61% respectively). The reason for saquinavir/ritonavir showing the greatest impact on maraviroc pharmacokinetics is unknown.

Interactions with CYP3A4 Inducers

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

Interactions with Antiretroviral Combinations

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 and therefore not suitable to study in healthy volunteers or in patients with higher CD4 counts. Unexpectedly, when compared with historical controls maraviroc pharmacokinetics appeared to be not affected by nevirapine, 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 Kaletra ™ 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.

Interactions with Other Drugs (Including Renal Transport Inhibitors)

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. Co-trimoxazole 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.

5.5.3. Summary of Drug Interactions

No drug-drug interaction program can be exhaustive. During the Phase 2b/3 program, 2 new HIV-1 drugs have been approved (tipranavir and darunavir) and 2 more drugs have entered expanded access programs (MK 0518 and TMC-125). The drug-drug interaction program 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 metabolized 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 3) and assuming that P-gp is solely responsible for the incomplete absorption). Some studies utilized maraviroc 100 mg BID, as this was initially thought to be the appropriate dose, but later studies used 300 mg BID. The Kaletra™ 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 program 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. Furthermore, the safety profile of maraviroc from the Phase 2b/3 studies was analysed by the concomitant use of drugs used to lower blood pressure (PDE5 inhibitors, antihypertensives, nitrates and alpha-blockers) and no additive adverse effects were observed.

Drug interaction dosing recommendations are discussed in Section 10.1.

5.6. Population Pharmacokinetics from the Phase 2b/3 Clinical Program

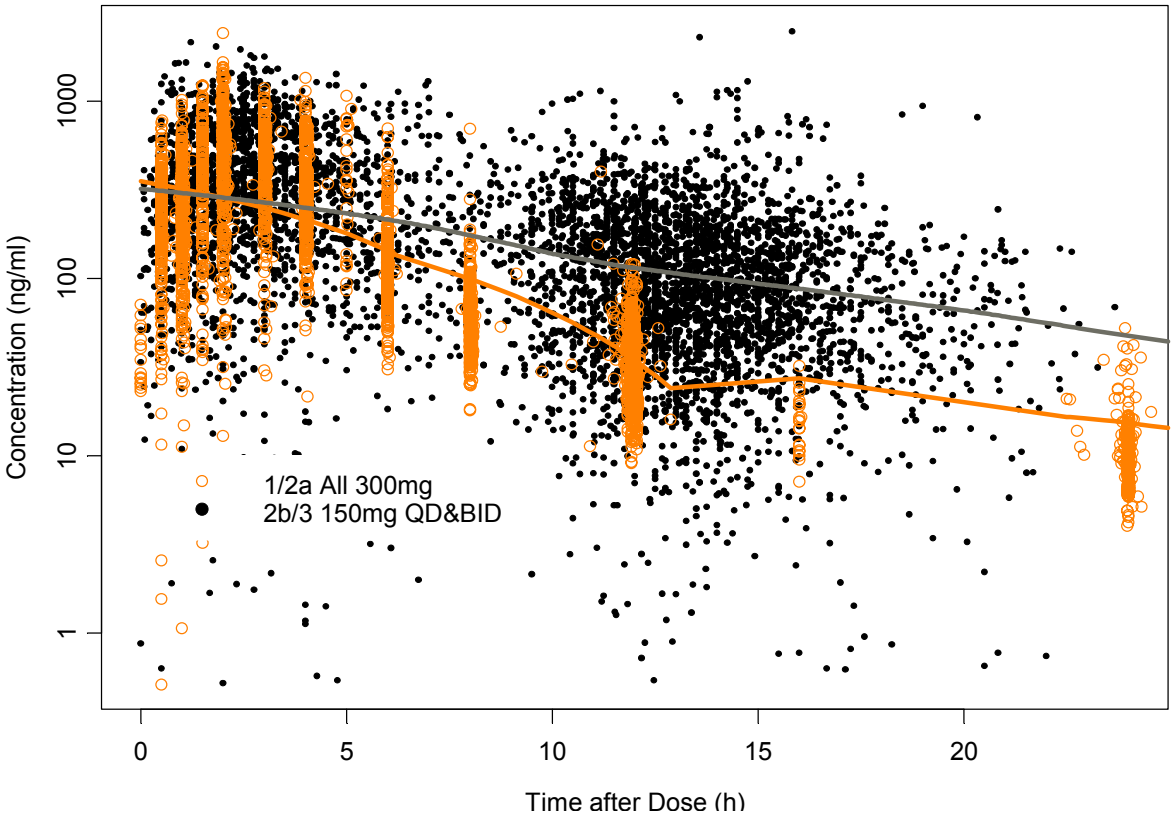
The drug-drug interaction program is comprehensive, covering most drug classes commonly used by HIV-1 infected patients, and facilitated dose adjustment strategies for the Phase 2b/3 studies utilising an optimised background design. The nominal unit dose was selected to be 300 mg QD or BID, adjusted downwards to 150 mg to correct for C_{max} 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 1049 patients recruited into Studies A4001027 and A400128 [810 received maraviroc] and all patients on maraviroc in Study

A4001029 [119]). 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 (using post hoc Bayesian estimates of pharmacokinetic parameters). 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 C_{ave} from 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.

The most important aim of the dose adjustment of maraviroc in the presence of CYP3A4 inhibitors in the background OBT was to correct for C_{max}. The figure below shows the observed plasma concentrations from the Phase 2b/3 studies when maraviroc was given at 150 mg QD and 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 4). 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 4. Maraviroc Concentration versus Time After Dose: 150 mg QD and BID Dose from Combined Phase 2b/3 Overlaid with all 300 mg Phase 1/2a Maraviroc Concentrations (lines=lowess smooth)



Taken together, these data indicate that the maraviroc dose modification recommendations for the Phase 2b/3 clinical studies were successful in limiting C_{max} 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, there was no clear difference in the median values between those taking efavirenz or nevirapine when compared with those not taking these agents in Phase 2b/3, nor with the Phase 2a reference groups. This is inconsistent with the Phase 1 drug interaction data for efavirenz. However, the numbers in the subgroups are small and these data should be viewed with caution. It is therefore considered that nevirapine should be considered an inducer of maraviroc metabolism and recommended dose adjustments should follow those for efavirenz (see recommendations for dose selection in Section 10.1).

5.7. Maraviroc Pharmacokinetics and Antiviral Activity

Early Studies

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 recognize 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 (C_{max} was 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 $\geq$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.

Exposure-Response Analysis (Phase 2b/3)

An exposure response analysis was performed with exposure and efficacy data pooled from thesubjects from studies A4001027 and A40010128. The effect of maraviroc exposure and various prognostic factors on binary viral load endpoints and CD4 count change from baseline at Week 24 in treatment-experienced HIV-1-infected patients with OBT has been analyzed using generalized additive models (GAM). For all virology endpoints studied, amongst other important prognostic factors identified (e.g. baseline viral load and overall susceptibility score), maraviroc exposure was always a better predictor of response than dose.

The planned interim 24-week analyses for studies A4001027 and A4001028, demonstrated statistical superiority of both maraviroc QD and maraviroc BID over placebo. In addition, all of the secondary endpoint results at Week 24 were consistent with the primary endpoint and support the superior efficacy of both maraviroc treatment regimens over placebo.

Although the studies were not specifically designed to compare the maraviroc QD and maraviroc BID doses, assessment of the primary and secondary endpoints indicated only small differences in efficacy between the QD and BID regimens. These findings should be viewed in the light of a wide and overlapping range of maraviroc concentrations observed in the 150 mg QD and BID maraviroc treatment groups due to the pharmacokinetic interactions of maraviroc with OBT. This has resulted in similar median exposure in patients who received 150 mg QD (with some boosted PIs) as was observed (and would be expected) in

patients taking 300 mg BID. Based on the exposure response relationships and with no safety or tolerability issues identified in the Phase 2b/3 treatment experienced HIV patient programme, maraviroc regimens of 150 QD with some boosted PIs and BID (with any PI (excepting tipranavir) and/or delavirdine) and 300 mg maraviroc BID would produce concentrations expected to be near maximal pharmacologically effective dose.

5.8. Clinical Pharmacology Conclusions

- The dose selected and the dose adjustment deployed in the Phase 2b/3 clinical trials achieved the intended maraviroc exposures and optimizes efficacy and tolerability. Therefore:

- In treatment-experienced patients infected with CCR5 tropic HIV-1 maraviroc should be administered at a dose equivalent of 300 mg BID.

- In patients receiving maraviroc co-administered with CYP3A4 inhibitors (including protease inhibitors (except tipranavir/ritonavir), delavirdine, ketoconazole, intraconazole, clarithromycin, nefazadone and telithromycin) the dose of maraviroc should be adjusted to 150 mg BID.

- The only revision to the intended dose regimens is to recommend that nevirapine (as well as efavirenz) should be considered an enzyme inducer. Therefore:

    - If nevirapine or efavirenz 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 (patients should receive 600 mg maraviroc BID).

- No dose adjustments are recommended on the basis of age, sex or racial differences.

- Maraviroc may be administered with or without food.

6. OVERVIEW OF MARAVIROC CLINICAL DEVELOPMENT PROGRAM

6.1. Introduction

At the time of the maraviroc NDA submission 28 Phase 1 clinical studies had been conducted in over 600 healthy volunteers and 37 patients infected with HIV-1, to explore the pharmacology (pharmacokinetics/pharmacodynamics), the safety profile of maraviroc, including studies deigned to address specific safety concerns such as haemodynamic effects and the potential for QTc prolongation and to conduct an extensive drug interaction program, a discussed in Section 5 above. Since this submission a further 2 Phase 1 studies have been completed; A4001023 to assess maraviroc pharmacokinetics in hepatically-impaired subjects and A4001052, a drug-drug interaction study with the recently approved PI, darunavir.

The pharmacokinetics/pharmacodynamics, dose response, safety and tolerability of maraviroc were initially evaluated in two randomised, double-blind, placebo-controlled

Phase 2a studies (A4001007 and A4001015) in patients infected with CCR5 tropic HIV-1 who were either treatment-naïve or had been off antiretroviral treatment for 8 weeks prior to study start. These studies demonstrated that maraviroc, given for 10-days as monotherapy, reduced viral load in this patient population. These studies, along with the Phase 1 clinical studies, assisted in the dose selection and dose adjustment for the Phase 2b/3 clinical program.

The Phase 2b/3 clinical program focused on the treatment of treatment-experienced patients infected with CCR5 tropic HIV-1. Two independent, randomised, double-blind registrational studies have been conducted in this patient population and formed the basis of the NDA submission for accelerated approval (A4001027 and A4001028). Supportive safety and efficacy data were included from a smaller safety study conducted in patients with non-CCR5 tropic (dual/mixed, CXCR4-tropic or non-phenotypable) HIV-1 (A4001029) and safety data from an ongoing study in treatment-naïve patients infected with CCR5 tropic HIV-1 (A4001026).

Clinical pharmacology and safety data are discussed in Sections 5 and 9 of this document respectively. The remainder of this section provides a summary of the Phase 2a dose-ranging studies and the subsequent design of the Phase 2b/3 clinical program.

6.2. Summary of Early Phase 2a Dose-Ranging Studies (A4001007 and A4001015)

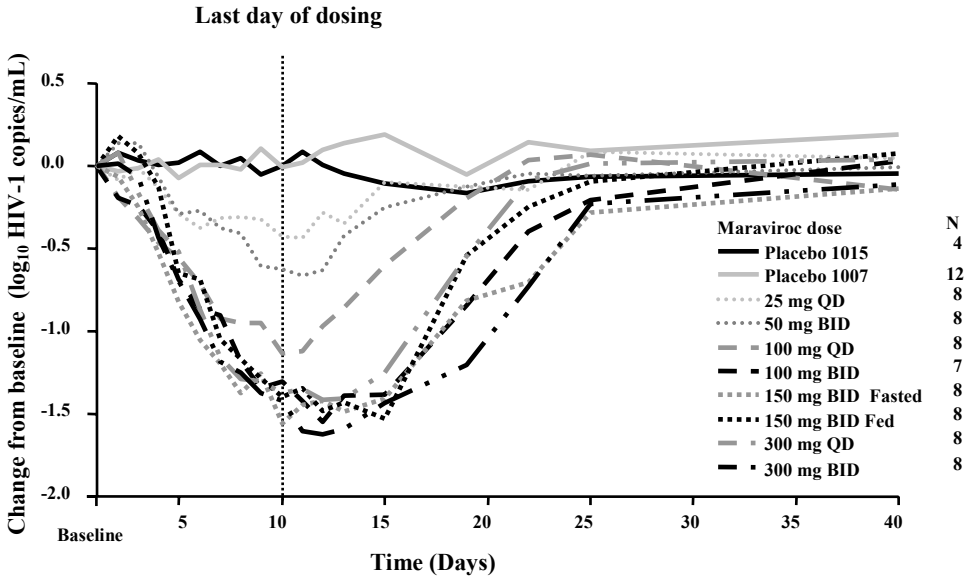
The objectives of Study A4001007 were to demonstrate that short-term maraviroc monotherapy decreased plasma viral load in HIV-1 infected patients and to assess the pharmacokinetic/pharmacodynamic relationship by determining the correlation of plasma viral load decline with plasma drug concentration, CCR5 saturation and in vitro antiviral $IC_{50/90}$. The objectives of Study A4001015 were to assess the effect of food and the effect of once daily (QD) and twice daily (BID) dosing on the antiviral effect and the pharmacokinetic/pharmacodynamic relationships in HIV-1 infected patients on short-term maraviroc monotherapy.

For both Phase 2a studies, patients were asymptomatic and infected with a confirmed CCR5 tropic virus as determined by the Monogram Biosciences recombinant virus assay (described in Appendix 1.1). Patients found to harbour mixed/dual tropic virus, CXCR4-using virus, or non-phenotypable virus at screening were excluded from the study.

Patients received double-blind study drug (25 mg QD, 50 mg BID, 100 mg QD and BID, 150 mg BID fed and fasted, 300 mg QD and BID or placebo) daily at the study visit for 10 days with follow up visits at Days 11-13, 15, 20, 25 and 40. The primary endpoint was determined as change in $\log_{10}$ HIV-1 RNA level from baseline to Day 11. The study design and patient populations were similar for both studies and therefore the results were combined for presentation (Fatkenhauer G, 2005). Baseline demographics and disease characteristics were similar across all treatment groups, with mean baseline viral load and CD4 cell counts of 4.62 (range 3.56-5.64) $\log_{10}$ HIV-1 RNA copies/mL and 544 (range 205-1137) cells/μL, respectively.

A statistically significantly larger decrease (at the 10% significance level) in HIV-1 RNA level from baseline compared with placebo was seen for all maraviroc dose groups. Doses of maraviroc ≥100 mg QD resulted in mean reductions of ≥1.0 $\log_{10}$ copies/mL HIV-1 RNA from baseline at Day 11 (Figure 5).

Figure 5. Change from Baseline in HIV-1 RNA ($\log_{10}$ copies/mL) (Combined Studies A4001007 and A4001015)



At the end of the dosing period viral rebound was not immediate; maximum viral load reduction occurred after Day 11 in several patients (median time to nadir was 10-15 days). At doses of ≥100 mg BID all patients (with the exception of one, who was inadvertently enrolled into the study but later found to harbour dual/mixed tropic virus at baseline) achieved a reduction in HIV-1 RNA >1 $\log_{10}$ copies/mL at nadir; mean (range) was -1.60 (-2.08, -1.14) and -1.84 (-2.42, -1.49) $\log_{10}$ copies/mL at doses of 300 mg QD and 300 mg BID respectively.

The changes in HIV-1 RNA from baseline were similar for the maraviroc 150 mg BID fed and fasted treatment groups and for the maraviroc 150 mg BID (fasted) and the maraviroc 300 mg QD (fasted) treatment groups indicating no effect of food or dosing regimen on reduction in viral load.

Mean CD4 cell count increases between Day 1 and Day 11 in the maraviroc treatment groups were variable and ranged from +5 cells/μL (150 mg BID fasted), to +150 cells/μL (50 mg BID). In the A4001007 and A4001015 placebo groups mean CD4 cell count decreased by 2 cells/μL and 31 cells/μL, respectively. There was no correlation between changes in CD4 cell count and viral load response or dose of maraviroc.

All maraviroc treatment groups had mean pre-dose CCR5 occupancy of >80% on Day 5, and for all doses except for 25 mg QD this remained >80% on Day 10 pre-dose and >60% on Day 15, 5 days post-therapy. This prolonged occupancy of CCR5 by maraviroc may be responsible for the delay in viral rebound, however, no association between CCR5 receptor occupancy (determined using an ex-vivo MIP-1 β internalization assay) and viral load reduction was observed. This apparent and counter-intuitive lack of correlation is thought to be due to the high efficiency of HIV-1 in infecting cells, requiring just a few percent of free receptor. The assay for CCR5 receptor occupancy is thought to be accurate to +/-20% typical of a bioassay system.

Sixty-two patients enrolled into these Phase 2a studies harbored CCR5-tropic virus at baseline and had a post-treatment phenotype result. Circulating virus remained CCR5-tropic in 60/62 patients, 51 of whom experienced a >1 $\log_{10}$ copies/mL HIV-1 RNA reduction from baseline, indicating that CXCR4-using variants were not rapidly selected despite CCR5-specific drug pressure. In two patients receiving maraviroc 100 mg QD in Study A4001015, viral load declined during treatment by a similar amount to other patients in the same dose group but CXCR4-using virus was detected at Day 11. In one patient emergence of CXCR4-using virus was transient and the population reverted back to CCR5-tropic virus by Day 40 follow up. In the second patient dual/mixed tropic virus remained detectable at Day 40 follow up; however, the majority of virus variants were CCR5 tropic. No pre-treatment factor (i.e., CD4 cell count, plasma viral load, previous antiretroviral therapy history) predicted the emergence of CXCR4-using virus during maraviroc therapy in these two patients. Phylogenetic analysis of envelope (Env) clones from pre- and post-treatment time points indicated that the CXCR4-using variants probably emerged by outgrowth of a pre-treatment CXCR4-using reservoir, rather than via co-receptor switch of a CCR5-tropic clone under selection pressure from maraviroc (Westby M, 2006).

Phylogenetic analysis was also performed on Env clones from a third patient harboring CXCR4-using virus prior to treatment (Study A4001007). This patient was enrolled due to a sample labelling error, as confirmed by sequencing of the envelope open reading frame from serial plasma samples. Although this patient experienced no overall reduction in viral load in response to treatment, the CCR5-tropic components of the circulating virus did appear to be suppressed whilst receiving maraviroc as monotherapy (Westby M, 2006).

In all three patients circulating virus reverted to predominantly CCR5-tropic following cessation of maraviroc treatment, as confirmed by clonal analysis of envelope clones at Day 40. These results suggest that CCR5 tropism is strongly selected for in HIV-1 infected patients, however, concern exists that selective pressure from a CCR5 antagonist could lead to early predominance of CXCR4-using virus in patients infected with dual/mixed tropic HIV-1 leading to a detrimental outcome. It was felt that longer term studies of CCR5 antagonists in HIV infected patients would be required in order to adequately address this issue.

In summary, the results of these Phase 2a studies demonstrated that blockade of the CCR5 co-receptor should be an effective target for the treatment of patients infected with CCR5 tropic HIV-1. Treatment with maraviroc as 10-day monotherapy resulted in a mean

maximum reduction in HIV-1 RNA of ≥1.6 $\log_{10}$ copies/mL at all doses ≥200 mg total daily dose and this maximum reduction occurred at a median of 10-15 days. These effects on viral load appeared to be independent of dosing frequency and food and therefore suggested that maraviroc should be evaluated using both QD and BID regimens, and with no food restrictions in the Phase 2b/3 clinical program.

6.3. Dose Selection for Phase 2b/3 Clinical Studies

The rationale for dose selection in the Phase 2b/3 treatment-experienced patient population was to maximize the benefit: risk ratio for maraviroc in these patients. The dose selection for the Phase 2b/3 studies was based on viral load reduction data from Studies A4001007 and A4001015, pharmacokinetic/pharmacodynamic modeling, clinical study simulations, pharmacokinetics, drug-drug interaction studies, pre-clinical serial passage resistance studies and a safety database of over 400 subjects dosed for up to 4 weeks.

The conclusions from the Phase 2a studies were that antiviral effects were related to daily dose/exposure, such that maximal anti-viral effects were seen for total daily doses ≥200 mg, administered as a once or twice a day regimen. Evaluation of safety data from the Phase 1/2a studies identified postural hypotension as the dose-limiting adverse event, occurring at a frequency greater than placebo at unit doses of >300 mg and was generally temporally associated with C_{max} rather than AUC or C_{min}. Based on these data, it was decided that exposure at a 300 mg dose equivalent would give an optimal balance between safety and efficacy, and doses of 300 mg QD and 300 mg BID were selected for further study.

Maraviroc is a substrate for both CYP3A4 and P-gp (see Section 5 for details), the potential for drug interactions with maraviroc and OBT had to be taken into account in the treatment experienced population. It was expected that the majority of patients would require a protease inhibitor in their OBT. Several protease inhibitors, with and without ritonavir boosting, have been shown to inhibit the metabolism of maraviroc resulting generally in increases in C_{max} and AUC of 2-3 fold, and 3-5 fold respectively. There were two exceptions to this; saquinavir/ritonavir, which led to a 4-5 fold and 8-10 fold increase in C_{max} and AUC respectively and tipranavir/ritonavir, which did not significantly increase exposure to maraviroc. Dose adjustment of maraviroc has been shown to compensate for changes in exposure with both CYP3A4 inhibitors and inducers. In order to keep dosing instructions as simple as possible, a single dose adjustment (50%) was recommended for maraviroc when given with all protease inhibitors (except tipranavir/ritonavir) and delavirdine. The intention was that this should adequately correct for C_{max} concentrations, although total exposure (AUC) may not be fully corrected. Hence the dose of maraviroc to be administered with protease inhibitors (except tipranavir/ritonavir) and delavirdine, was recommended to be 150 mg QD or BID. Safety data were analysed during the Phase 2b/3 clinical program for the interaction with the most potent CYP3A4 inhibitor studied, saquinavir/ritonavir, to ensure there were no clinically significant adverse effects noted in this greatest exposure scenario. These data are presented in Section 9.7.1 of this document. CYP3A4 inducers (including efavirenz) have been shown to reduce maraviroc exposure, however when given with protease inhibitors, the net effect was shown to be inhibition, and hence the downward dose

adjustment of maraviroc was still recommended even if both potent CYP3A4 inducers and PIs are contained within the OBT.

6.4. Phase 2b/3 Clinical Development Program

6.4.1. Phase 2b/3 Clinical Program Overview

More than 2000 HIV-1 infected patients have received blinded study drug in the maraviroc Phase 2b/3 development program, which included 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) (Table 3). The design and conduct of all studies in the Phase 2b/3 clinical program were reviewed and agreed with the FDA prior to commencement of the studies.

Table 3. Maraviroc Phase 2b/3 Program Overview

	A4001026	A4001027 & -1028	A4001029
Patient Population	ARV-Naïve CCR5 Tropic	ARV-Experienced CCR5 Tropic	ARV-Experienced Non-CCR5 Tropic
Design	Phase 2b→3	Phase 3	Phase 2b
Primary Endpoints	% patients HIV-1 RNA <400/50 copies/mL at Week 48/96	Change in HIV-1 RNA at Week 24/48	Change in HIV-1 RNA at Week 24
Patients Randomised	917[a] (1:1:1)	601 (A4001027) / 475 (A4001028) (2:2:1)	190 (1:1:1)
Treatment[b]	MVC QD: MVC BID: EFV QD	MVC QD: MVC BID: Placebo	MVC QD: MVC BID: Placebo
Region	NA, EU, AUS, LA, RSA	NA / EU, AUS, USA	NA, EU, AUS
Study Status	Phase 3 Primary Analysis at Week 48 Ongoing to Week 96	Phase 3 Interim Analysis at Week 24 Primary Analysis at Week 48	Phase 2b Primary Analysis at Week 24 Ongoing to Week 48

[a] Originally targeted as 1071. This is reduced to a projected number of 917 following discontinuation of QD dosing arm after DSMB recommendation (as discussed below).
[b] Maraviroc doses for A4001026 are 300 mg and for all other studies the dose is adjusted to 150 mg QD or BID when administered with a PI (except tipranavir/ritonavir) and/or delavirdine in the OBT.
ARV = Antiretroviral Therapy; MVC = Maraviroc; EFV = Efavirenz; NA = North America; EU = Europe; AUS = Australia; LA = Latin America (Mexico and Argentina); RSA = South Africa.

Pre-specified interim analyses at 24 weeks have been conducted by the Sponsor for the two independent, double-blind, randomised, placebo-controlled Phase 3 registrational trials (A4001027 and A4001028) evaluating maraviroc 300 mg QD and BID dose equivalents, which provide the efficacy and safety data for treatment-experienced patients infected with CCR5 tropic HIV-1 and form the basis of the maraviroc NDA submission. 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 USA). Over 1,000 patients in total were treated in these 2 studies.

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. Information from this study is included in the maraviroc NDA submission and in this briefing document to provide data in patients infected with dual/mixed-tropic, CXCR4-tropic or non-phenotypable HIV-1.

To ensure the safety of study participants a Data Safety Monitoring Board (DSMB) was formed to oversee all the studies in the maraviroc Phase 2b/3 clinical development program. The DSMB were responsible for evaluating the progress of all clinical studies including pre-planned periodic assessments of efficacy and safety data, which were provided to them in a semi-blinded manner. At each of their specified review meetings, held every 12-16 weeks, the DSMB recommended continuation of Studies A4001027, A4001028 and A4001029 unchanged. In addition, the DSMB Chairman and statistician reviewed monthly tables, in a semi-blinded manner. Two of the pre-specified full DSMB meetings were arranged to coincide with interim analyses of Studies A4001029 and A4001026.

For Study A4001029, an interim analysis was performed when the first 75 patients (approximately 25 patients per treatment group) had been treated for 8 weeks to ensure that maraviroc was not causing harm in patients infected with dual/mixed-tropic or non-phenotypable HIV-1. No formal analysis was conducted for virologic endpoints and the DSMB recommended continuation of the study as planned.

Study A4001026 is an ongoing study in treatment-naïve patients infected with CCR5 tropic HIV-1. An interim analysis was conducted by the DSMB when 205 patients had been treated with blinded therapy for 16 weeks, which was the Phase 2b run-in portion of this study. The prespecified interim analysis had the following criteria for comparing the maraviroc 300 mg QD and BID treatment groups to the efavirenz 600 mg QD treatment group:

- Time averaged difference (TAD) in HIV-1 RNA level: To demonstrate non-inferiority the upper bound of the 97.5% confidence interval should be below 0.5;

- Response rate (% of patients with an HIV-1 RNA level <400 copies/mL): To demonstrate non-inferiority the lower bound of the 97.5% confidence interval should be above –20%.

For the maraviroc 300 mg QD treatment group, neither of these criteria were met. Therefore, the DSMB recommended discontinuation of the maraviroc 300 mg QD treatment group. They recommended continuation of the other two treatment groups without additional changes.

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 original maraviroc 300 mg BID and efavirenz 600 mg QD treatment groups remain blinded to the Sponsor at the date of this submission. Therefore, a full efficacy analysis for this treatment-naïve patient population will not be included.

6.4.2. Selection of Patient Populations for Pivotal Treatment Experienced Studies

Maraviroc is a selective CCR5 co-receptor antagonist and is therefore designed to be maximally effective in patients infected with CCR5 tropic HIV-1 only. Efficacy of maraviroc for the target indication of this application, the management of treatment-experienced patients infected with CCR5 tropic HIV-1, has been demonstrated in two independent, randomised, double-blind, placebo-controlled superiority studies. These studies were designed to reflect a heavily treatment-experienced HIV-1-infected population who were failing their current antiretroviral therapy or were infected with multi-drug resistant virus. Patients had at least 6 months of prior treatment with at least 1 agent (2 agents for PIs) from 3 of 4 antiretroviral drug classes and/or documented resistance to 3 of the 4 antiretroviral drug classes and plasma HIV-1 RNA ≥5000 copies/mL. These Phase 3 studies were designed and carried out in accordance with the FDA Guidance for Industry (Antiretroviral Drugs Using Plasma HIV RNA measurements – Clinical Considerations for Accelerated and Traditional Approval, October 2002). Despite selecting patients with CCR5 tropic HIV-1 these 2 studies demonstrated similar baseline viral loads and CD4 cell counts to recent clinical studies of antiretroviral agents (Table 4).

Table 4. Baseline Viral Loads and CD4 Cell Counts for Some Antiretroviral Agents

	Darunavir[a]	Tipranavir[b]	Enfuvirtide (TORO-1)[c]	Maraviroc	Raltegravir (MK-0518)[d]
Median Viral Load (log_{10} copies/mL)	4.52	4.82	5.2	4.86	4.63 (mean)
Median CD4 Cell Count (cells/μL)	153	155	76	167	155 (mean)
% Patients Screening Viral Load ≥100,000 copies/mL	24	40	N/A	41	N/A
% Patients Baseline CD4 Cell Count <200 cells/μL	67	61	N/A	58	N/A

[a] Darunavir only (taken from the US Package Insert [USPI])
[b] Tipranavir+ placebo (taken from the US Package Insert [USPI])
[c] Enfuvirtide (Lalezari JP, 2003).
[d] Mean values calculated from BENCHMRK-1 and -2 studies (Abstract #105, CROI February 2007).

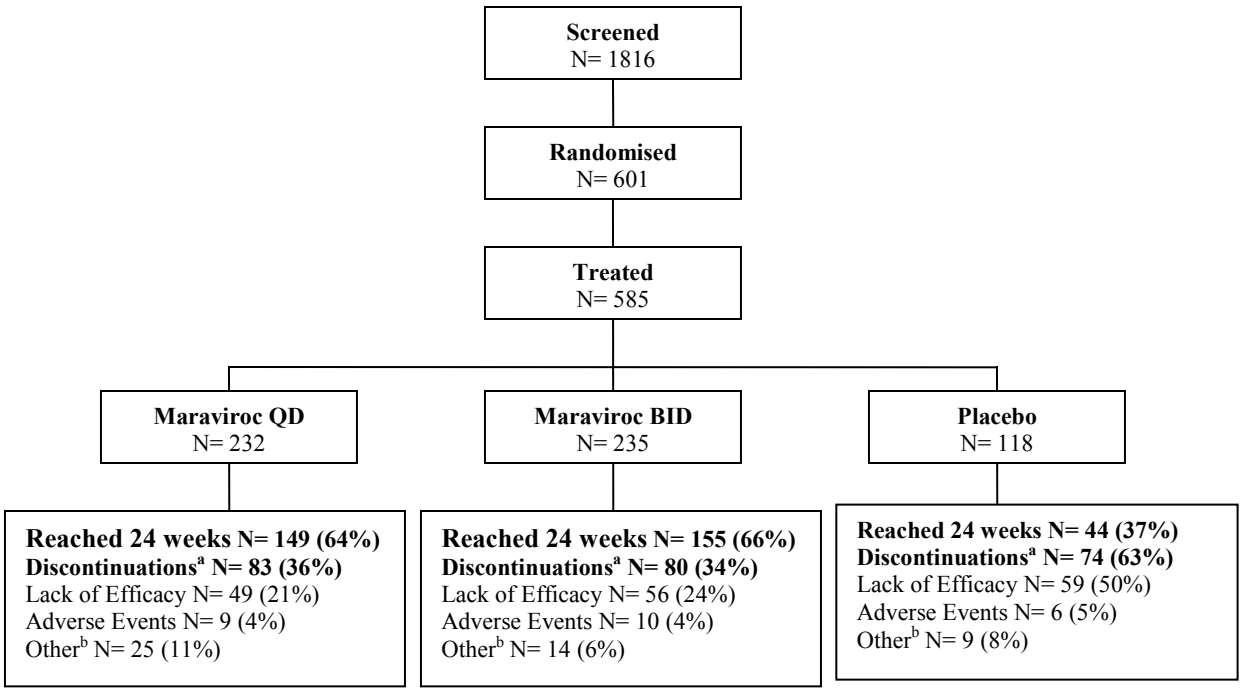
Study A4001029 was designed as a Phase 2b safety study in treatment-experienced patients infected with non-CCR5 tropic HIV-1, which included patients infected with dual/mixed tropic, CXCR4-tropic and non-phenotypable virus who had an HIV-1 RNA ≥5000 copies/mL and with genotypic or phenotypic resistance to 2 of the 4 antiretroviral drug classes, or ≥3 months of antiretroviral class experience with ≥3 of the following: 1 NRTI, 1 NNRTI, 1 PI (except low dose ritonavir) and enfuvirtide.

The patient population initially screened for recruitment into Studies A4001027, A4001028 and A4001029 was essentially similar. At screening, patients underwent phenotypic testing for the presence of CCR5 tropic HIV-1 by Monogram Biosciences (Trofile™ HIV Entry Tropism assay). Those patients confirmed to be infected with CCR5 tropic HIV-1 were

randomised into studies A4001027 and A4001028. Those patients who were found to harbour dual/mixed tropic virus, CXCR4-using virus or patients whose virus was non-phenotypable were then considered for randomization into study A4001029, providing they had at least one active drug (i.e., a PI, NNRTI or enfuvirtide) available to them for use in their OBT regimen. In addition, all patients underwent testing for resistance to NRTIs, NNRTIs, PIs and enfuvirtide to guide the Investigator's choice of OBT. All OBT selections were reviewed by the Sponsor's medical monitors from the Anti-Infective Therapeutic area versus Phenosense GT™ and enfuvirtide resistance testing results and if necessary discussed with the Investigator. The primary purpose for this review was for safety in avoiding potentially less safe or less effective regimens (e.g., tenofovir + didanosine). An overview of the methods of analysis for the virus tropism testing and the resistance testing to drugs available for inclusion in a patient's OBT is provided in Appendix 1.

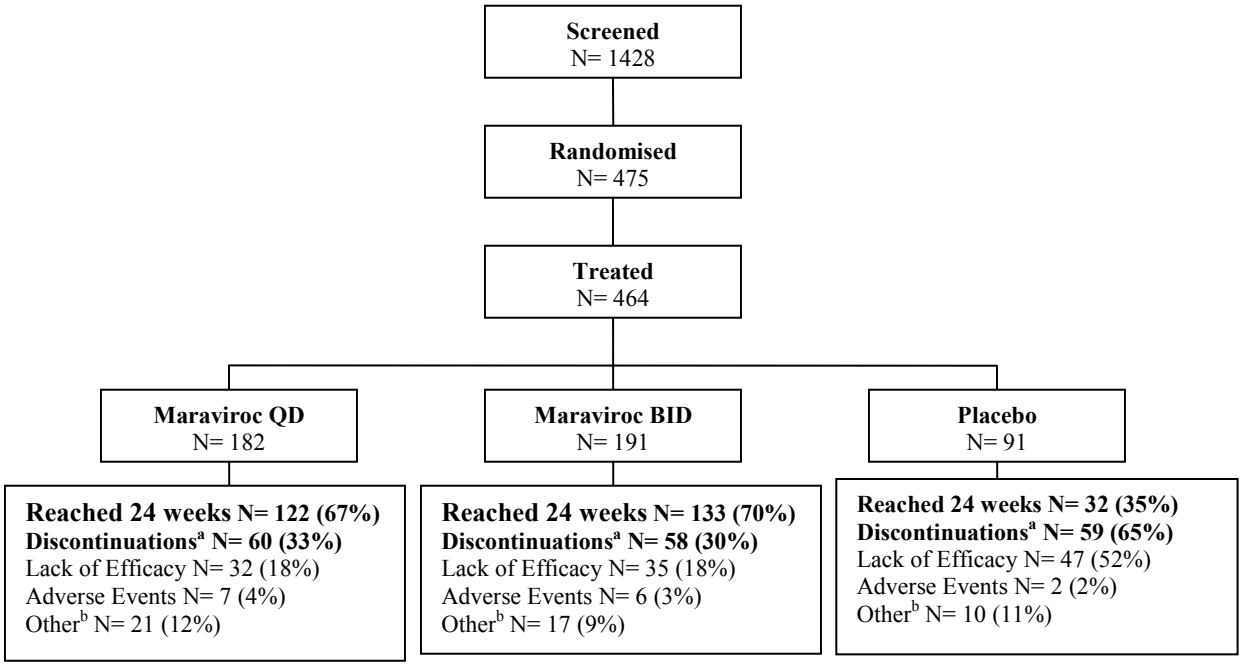
Figure 6, Figure 7 and Figure 8 below present the process of patient recruitment into the maraviroc Phase 2b/3 clinical studies and the derivation of the populations evaluated for efficacy. The most common reason for screen failure in Studies A4001027 and A4001028 was presence of a dual/mixed or CXCR4 tropism result, which was demonstrated in 44% of patients for whom a tropism sample was tested (Coakley E, 2006).

Figure 6. Derivation of Efficacy Population for Studies A4001027



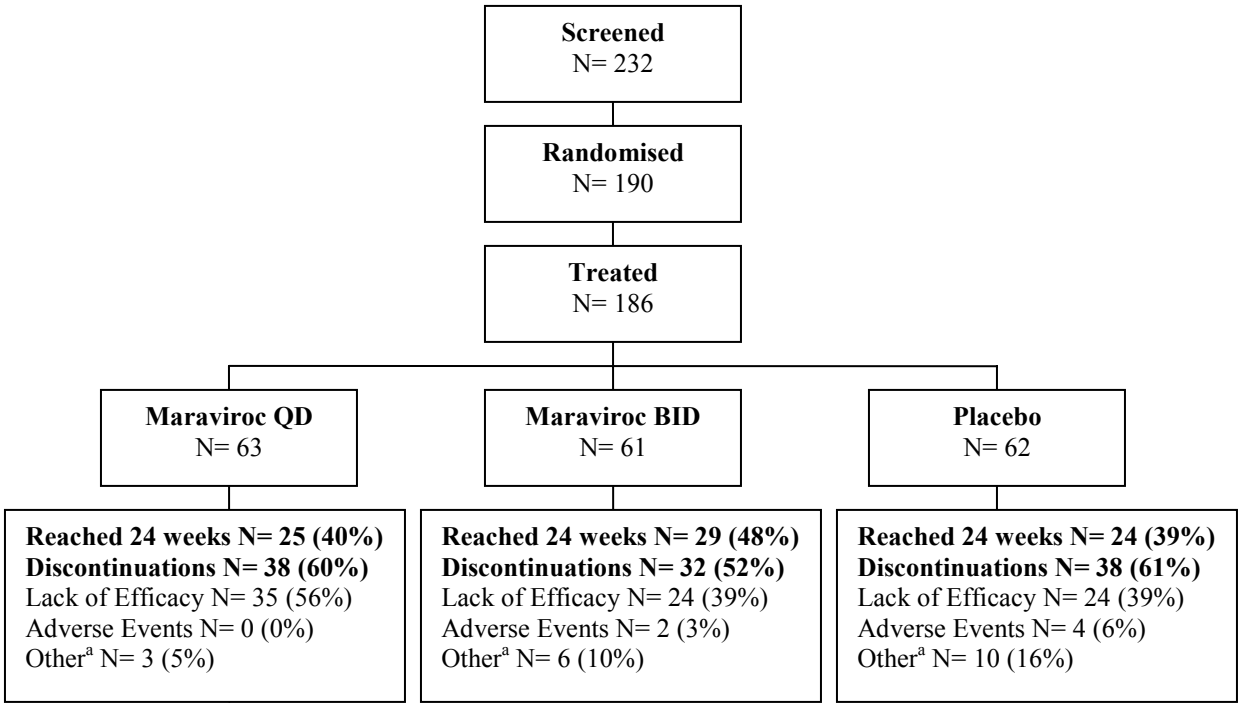
[a] Discontinuations from study reflect data up to 48-weeks of treatment.
[b] 'Other' may include subject died and subject defaulted.

Figure 7. Derivation of Efficacy Population for Studies A4001028



[a] Discontinuations from study reflect data up to 48-weeks of treatment.
[b] 'Other' may include subject died and subject defaulted.

Figure 8. Derivation of Efficacy Population for Study A4001029



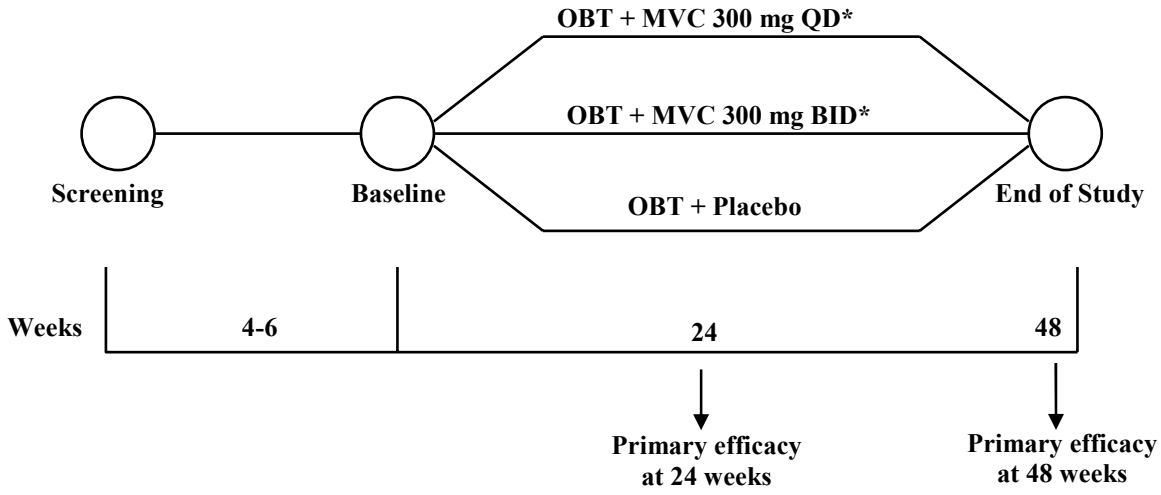
[a] 'Other' may include subject died and subject defaulted.

6.4.3. Study Design

The primary objective for the Phase 2b/3 pivotal efficacy studies was to confirm the hypothesis that maraviroc in combination with OBT provided an additional reduction in plasma HIV-1 RNA level compared with OBT alone, as measured by the difference between each of the two maraviroc dosing regimens (QD and BID) versus the placebo regimen in the mean changes from baseline in $\log_{10}$ plasma HIV-1 RNA level at Week 24. The secondary objective included the assessment of safety and tolerability of maraviroc when given in combination with OBT versus OBT alone.

The Phase 2b Study (A4001029) was similar in study design but investigated the effects of maraviroc in patients infected with dual/mixed-tropic, CXCR4-tropic, or non-phenotypable HIV-1. The study design for these Phase 2b/3 studies in the maraviroc clinical program is presented in the schematic diagram below (Figure 9).

Figure 9. Outline of Study Design for Maraviroc Phase 2b/3 Clinical Studies



* Patients whose OBT included a PI (except for tipranavir/ritonavir) and/or delavirdine received 150 mg QD or 150 mg BID as dose adjustment

Patients were screened for entry into the studies 4-6 weeks prior to randomization and starting study drug. The delay before randomization was necessary to determine the tropism assignment of the patients' virus and to perform genotypic and phenotypic susceptibility (using the Phenosense™ GT [PSGT] assays and gp41 sequencing, details provided in Appendix 1), which were available 3-5 weeks after receipt of the samples.

If patients fulfilled the entry criteria they were randomised to study treatment and the Investigator selected appropriate OBT 4-7 days before their baseline visit, at the randomization visit. Patients were randomised to receive maraviroc 300 mg QD dose equivalent, maraviroc 300 mg BID dose equivalent or placebo all in combination with OBT; the maraviroc dose was adjusted to maraviroc 150 mg QD or BID in those patients receiving

a PI (except for tipranavir/ritonavir) and/or delavirdine in their OBT due to the increased exposure of maraviroc observed or predicted in the presence of these co-administered antiretroviral agents due to enzyme inhibition. Investigators chose OBT with 3-6 approved antiretroviral agents, not including low dose ritonavir, on an individual patient basis, based on the results of phenotypic and genotypic susceptibility testing carried out at screening, treatment history and safety/tolerability considerations. The OBT was administered as open-label therapy and not provided by the Sponsor. Experimental antiretroviral agents available through pre-approval access programs or other means were permitted as part of a patient's OBT provided that adequate information was available to allow for safe co-administration with maraviroc. If a patient experienced toxicity to a particular drug within their OBT, a substitution to another drug within the same class was allowed in consultation with the medical monitor for the trial. Changes to background therapy could also be made within the first two weeks, in consultation with the medical monitor, due to documented human error in interpretation of screening resistance test results. No other changes in antiretroviral agents were permitted during the study period.

Following the Day 1 (baseline) visit, patients attended for follow up visits at Weeks 2 and 4 and every 4 weeks thereafter until Week 24 and then continued every 8 weeks until Week 48. At Weeks 24 and 48 patients had visits for primary efficacy analysis.

Study Endpoints

For the Phase 2b/3 Studies A4001027, A4001028 and A4001029 the primary and secondary endpoints for analysis of efficacy are listed below.

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

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

(a) The % of subjects with an HIV-1 RNA <400 copies/mL at Week 24;

(b) The % of subjects with an HIV-1 RNA <50 copies/mL at Week 24;

(c) The % of subjects who achieved at least a 0.5 $\log_{10}$ reduction in HIV-1 RNA from baseline or <400 copies/mL at Week 24;

(d) The % of subjects who achieved at least a 1.0 $\log_{10}$ reduction in HIV-1 RNA from baseline or <400 copies/mL at Week 24;

(e) The differences in the magnitude of change in CD4 cell count from baseline to Week 24;

(f) The differences in the magnitude of change in CD8 cell count from baseline to Week 24;

(g) The Time-Averaged Difference (TAD) in $\log_{10}$ HIV-1 RNA at Week 24;

(h) To assess HIV-1 genotype and phenotype at baseline and at the time of failure.

Additional Endpoints:

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

Definitions of Treatment Failure:

For all of the Phase 2b/3 maraviroc clinical studies patients were defined as treatment failures if they met any one of the following virological endpoints:

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

6.4.4. Statistical Analysis Plans

For Studies A4001027, A4001028 and A4001029 two analysis populations were used to determine efficacy at 24 weeks.

- The Full Analysis Set (FAS) population consisted of all randomised patients who received at least 1 study drug dose, both 'As Randomised' and 'As Treated'. Both of these were used to analyse the primary endpoint, but the 'Full Analysis Set – As Treated' population only was used for the analysis of all secondary endpoints and summary tables. There were two patients, in Study A400127, who had their medication swapped with each other, and so received a different treatment to which they were randomised. An additional 2 patients appear in the database under the incorrect treatment, due to the Investigator's transcription error.
- The Per Protocol population consisted of all randomised patients who met the following criteria:

- Received at least 1 dose of study medication;
- Treated for at least 14 days or discontinued before this time due to treatment failure;
- More than 80% compliant with randomised treatment;
- No violation of any inclusion or exclusion criteria, which would affect efficacy (such as tropism status).

Two separate versions of the Per Protocol population were constructed relating to whether a subject was considered 'As Randomised' or 'As Treated'. These populations were labeled 'Per Protocol – As Randomised' and 'Per Protocol – As Treated'. Both of these were used to analyse the primary endpoint, but the 'Per Protocol – As Treated' population only was used for the analysis of all secondary endpoints and summary tables.

A Sensitivity analysis was performed in which those subjects who met at least one of the treatment failure criteria, but had not been discontinued from the study by the Investigator, were considered as treatment failures.

For Studies A4001027 and A4001028, for the primary endpoint of mean change from baseline in HIV-1 RNA, 2-sided 97.5% confidence intervals (alpha = 0.025, Bonferroni correction for multiple comparisons) for the difference between maraviroc and placebo (OBT alone) were constructed. The decision to use this endpoint at the time of study design in 2004 was because of the similarity of the trial designs to TORO-1/2 for enfuvirtide. These trials used this same primary endpoint and allowed more confidence in power calculations for patient enrolment numbers. Patients who failed virologically or discontinued for any reason had their change in viral load imputed as zero for primary and secondary virological analyses. Subgroup and other exploratory analyses used last observation carried forward methodology as did CD4 count change from baseline.

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

For Study A4001029, a 97.5% confidence interval (adjusted for multiple comparisons) was presented for the difference between each dose of maraviroc (QD and BID) and placebo. If the upper bound of the confidence interval for a dose was below 0, it was concluded that the dose was superior to placebo. If this was not the case, but the upper bound was below 0.25, it was concluded that efficacy was not reduced by administration of maraviroc. This non-inferiority test assumed a small treatment benefit of 0.25 $\log_{10}$ HIV-1 RNA copies/mL for each of the two maraviroc treatment groups, relative to the placebo group. As for Studies A4001027 and A4001028, negative values for change from baseline indicated a benefit of treatment and negative values for the maraviroc comparison to placebo indicated an advantage of treatment with maraviroc over placebo.

6.5. Additional Maraviroc Clinical Studies

Clinical Studies Completed Post-NDA Filing Date

Hepatic Impairment Study (A4001023)

A study of maraviroc use in subjects with hepatic impairment was ongoing at the time of the initial NDA submission and therefore the results were not included in the dossier. The geometric mean ratios for C_{max} and AUC_{last} were 111% (74.6%, 166%) and 125% (84.7%, 185%), respectively for subjects with mild hepatic impairment compared to subjects with normal hepatic function, and 132% (89.6%, 194%) and 145% (100%, 212%), respectively for subjects with moderate hepatic impairment compared to subjects with normal hepatic function. Tmax and t1/2 were similar in all 3 treatment groups.

The results indicate that mild to moderate hepatic impairment has limited impact on the pharmacokinetic profile of maraviroc given at the therapeutic dose and therefore no dose adjustment for patients with mild to moderate hepatic impairment is therefore recommended.

TMC-114 (Darunavir) Drug-Drug Interaction Study (A4001052)

This Phase 1 drug-drug interaction study was designed to investigate the effect of TMC-114 (darunavir) on maraviroc pharmacokinetics. Darunavir was an investigational drug during the development program of maraviroc and was only approved by the FDA in June 2006. The results indicate that co administration of maraviroc with TMC114/ritonavir leads to an increase in maraviroc exposure. Geometric mean ratios for AUC_{12} and C_{max} are 405% and 229% respectively. These data are consistent with the effects of other Protease Inhibitors (except tipranavir/ritonavir) and other potent CYP3A4 inhibitors on maraviroc pharmacokinetics. Hence, it is recommended that a dose adjustment of 0.5 fold is made for maraviroc when co-administered with TMC114/ritonavir.

Ongoing Maraviroc Clinical Studies

Phase 3 Registrational Studies (A4001027 and A4001028)

These registrational studies are still blinded to Investigator and patients until the last patient reaches 48 weeks, when patients and Investigators may be unblinded to treatment to reoptimize therapy. It is anticipated that the completed 48 week analyses will be available in 3Q 2007. The studies are currently planned to continue until the last patient reaches 96 weeks.

Phase 3 Study in Treatment-Naïve Patients Infected with CCR5 Tropic HIV-1 (A4001026)

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 reviewed by the DSMB, at which the maraviroc 300 mg QD arm was dropped on the recommendation of the DSMB, this study is ongoing to a formal statistical analysis at

48 weeks to which the Sponsor (but not the patients or Investigators) will be unblinded and will be continued out to 96 weeks study end.

Expanded Access Program (A4001050)

The expanded access program (EAP) is available multi-nationally. Provision is available to recruit up to 6000 treatment-experienced patients infected with CCR5 tropic HIV-1 and the inclusion/exclusion criteria are similar to the proposed label. Maraviroc is 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 ongoing 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.

7. EFFICACY

Maraviroc is a selective and slowly reversible CCR5 antagonist that has been shown to be active in vitro against a wide range of clinical isolates, including those resistant to existing drug classes. In healthy volunteers and asymptomatic HIV-1 infected patients, maraviroc, at doses up to 300 mg twice daily (BID) for up to 28 days, demonstrated a safety and tolerability profile that was not significantly different to placebo.

This section of the document summarizes the efficacy results from the two Phase 3 registrational studies in the target patient population, treatment-experienced patient infected with CCR5 tropic HIV-1, who were failing their current antiretroviral regimen and a smaller Phase 2b supportive safety study in patients infected with non-CCR5 tropic HIV-1. The results indicate that treatment with maraviroc (QD and BID regimens) in combination with OBT) produced statistically significant differences favoring maraviroc in comparison to placebo in combination with OBT (OBT alone) in:

- Reduction in HIV-1 RNA level from baseline to Week 24, with a mean reduction in HIV-1 RNA from baseline of at least 1.8 $\log_{10}$ copies/mL compared with approximately 1.0 $\log_{10}$ copies/mL with OBT alone;

- Percentage of patients with an HIV-1 RNA level <400 and <50 copies/mL at Week 24, a greater percentage of patients who achieved at least a 0.5 and 1.0 $\log_{10}$ reduction from baseline in HIV-1 RNA, and a larger time averaged difference in HIV-1 RNA level from baseline to Week 24;

- Increase in absolute CD4 cell count from baseline to Week 24.

In addition, the analyses of the studies presented in this document demonstrate that:

- The greater efficacy provided by maraviroc compared with placebo in patients infected with CCR5 tropic HIV-1 was observed regardless of a patient's screening HIV-1 RNA level (<100,000 copies/mL or ≥100,000 copies/mL) or CD4 cell count at baseline, and was also independent of enfuvirtide use as part of OBT;

- The dose adjustment implemented for patients receiving a PI (except for tipranavir/ritonavir) or delavirdine in their OBT was appropriate and did not adversely affect the efficacy outcome;

- Maraviroc administration in patients infected with dual/mixed tropic or CXCR4-using HIV-1, or in patients whose virus was non-phenotypable, did not result in adverse effects on viral load or CD4 count.

7.1. Efficacy Results from the Phase 3 Registrational Studies (A4001027 and A4001028)

7.1.1. Study Populations

7.1.1.1. Patient Demographics and Baseline Characteristics

In Studies A4001027 and A4001028 more than 1,000 patients were treated with blinded study drug, of which 840 received maraviroc either once daily (QD) or twice daily (BID) in combination with OBT. An additional 209 patients received placebo in combination with OBT. Nearly 90% of the patients enrolled were male and more than 80% were white. The mean age was approximately 46 years. Plasma HIV-1 RNA and CD4 cell count at baseline was very similar across the three treatment groups. In addition, the median resistance mutations associated with PIs, NNRTIs, NRTIs and enfuvirtide were similar between treatment groups. Table 5 presents the patient demographics and baseline characteristics for the patients recruited into Studies A4001027 and A4001028. There was no difference between treatment groups in any of the parameters.

Table 5. Patient Demographics and Baseline Characteristics (Studies A4001027 and A4001028)

Characteristic	Study A4001027			Study A4001028		
	Maraviroc QD	Maraviroc BID	Placebo	Maraviroc QD	Maraviroc BID	Placebo
N	232	235	118	182	191	91
Male Sex, n (%)	210 (91)	212 (90)	106 (90)	153 (84)	170 (89)	79 (87)
White Race, n (%)	187 (81)	197 (84)	99 (84)	149 (82)	166 (87)	79 (87)
Mean Age (range), yrs	46 (19-75)	46 (25-69)	46 (31-71)	45.2 (17-75)	47.0 (21-73)	45.3 (29-72)
Mean HIV-1 RNA (SD), log_{10} copies/mL	4.85 (0.641)	4.86 (0.614)	4.84 (0.556)	4.87 (0.664)	4.84 (0.621)	4.89 (0.696)
Screening Stratum of HIV-1 RNA level, n (%)						
<100,000 copies/mL	135 (58.2)	139 (59.1)	70 (59.3)	103 (56.6)	104 (54.5)	53 (58)
≥100,000 copies/mL	93 (40.1)	95 (40.4)	46 (39.0)	77 (42.3)	81 (42.4)	38 (42)
Median CD4 Cell Count (range), cells/μL	167.5 (1.0 – 811.5)	150.0 (2.0 – 677.5)	163.3 (1.0 – 675.0)	174.3 (0.5 – 965.5)	182.0 (3.0 – 820.0)	174.3 (2.0 – 544.5)
Mean Duration of Diagnosis (years)	14.0 (1.0-27.8)	13.9 (2.3-24.3)	14.3 (3.4-25.1)	14.3 (5.1-23.1)	13.8 (4.1-26.1)	14.4 (4.1-24.0)
PI[a] and/or Delavirdine in OBT, n (%)	202 (87.1)	191 (81.3)	99 (83.9)	118 (64.8)	144 (75.4)	72 (79.1)
Genotypic Susceptibility Score (PSS) – n (%)						
0	52 (22.4)	59 (25.1)	31 (26.3)	39 (21.4)	43 (22.5)	20 (22.0)
1	82 (35.3	80 (34.0)	29 (24.6)	64 (35.2)	58 (30.4)	24 (26.4)
2	38 (16.4)	48 (20.4)	21 (17.8)	25 (13.7)	32 (16.8)	20 (22.0)
≥3	57 (24.6)	47 (20.0)	34 (28.8)	52 (28.6)	57 (29.8)	25 (27.5)
Phenotypic Susceptibility Score (GSS) – n (%)						
0	25 (10.8)	24 (10.2)	17 (14.4)	20 (11.0)	26 (13.6)	12 (13.2)
1	70 (30.2)	73 (31.1)	18 (15.3)	46 (25.3)	42 (22.0)	20 (22.0)
2	51 (22.0)	69 (29.4)	35 (29.7)	42 (23.1)	38 (19.9)	23 (25.3)
≥3	83 (35.8)	66 (28.1)	45 (38.1)	71 (39.0)	84 (44.0)	34 (37.4)
Overall Susceptibility Score (OSS) – n (%)						
0	30 (12.9)	27 (11.5)	19 (16.1)	22 (12.1)	30 (15.7)	16 (17.6)
1	78 (33.6)	86 (36.6)	21 (17.8)	55 (30.2)	50 (26.2)	23 (25.3)
2	51 (22.0)	65 (27.7)	38 (32.2)	37 (20.3)	39 (20.4)	21 (23.1)
≥3	69 (29.7)	54 (23.0)	37 (31.4)	65 (35.7)	71 (37.2)	29 (31.9)
Δ32 Genotype (W/W, W/D)	200/17	207/13	101/11	157/15	166/15	75/5

[a] Except for tipranavir/ritonavir.
ARVs = Antiretroviral agents; QD = Once daily dosing; BID = Twice daily dosing; W/W = Wild-type, wild-type; W/D = Wild-type, deletion.

7.1.1.2. Patient Disposition

In both studies the proportion of subjects who discontinued in the placebo treatment groups was almost double the proportion of subjects who had discontinued from the maraviroc treatment groups (Table 6). The main reason for discontinuation in all treatment groups was lack of efficacy. The proportion of subjects who discontinued from the placebo treatment groups due to lack of efficacy was more than twice the proportion discontinuing for the same reason in the maraviroc groups.

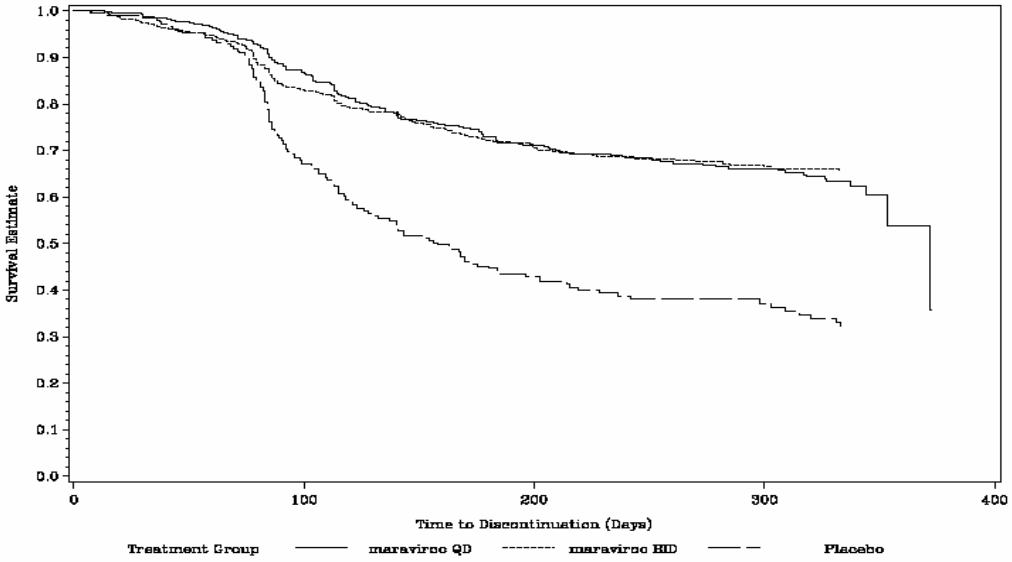
Table 6. Patient Evaluation Groups - Studies A4001027 and A4001028

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

[a] Full analysis set.
QD = Once daily dosing; BID = Twice daily dosing.

Time to discontinuation in both studies was longer in the maraviroc treatment groups compared with the placebo treatment groups (Figure 10).

Figure 10. Kaplan Meier Plot of Time to Discontinuation (Combined Studies A4001027 and A4001028)



The apparent steep drop an the end of the maraviroc QD curve is due to one subject discontinuing at day 372 when only 3 subjects had reached this timepoint.

7.1.2. Primary Efficacy Endpoint

The primary efficacy endpoint for Studies A4001027 and A4001028 was change in $\log_{10}$ HIV-1 RNA from baseline to Week 24 and was analysed using analysis of covariance (ANCOVA). Baseline was calculated as the mean of 3 values; screening, randomization and pre-dose on Day 1. Discontinuation from treatment before Week 24, for any reason, led to imputation of zero change from baseline. Missing data at Week 20 from a patient still in study and on medication was carried forward from their Week 20 visit.

In Studies A4001027 and A4001028 there was a greater mean decrease in HIV-1 RNA from baseline to Week 24 in both maraviroc treatment groups compared with placebo (Table 7).

Both dosing regimens of maraviroc demonstrated superiority compared with placebo as the 2-sided 97.5% confidence intervals for the difference between the maraviroc doses and placebo were completely to the left side and completely excluded zero; the treatment difference from placebo was -0.788 (97.5% CI -1.141, -0.435) for maraviroc QD and -0.922 $\log_{10}$ copies/mL (97.5% CI -1.275, -0.570) for maraviroc BID in Study A4001027 and -1.021 (97.5% CI -1.426, -0.616) for maraviroc QD and -1.042 $\log_{10}$ copies/mL (97.5% CI -1.444, -0.640) for maraviroc BID in Study A4001028.

Table 7. Summary of Change from Baseline in HIV-1 RNA to Week 24 Studies A4001027 and A4001028

Treatment Group	Study A4001027			Study A4001028		
	HIV-1 RNA ($\log_{10}$ copies/mL)			HIV-1 RNA ($\log_{10}$ copies/mL)		
	N	Adjusted Mean (se)	Difference[a] (97.5% CI)	N	Adjusted Mean (se)	Difference[a] (97.5% CI)
Maraviroc QD	232	-1.818 (0.092)	-0.788 (-1.141, -0.435)	182	-1.950 (0.105)	-1.021 (-1.426, -0.616)
Maraviroc BID	235	-1.952 (0.091)	-0.922 (-1.275, -0.570)	191	-1.971 (0.103)	-1.042 (-1.444, -0.640)
Placebo	118	-1.030 (0.129)	N/C	91	-0.929 (0.147)	N/C

[a] Compared with placebo.
QD = Once daily dosing; BID = Twice daily dosing; CI = Confidence interval; N/C = Not calculated; se = Standard error.

For both studies, the results of the 'FAS – As Randomised', 'Per Protocol – As Randomised' and 'Per Protocol – As Treated' population were consistent with the results for the 'FAS – As Treated' population presented above.

An additional sensitivity analysis was conducted for Studies A4001027 and A4001028, which was identical to the analysis of the primary endpoint presented above apart from those patients who met at least one of the protocol-defined treatment failure criteria (detailed in Section 6.4.3), but were not discontinued from the study by the Investigator, and were considered treatment failures, so their change from baseline was imputed as zero. The results of these analyses are presented in Table 8 below.

Table 8. Summary of Change from Baseline in HIV-1 RNA to Week 24 – Sensitivity Analysis (Treatment Failure Classification, No Change) (Studies A4001027 and A4001028)

Treatment Group	Study A4001027			Study A4001028		
	HIV-1 RNA ($\log_{10}$ copies/mL)			HIV-1 RNA ($\log_{10}$ copies/mL)		
	N	Adjusted Mean (se)	Difference[a] (97.5% CI)	N	Adjusted Mean (se)	Difference[a] (97.5% CI)
Maraviroc QD	232	-1.798 (0.093)	-0.790 (-1.145, -0.434)	182	-1.943 (0.106)	-1.047 (-1.454, -0.641)
Maraviroc BID	235	-1.946 (0.092)	-0.938 (-1.293, -0.583)	191	-1.967 (0.130)	-1.072 (-1.475, -0.668)
Placebo	118	-1.008 (0.130)	N/C	91	-0.896 (0.148)	N/C

[a] Compared with placebo.
QD = Once daily dosing; BID = Twice daily dosing; CI = Confidence interval; N/C = Not calculated; se = Standard error.

The results of the sensitivity analyses were consistent with the primary endpoint analysis described above, with maraviroc QD and BID consistently showing statistically significant differences compared with placebo.

A further efficacy analysis was performed for patients who discontinued for any reason or who had missing data at Week 24. This reanalysis only affected 14 patients and is therefore presented for the combined study dataset (Table 9). The results of this analysis did not change the conclusions of the primary analysis as described above.

Table 9. Summary of Change from Baseline in HIV-1 RNA to Week 24 – Sensitivity Analysis for All Missing Data (Treatment Failure Classification, No Change) (Combined Studies A4001027 and A4001028)

Treatment Group	Change from Baseline to Week 24				Treatment Difference Maraviroc - Placebo	
	N	Raw Mean (se)	Median	Adjusted Mean (se)	Estimate (se)	97.5% CI
Maraviroc QD	414	-1.825 (0.070)	-2.229	-1.833 (0.069)	-0.872 (0.119)	-1.138, -0.605
Maraviroc BID	426	-1.946 (0.069)	-2.409	-1.950 (0.068)	-0.988 (0.118)	-1.253, -0.723
Placebo	209	-0.960 (0.091)	0.000	-0.962 (0.097)	N/C	N/C

QD = Once daily dosing; BID = Twice daily dosing; CI = Confidence interval; N/C = Not calculated; se = Standard error.

7.1.3. Secondary Efficacy Endpoints

Analyses compared the percentage of patients with viral load <400 and <50 copies/mL, the percentage of patients with a ≥0.5 (or viral load <400 copies/mL) and ≥1.0 $\log_{10}$ (or viral load <400 copies/mL) decrease in viral load from baseline, for each of the 2 maraviroc regimens versus placebo. The difference in the percentage of patients with the specified response was assessed at Week 24 and a 2-sided 95% CI was calculated, adjusting for screening viral load and enfuvirtide use in OBT.

In addition, the difference in the mean change from baseline in CD4 cell count, for each of the 2 maraviroc treatment groups versus placebo, was analysed. Baseline was calculated as the average of 2 pre-dose measurements (screening and pre-dose on Day 1). An ANCOVA model was fitted, including terms for treatment, baseline CD4 cell count and enfuvirtide use in OBT. The difference between the least square means was presented for each comparison with a 2-sided 95% CI. For the analysis of change from baseline in CD4/CD8 cell count, last observation carried forward (LOCF) was used to impute missing values.

There was a higher proportion of patients achieving an HIV-1 RNA <400 copies/mL, <50 copies/mL, with at least a ≥1.0 $\log_{10}$ viral load decrease or <400 copies/mL and at least a ≥0.5 $\log_{10}$ copies/mL viral load decrease or <400 copies/mL in both maraviroc treatment groups compared with placebo at Week 24 (Table 10). The results for all secondary endpoint analyses demonstrated statistical significance for both maraviroc groups over placebo as the confidence intervals were completely to the left side of and completely excluded zero.

Table 10. Overview of Patients with Viral Loads <400 and <50 copies/mL at Week 24 (Studies A4001027 and A4001028)

Parameter (HIV-1 RNA)	Study A4001027			Study A4001028		
	Maraviroc QD (N= 232)	Maraviroc BID (N= 235)	Placebo (N= 118)	Maraviroc QD (N= 182)	Maraviroc BID (N= 191)	Placebo (N= 91)
<400 copies/mL, n (%)	127 (54.7)	142 (60.4)	37 (31.4)	101 (55.5)	117 (61.3)	21 (23.1)
<50 copies/mL, n (%)	98 (42.2)	114 (48.5)	29 (24.6)	83 (45.6)	78 (40.8)	19 (20.9)
≥0.5 $\log_{10}$ Viral Load Decrease, n (%)	157 (67.7)	163 (69.4)	54 (45.8)	127 (69.8)	138 (72.3)	34 (37.4)
≥1.0 $\log_{10}$ Viral Load Decrease, n (%)	150 (64.7)	159 (67.7)	45 (38.1)	121 (66.5)	133 (69.6)	28 (30.8)

QD = Once daily dosing; BID = Twice daily dosing.

For both studies, there was a significantly greater mean increase in CD4 from baseline in both maraviroc treatment groups compared with placebo (Table 11).

Table 11. Summary of Mean Changes from Baseline to Week 24 in CD4 Cell Count (Studies A4001027 and A4001028)

Treatment Group	Study A4001027			Study A4001028		
	CD4 Cell Count (cells/μL)			CD4 Cell Count (cells/μL)		
	N	Adjusted Mean (se)	Difference[a] (95% CI)	N	Adjusted Mean (se)	Difference[a] (95% CI)
Maraviroc QD	227	106.6 (7.3)	54.5 (30.1, 78.9)	180	111.7 (7.8)	47.9 (21.6, 74.3)
Maraviroc BID	233	111.1 (7.1)	58.9 (34.6, 83.3)	185	101.9 (7.7)	38.1 (12.0, 64.3)
Placebo	116	52.1 (10.1)	N/C	90	63.8 (10.9)	N/C

[a] Compared with placebo.
QD = Once daily dosing; BID = Twice daily dosing; CI = Confidence interval; N/C = Not calculated; se = Standard error.

7.1.4. Combined Efficacy Analysis of Phase 3 Studies A4001027 and A4001028

A pre-planned combined analysis for efficacy was conducted (and described in the Summary of Clinical Efficacy analysis plan), which included the analysis of primary and secondary endpoints in sub-populations from Studies A4001027 and A4001028. The results of these analyses are described in this section, which further explores the comparative efficacy of maraviroc QD and BID.

7.1.4.1. Patient Demographics and Baseline Characteristics

In Studies A4001027 and A4001028 more than 1,000 patients were treated with blinded study drug, of which 840 received maraviroc either once daily (QD) or twice daily (BID) in combination with OBT. An additional 209 patients received placebo in combination with OBT. Nearly 90% of the patients enrolled were male and more than 80% were white. The mean age was approximately 46 years. Plasma HIV-1 RNA at baseline (the mean of 3 pre-dose assessments) was very similar across the three treatment groups; 4.86, 4.85 and 4.86 $\log_{10}$ copies/mL in the maraviroc QD, maraviroc BID and the placebo groups

respectively. Mean baseline CD4 cell count was also similar between the three treatment groups, ranging from 187.2-195.7 cells/μL (Table 12).

Table 12. Demographics and Baseline Characteristics of the Patients in the Combined Analysis of Studies A4001027 and A4001028

	Maraviroc QD	Maraviroc BID	Placebo
N	414	426	209
Female Sex, n (%)	51 (12.3)	44 (10.3)	24 (11.5)
White Race, n (%)	336 (81.2)	363 (85.2)	178 (85.2)
Mean Age (years)	45.6	46.3	45.8
Mean HIV-1 RNA (log_{10} copies/mL)[a]	4.86	4.85	4.86
Mean CD4 Cell Count (cells/μL)[a,b]	195.7	189.2	187.2
PI Resistance Mutations at Screening, Median (Range)	N= 412[c] 10 (0, 18)	N= 425[c] 10 (0, 17)	N=206[c] 10 (0, 17)
NNRTI Resistance Mutations at Screening, Median (Range)	N= 412[c] 1 (0, 5)	N= 425[c] 1 (0, 5)	N=206[c] 1 (0, 5)
NRTI Resistance Mutations at Screening, Median (Range)	N= 412[c] 6 (0, 11)	N= 425[c] 6 (0, 11)	N=206[c] 6 (0, 13)
Patients with Enfuvirtide Mutations at Screening, n (%)	N=411[c] 78 (19.0)	N= 424[c] 90 (21.2)	N= 209[c] 45 (21.5)

[a] Mean of all pre-dose assessments (screening, randomization (HIV-1 RNA only), and baseline visits).
[b] One value missing from Maraviroc QD and from Placebo groups.
[c] Number of patients with a valid assessment at screening that have contributed to summary statistics.

Patients receiving a PI (with or without ritonavir boosting) other than tipranavir, or delavirdine as part of OBT, received a 150 mg unit dose of maraviroc (either QD or BID). Patients on all other regimens, including those with tipranavir/ritonavir, received a 300 mg unit dose of maraviroc (QD or BID). More than 75% of the patients in each group received an optimised regimen that contained a PI (other than tipranavir/ritonavir) and/or delavirdine Table 13).

Table 13. Percentage of Patients Receiving a Protease Inhibitor (PI) and/or Delavirdine or Tipranavir/Ritonavir as Part of Their OBT (Combined Studies A4001027 and A4001028)

	Maraviroc QD	Maraviroc BID	Placebo
Na	408	419	207
PI and/or Delavirdine – Yes, n (%)	316 (76.3)	329 (77.2)	169 (80.9)
PI and/or Delavirdine – No, n (%)	92 (22.2)	90 (21.1)	38 (18.2)
Tipranavir/ritonavir – Yes, n (%)	65 (15.7)	62 (14.6)	29 (13.9)
Tipranavir/ritonavir – No, n (%)	343 (82.9)	357 (83.8)	178 (85.2)

[a] Number of patients contributing to the summary statistics, which were patients with valid values for baseline and on treatment.
Patients receiving a PI and/or delavirdine as part of their OBT received maraviroc at a dose of 150 mg, while all other dosing regimens received a 300 mg dose. Subjects receiving tipranavir/ritonavir also received a 300 mg dose.

In Study A4001027, 75%, 65% and 71% of subjects had GSS, PSS and OSS of <2 respectively. The baseline resistance for patients in Study A4001028 was similar with 70%, 60% and 63% of subjects having GSS, PSS and OSS of ≤2, respectively. This is consistent

with a heavily treatment experienced population. The distribution of GSS, PSS and OSS was balanced across the three treatment groups in both studies.

7.1.4.2. Primary Endpoint Analysis

At Week 24 there was a >1.8 log_{10} mean reduction in viral load for both maraviroc treated groups, which was greater than placebo (adjusted means: -1.865, -1.960 compared with -0.987 log_{10} copies/mL for maraviroc QD, BID and placebo, respectively). The statistical analysis of viral load change from baseline to Week 24 demonstrated that both doses of maraviroc were superior to placebo, as the pre-defined criteria for superiority to placebo were met for both QD and BID doses. Table 14 presents the mean change from baseline to Week 24 in HIV-1 RNA level and the statistical analysis of this change for both doses of maraviroc compared with placebo.

Table 14. Statistical Analysis of Change from Baseline to Week 24 in log_{10} HIV-1 RNA (Combined Studies A4001027 and A4001028)

Treatment Group	N	Change from Baseline to Week 24 in HIV-1 RNA (log_{10} copies/mL)			Treatment difference Maraviroc-Placebo	
		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

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.

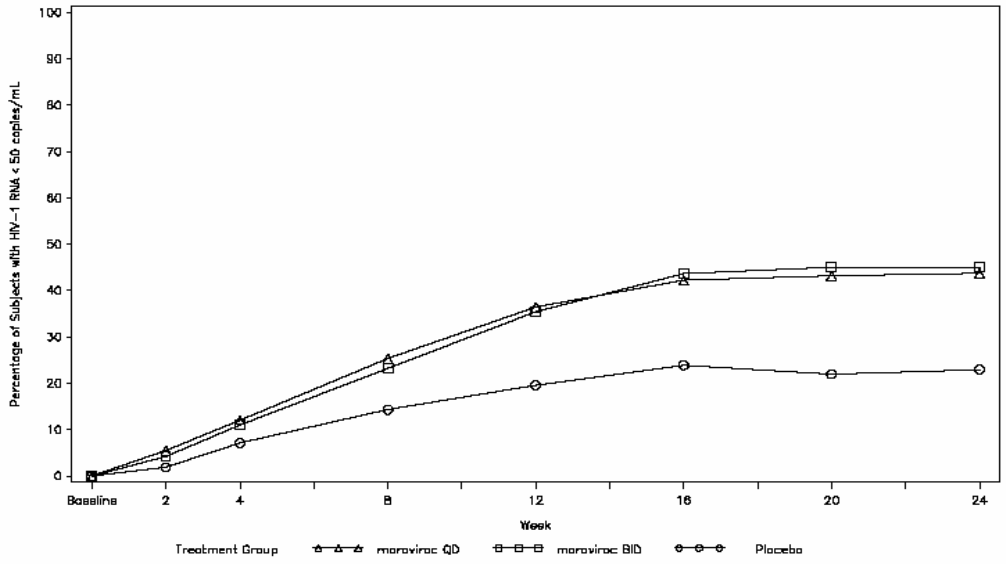
As in the individual studies, the 2-sided 97.5% confidence intervals were completely to the left side of zero, excluding zero, indicating the superiority of maraviroc QD and maraviroc BID over placebo. In addition, the upper bound of the 97.5% confidence intervals was to the left of 0.5 log_{10} copies/mL. A reduction in viral load of ≥0.5 log_{10} copies is recognized as clinically significant.

7.1.4.3. Secondary Endpoint Analysis

Proportion of Patients with an HIV-1 RNA <50 copies/mL at Week 24

There was a higher proportion of patients in the maraviroc QD and BID treatment groups with an HIV-1 RNA level <50 copies/mL compared with placebo at each study visit (Figure 11).

Figure 11. Percentage of Subjects with HIV-1 RNA Level <50 copies/mL by Visit (Combined Studies A4001027 and A4001028)



Discontinuations and failures are included at all timepoints.

The difference in proportion of patients with HIV-1 RNA level <50 copies/mL compared with placebo was 0.21 (95% CI: 0.14, 0.27) and 0.23 (95% CI: 0.16, 0.30) for maraviroc QD and BID respectively. Table 15 presents the statistical analysis of difference in proportions and logistic regression of an HIV-1 RNA level <50 copies/mL at Week 24 for the maraviroc treatment groups compared with placebo.

Table 15. Statistical Analysis of Proportion of Patients with HIV-1 RNA Level <50 copies/mL at Week 24 (Logistic Regression) (Combined Studies A4001027 and A4001028)

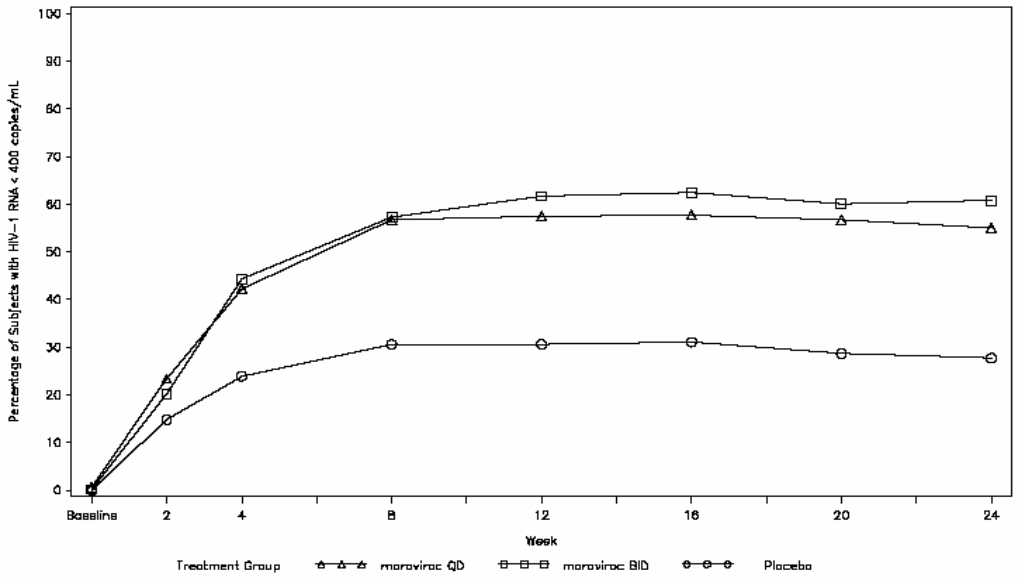
Treatment Group	N	Positive Response (%)	Treatment Comparison Maraviroc-Placebo Odds Ratio	95% CI for Odds Ratio	P-Value
Maraviroc QD	414	44.0	2.87	1.95, 4.22	<0.0001
Maraviroc BID	426	45.3	3.02	2.05, 4.44	<0.0001
Placebo	209	23.0	N/C	N/C	N/C

Missing values at Week 24 were defined as responders if they were responders at both Weeks 20 and 32.
If a patient's Week 20 or 32 value was missing, or they had discontinued prior to Week 32 then they were defined as a non-responder.
An odds ratio of >1 indicates a beneficial response for patients on maraviroc compared with placebo.
CI = Confidence interval.

Proportion of Patients with an HIV-1 RNA <400 copies/mL at Week 24

There was a higher proportion of patients in the maraviroc QD and BID treatment groups with an HIV-1 RNA level <400 copies/mL compared with placebo at each study visit (Figure 12).

Figure 12. Percentage of Subjects with HIV-1 RNA Level <400 copies/mL by Visit (Combined Studies A4001027 and A4001028)



Discontinuations and failures are included at all timepoints.

The difference in proportion of patients with HIV-1 RNA level <400 copies/mL compared with placebo was 0.28 (95% CI: 0.21, 0.35) and 0.35 (95% CI: 0.27, 0.42) for maraviroc QD and BID respectively. Table 16 presents the results of the difference in proportions and logistic regression for patients with an HIV-1 RNA level <400 copies/mL at Week 24 for maraviroc treatment groups compared with placebo.

Table 16. Statistical Analysis of Proportion of Patients with HIV-1 RNA Level <400 copies/mL at Week 24 (Logistic Regression) (Combined Studies A4001027 and A4001028)

Treatment Group	N	Positive Response (%)	Treatment Comparison Maraviroc-Placebo Odds Ratio	95% CI for Odds Ratio	P-Value
Maraviroc QD	414	55.1	3.48	2.41, 5.04	<0.0001
Maraviroc BID	426	61.0	4.49	3.10, 6.51	<0.0001
Placebo	209	27.8	N/C	N/C	N/C

Missing values at Week 24 were defined as responders if they were responders at both Weeks 20 and 32.
If a patient's Week 20 or 32 value was missing, or they had discontinued prior to Week 32 then they were defined as a non-responder.
An odds ratio >1 indicates a beneficial response for patients on maraviroc compared with placebo.
CI = Confidence interval; N/C = Not calculated.

Proportion of Patients with an HIV-1 RNA >1.0 $\log_{10}$ Change from Baseline or <400 copies/mL at Week 24

The difference in proportion of patients who achieve at least a 1.0 $\log_{10}$ reduction in HIV-1 RNA level from baseline or <400 copies/mL at Week 24 compared with placebo was 0.30 (95% CI: 0.22, 0.38) and 0.34 (95% CI: 0.26, 0.42) for maraviroc QD and BID respectively. Table 17 presents the logistic regression analysis of difference in proportions and logistic regression for patients achieving at least a 1.0 $\log_{10}$ copies/mL reduction in HIV-1 RNA level from baseline or <400 copies/mL at Week 24 for maraviroc treatment groups compared with placebo.

Table 17. Statistical Analysis of Proportion of Patients with at Least a 1.0 $\log_{10}$ Reduction in HIV-1 RNA from baseline or <400 copies/mL at Week 24 (Logistic Regression) (Combined Studies A4001027 and A4001028)

Treatment Group	N	Positive Response (%)	Treatment Comparison Maraviroc-Placebo Odds Ratio	95% CI for Odds Ratio	P-Value
Maraviroc QD	414	65.7	3.63	2.55, 5.17	<0.0001
Maraviroc BID	426	69.2	4.25	2.98, 6.07	<0.0001
Placebo	209	35.9	N/C	N/C	N/C

Missing values at Week 24 were defined as responders if they were responders at both Weeks 20 and 32.
If a patient's Week 20 or 32 value was missing, or they had discontinued prior to Week 32 then they were defined as a non-responder.
An odds ratio of >1 indicates a beneficial response for patients on maraviroc compared with placebo.
CI = Confidence interval; N/C = Not calculated.

Proportion of Patients with an HIV-1 RNA >0.5 $\log_{10}$ Change from Baseline or <400 copies/mL at Week 24

The difference in proportion of patients who achieve at least a 0.5 $\log_{10}$ reduction in HIV-1 RNA level from baseline or <400 copies/mL at Week 24 compared with placebo was 0.28 (95% CI: 0.20, 0.36) and 0.30 (95% CI: 0.22, 0.38) for maraviroc QD and BID respectively. Table 18 presents the logistic regression analysis of the difference in proportions and logistic regression for patients achieving at least a 0.5 $\log_{10}$ reduction in HIV-1 RNA level from baseline or <400 copies/mL at Week 24 for maraviroc treatment groups compared with placebo.

Table 18. Statistical Analysis of Proportion of Patients with at Least a 0.5 log_{10} Reduction in HIV-1 RNA or <400 copies/mL at Week 24 (Logistic Regression) (Combined Studies A4001027 and A4001028)

Treatment Group	N	Positive Response (%)	Treatment Comparison Maraviroc-Placebo Odds Ratio	95% CI for Odds Ratio	P-Value
Maraviroc QD	414	69.3	3.34	2.35, 4.74	<0.0001
Maraviroc BID	426	71.1	3.62	2.55, 5.14	<0.0001
Placebo	209	41.6	N/C	N/C	N/C

Missing values at Week 24 were defined as responders if they were responders at both Weeks 20 and 32.
If a patient's Week 20 or 32 value was missing, or they had discontinued prior to Week 32 then they were defined as a non-responder.
An odds ratio of >1 indicates a beneficial response in patients on maraviroc compared with placebo.
CI = Confidence interval; N/C = Not calculated.

Time Averaged Difference (TAD) in log_{10} HIV-1 RNA from Baseline to Week 24

The estimated TAD from baseline to Week 24 was larger for both doses of maraviroc compared with placebo (adjusted mean: -1.686 and -1.748 compared with -0.911 for maraviroc QD, BID and placebo respectively). Table 19 presents the statistical analysis of TAD from baseline to Week 24. As observed for the primary endpoint, the 2-sided (95%) confidence intervals were completely to the left side of zero, indicating the superiority of maraviroc QD and maraviroc BID over placebo. In addition, the upper bounds of the confidence intervals were to the left of 0.5, excluding the possibility of a clinically insignificant change in TAD in viral load.

Table 19. Statistical Analysis for Time Averaged Difference (TAD) from Baseline to Week 24 in log_{10} HIV-1 RNA (Combined Studies A4001027 and A4001028)

Treatment Group	N	Change from Baseline to Week 24 in TAD (log10 copies/mL)			Treatment Difference Maraviroc-Placebo	
		Raw Median	Raw Mean (se)	Adjusted Mean (se)	Estimate (se)	95% CI
Maraviroc QD	414	-2.105	-1.683 (0.059)	-1.686 (0.059)	-0.775 (0.101)	-0.973, -0.576
Maraviroc BID	426	-2.197	-1.748 (0.058)	-1.748 (0.058)	-0.836 (0.101)	-1.033, -0.639
Placebo	209	0.000	-0.915 (0.080)	-0.911 (0.083)	N/C	N/C

Discontinuations prior to the time point of analysis have been imputed as zero for the purpose of this analysis.
CI = Confidence interval; N/C = Not calculated; se = Standard error.

Change from Baseline to Week 24 in CD4 Cell Count

There was a greater increase in CD4 cell count from baseline to Week 24 for both maraviroc treatment groups compared with placebo (adjusted mean: +108.6 and +106.3 compared with +57.4 cells/μL for maraviroc QD, BID and placebo respectively). Table 20 presents the statistical analysis for the change from baseline to Week 24 in CD4 cell count for both maraviroc treatment groups compared with placebo.

Table 20. Statistical Analysis for Change in CD4 Cell Count from Baseline to Week 24 (Combined Studies A4001027 and A4001028)

Treatment Group	N	Change from Baseline to Week 24 in CD4 Cell Count (cells/μL)			Treatment Difference Maraviroc-Placebo	
		Raw Median	Raw Mean (se)	Adjusted Mean (se)	Estimate (se)	95% CI
Maraviroc QD	407	86.0	108.7 (6.0)	108.6 (5.3)	51.2 (9.2)	33.3, 69.2
Maraviroc BID	418	88.3	105.8 (4.9)	106.3 (5.3)	49.0 (9.1)	31.1, 66.9
Placebo	206	30.8	56.5 (6.7)	57.4 (7.5)	N/C	N/C

Last Observation Carried Forward (LOCF) was used to impute missing values.
CI = Confidence interval; N/C = Not calculated; se = Standard error.

Change from Baseline to Week 24 in CD8 Cell Count

There was a greater increase in CD8 cell count from baseline to Week 24 for both maraviroc treatment groups compared with placebo (adjusted mean: +305.5 and +278.9 compared with +54.3 cells/μL for maraviroc QD, BID and placebo respectively). Table 21 presents the statistical analysis for the change from baseline to Week 24 in CD8 cell count for both maraviroc treatment groups compared with placebo.

Table 21. Statistical Analysis for Change in CD8 Cell Count from Baseline to Week 24 (Combined Studies A4001027 and A4001028)

Treatment Group	N	Change from Baseline to Week 24 in CD8 Cell Count (cells/μL)			Treatment Difference Maraviroc-Placebo	
		Raw Median	Raw Mean (se)	Adjusted Mean (se)	Estimate (se)	95% CI
Maraviroc QD	407	211.0	295.9	305.5 (25.0)	251.2 (42.9)	167.1, 335.3
Maraviroc BID	418	208.5	274.1	278.9 (24.6)	224.6 (42.6)	140.9, 308.2
Placebo	206	9.3	51.7	54.3 (35.0)	N/C	N/C

Last Observation Carried Forward (LOCF) was used to impute missing values.
CI = Confidence interval; N/C = Not calculated; se = Standard error.

7.1.4.4. Efficacy Results in Sub-Populations

For all the subpopulation analyses conducted on the primary and selected secondary endpoints 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 of virus, CCR5 Δ32 genotype or CCR5 promoter haplotype even though numbers of patients in these subgroups were too small to draw any definite conclusions. Other selected subgroup analyses are discussed below.

7.1.4.4.1. Screening HIV-1 RNA

HIV-1 RNA at screening (<100,000 and ≥100,000 copies/mL) was incorporated as a stratification factor into the randomization of Studies A4001027 and A4001028 to ensure that

the proportion of patients with high and low viral loads were randomised into each treatment group were similar. Overall, there were slightly more patients recruited with a lower viral load; 58% of the total number of patients in the combined analysis had a screening HIV-1 RNA of <100,000 copies/mL.

There was no apparent difference in the primary efficacy endpoint between those patients receiving either dose of maraviroc who had high (≥100,000 copies/mL) and low (<100,000 copies/mL) viral loads. Patients with a low viral load who received placebo, however, appeared to have a greater response than those patients who received placebo with high viral loads (Table 22).

Table 22. 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

[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 analyses of percentage of patients with an HIV-1 RNA <50 and <400 copies/mL at Week 24 by viral load at screening, there were a greater percentage of patients with a baseline viral load of <100,000 copies/mL who achieved both <50 and <400 copies/mL at Week 24 in each of the treatment groups (Table 23 and Table 24). Both doses of maraviroc consistently demonstrated superiority over placebo for patients with low and high viral loads.

Table 23. Percentage of Patients with an HIV-1 RNA <50 copies/mL at Week 24 (Combined Studies A4001027 and A4001028)

HIV-1 RNA (copies/mL)	Percentage of Patients with HIV-1 RNA <50 copies/mL					
	Maraviroc QD (N= 414)[a]		Maraviroc BID (N= 426)[a]		Placebo (N= 209)[a]	
	N[b]	n (%)	N[b]	n (%)	N[b]	n (%)
<100,000	238	146 (61.3)	243	140 (57.6)	123	42 (34.2)
≥100,000	170	48 (28.2)	176	61 (34.7)	84	9 (10.7)

[a] Number of patients in treatment group.
[b] Number of patients with a post-baseline observation used to calculate the percentage.
QD = Once daily dosing; BID = Twice daily dosing.

There was no apparent difference in response between maraviroc dose groups for patients with a baseline viral load <100,000 copies/mL. However, in patients with a baseline viral load ≥100,000 copies/mL more patients receiving maraviroc BID achieved an HIV-1 RNA of <50 copies/mL at Week 24 compared with maraviroc QD (34.7% versus 28.2%) (Table 23), although slightly more patients with a viral load below 100,000 copies/mL achieved viral suppression to <50 copies/mL on maraviroc QD therapy (61.3% versus 57.6%).

A similar result was observed for patients achieving an HIV-1 RNA of <400 copies/mL at Week 24 (Table 24), with a greater proportion of patients receiving maraviroc BID achieving viral suppression than maraviroc QD, notably in the >100,000 copies/mL strata (51.7% versus 44.7%).

Table 24. Percentage of Patients with an HIV-1 RNA <400 copies/mL at Week 24 (Combined Studies A4001027 and A4001028)

HIV-1 RNA (copies/mL)	Percentage of Patients with HIV-1 RNA <400 copies/mL					
	Maraviroc QD (N= 414)[a]		Maraviroc BID (N= 426)[a]		Placebo (N= 209)[a]	
	N[b]	n (%)	N[b]	n (%)	N[b]	n (%)
<100,000	238	172 (72.3)	243	182 (74.9)	123	50 (40.7)
≥100,000	170	76 (44.7)	176	91 (51.7)	84	13 (15.5)

[a] Number of patients in treatment group.
[b] Number of patients with a post baseline observation used to calculate the percentage.
Last Observation Carried Forward (LOCF) was used to impute missing values.
QD = Once daily dosing; BID = Twice daily dosing.

Patients with a higher viral load (≥100,000 copies/mL) who were receiving maraviroc (either QD or BID) had a greater increase in CD4 cell count from baseline compared with patients with a lower viral load (<100,000 copies/mL) (Table 25). The increase in CD4 cell count for patients receiving placebo appeared to be independent of baseline viral load. For patients with high and low baseline viral loads, those receiving maraviroc had an increase in CD4 cell count from baseline that was approximately twice that of the corresponding placebo treatment group; mean change from baseline 94.8, 99.8 and 58.6 cells/μL for maraviroc QD, BID and placebo respectively for patients with <100,000 HIV-1 RNA copies/mL and 128.3, 114.1 and 53.5 cells/μL for maraviroc QD, BID and placebo respectively for patients with

≥100,000 HIV-1 RNA copies/mL (Table 25). There was no consistent pattern of effect for maraviroc QD versus BID dose groups.

Table 25. Summary of Change in CD4 Cell Count from Baseline to Week 24 by HIV-1 RNA at Screening (Combined Studies A4001027 and A4001028)

HIV-1 RNA (copies/mL)		Change in CD4 Cell Count from Baseline (cells/μL)		
		Maraviroc QD (N= 414)[a]	Maraviroc BID (N= 426)[a]	Placebo (N= 209)[a]
<100,000	N[b]	238	242	122
	Mean (SD)	94.8 (106.0)	99.8 (99.8)	58.6 (100.2)
	Median (Range)	74.3 (-193.0, 585.0)	88.3 (-277.0, 536.5)	34.3 (-184.5, 452.5)
≥100,000	N[b]	169	176	84
	Mean (SD)	128.3 (136.8)	114.1 (99.8)	53.5 (90.8)
	Median (Range)	106.5 (-263.5, 834.5)	89.0 (-93.5, 561.0)	19.3 (-301.0, 298.5)

[a] Number of patients in treatment group.
[b] Number of patients contributing to summary statistics, which were patients with valid values for baseline and on treatment. Last Observation Carried Forward (LOCF) was used to impute missing values.
QD = Once daily dosing; BID = Twice daily dosing; SD = Standard deviation.

7.1.4.4.2. Baseline CD4 Cell Count

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 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) (Table 26). 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.

Table 26. Summary of Change from Baseline to Week 24 in HIV-1 RNA Split by CD4 Cell Count at Baseline (Combined Studies A4001027 and A4001028)

CD4 Cell Count		Change from Baseline in HIV-1 RNA (log_{10} copies/mL)		
		Maraviroc QD (N= 414)[a]	Maraviroc BID (N= 426)[a]	Placebo (N= 209)[a]
<50 cells/μL	N[b]	85	85	37
	Mean (SD)	-1.311 (1.450)	-1.351 (1.632)	-0.632 (0.958)
	Median (Range)	-0.734 (-4.492, 0.505)	-0.632 (-4.407, 1.317)	-0.309 (-3.510, 0.483)
50-100 cells/μL	N[b]	51	55	25
	Mean (SD)	-2.181 (1.306)	-2.258 (1.396)	-0.943 (1.286)
	Median (Range)	-2.599 (-3.872, 0.822)	-2.645 (-4.547, 0.021)	-0.396 (-3.588, 0.472)
101-200 cells/μL	N[b]	93	104	56
	Mean (SD)	-2.229 (1.146)	-2.360 (1.069)	-1.157 (1.431)
	Median (Range)	-2.540 (-4.428, 0.450)	-2.613 (-4.504, 0.532)	-0.474 (-4.148, 0.965)
201-350 cells/μL	N[b]	116	116	62
	Mean (SD)	-2.400 (1.099)	-2.336 (1.016)	-1.439 (1.315)
	Median (Range)	-2.582 (-4.303, 2.039)	-2.571 (-3.871, 0.602)	-1.014 (-3.665, 0.641)
>350 cells/μL	N[b]	62	59	26
	Mean (SD)	-2.290 (1.059)	-2.520 (0.895)	-1.397 (1.151)
	Median (Range)	-2.465 (-3.834, 1.080)	-2.620 (-4.068, 0.647)	-1.306 (-3.519, 0.300)

[a] Number of patients in the treatment group.
[b] Number of patients contributing to the summary statistics, which were patients with valid values for baseline and on treatment.
Last Observation Carried Forward (LOCF) was used to impute missing values.
The baseline CD4 cell count value is calculated as the average of the pre-dose measurements collected at the screening and baseline visit.
QD = Once daily dosing; BID = Twice daily dosing; SD = Standard deviation.

Table 27 presents the percentage of patients achieving an HIV-1 RNA <50 copies/mL at Week 24 by patients' CD4 cell count at baseline.

Table 27. Percentage of Patients with HIV-1 RNA <50 copies/mL at Week 24 by CD4 Cell Count at Baseline (Combined Studies A4001027 and A4001028)

CD4 Cell Count (cells/μL)	Number (Percentage) of Patients with HIV-1 RNA <50 copies/mL at Week 24					
	Maraviroc QD (N= 414)[a]		Maraviroc BID (N= 426)[a]		Placebo (N= 209)[a]	
	N[b]	n (%)	N[b]	n (%)	N[b]	n (%)
<50	85	9 (10.6)	85	17 (20.0)	37	1 (2.7)
50-100	51	23 (45.1)	55	22 (40.0)	25	4 (16.0)
101-200	93	47 (50.5)	104	51 (49.04)	56	16 (28.6)
201-350	116	74 (63.8)	116	73 (62.9)	62	18 (29.0)
≥350	62	41 (66.1)	59	38 (64.4)	26	11 (42.3)

[a] Number of patients in treatment group.
[b] Number of patients with a post-baseline observation used to calculate the percentage.
Last Observation Carried Forward (LOCF) was used to impute missing values.
The baseline CD4 cell count was calculated as the average of the pre-dose measurements collected at the screening and baseline visit.
QD = Once daily dosing; BID = Twice daily dosing.

As expected, fewer patients with a baseline CD4 cell count <50 cells/μL in all treatment groups achieved an HIV-1 RNA of <50 copies/mL. A much larger percentage of patients achieved <50 copies/mL at baseline CD4 cell counts of 50-100 cells/μL and this percentage

appeared to increase thereafter with higher baseline CD4 cell counts. For each category of baseline CD4 cell count both maraviroc dose groups were superior to placebo. At CD4 cell counts <50 cells/μL, however, there were approximately twice as many patients achieving an HIV-1 RNA <50 copies/mL in the maraviroc BID group than maraviroc QD (17 [20.0%] versus 9 [10.6%]). However, maraviroc QD remained much higher than placebo (1 [2.7%]). At each other level of CD4 cell count at baseline there was no observed difference in response between maraviroc treatment groups.

A similar pattern was observed for the percentage of patients achieving an HIV-1 RNA of <400 copies/mL (Table 28).

Table 28. Percentage of Patients with HIV-1 RNA <400 copies/mL at Week 24 by CD4 Cell Count at Baseline (Combined Studies A4001027 and A4001028)

CD4 Cell Count (cells/μL)	Number (Percentage) of Patients with HIV-1 RNA <400 copies/mL at Week 24					
	Maraviroc QD (N= 414)[a]		Maraviroc BID (N= 426)[a]		Placebo (N= 209)[a]	
	N[b]	n (%)	N[b]	n (%)	N[b]	n (%)
<50	85	17 (20.0)	85	26 (30.6)	37	2 (5.4)
50-100	51	29 (56.9)	55	29 (52.7)	25	6 (24.0)
101-200	93	61 (65.6)	104	77 (74.0)	56	19 (33.9)
201-350	116	92 (79.3)	116	89 (76.7)	62	23 (37.1)
≥350	62	48 (77.4)	59	52 (88.1)	26	12 (46.2)

[a] Number of patients in treatment group.
[b] Number of patients with a post-baseline observation used to calculate the percentage.
Last Observation Carried Forward (LOCF) was used to impute missing values.
The baseline CD4 cell count was calculated as the average of the pre-dose measurements collected at the screening and baseline visit.
QD = Once daily dosing; BID = Twice daily dosing.

Table 29 presents the change in CD4 cell count from baseline to Week 24 split by CD4 cell count at baseline.

Table 29. Summary of Change in CD4 Cell Count from Baseline to Week 24 by CD4 Cell Count at Baseline (Combined Studies A4001027 and A4001028)

CD4 Cell Count (cells/μL)		Change in CD4 Cell Count (cells/μL) from Baseline		
		Maraviroc QD (N= 414)[a]	Maraviroc BID (N= 426)[a]	Placebo (N= 209)[a]
<50	N[b]	85	85	37
	Mean (SD)	73.7 (82.1)	73.6 (75.5)	25.3 (48.9)
	Median (Range)	45.0 (-31.0, 431.0)	59.0 (-29.0, 307.0)	6.5 (-13.0, 172.0)
50-100	N[b]	51	55	25
	Mean (SD)	102.9 (70.0)	111.1 (74.5)	42.9 (61.3)
	Median (Range)	86.0 (-11.5, 270.0)	89.0 (8.0, 322.0)	25.5 (-47.5, 191.5)
101-200	N[b]	93	103	56
	Mean (SD)	111.8 (93.7)	115.8 (95.1)	47.4 (76.6)
	Median (Range)	90.0 (-52.0, 476.5)	103.5 (-77.0, 561.0)	31.5 (-65.0, 165.0)
201-350	N[b]	116	116	62
	Mean (SD)	120.8 (137.0)	110.3 (103.4)	73.1 (113.7)
	Median (Range)	102.8 (-193.0, 588.0)	102.3 (-174.0, 428.0)	58.0 (-184.5, 440.5)
≥350	N[b]	62	59	26
	Mean (SD)	134.3 (179.8)	121.0 (138.8)	94.2 (143.4)
	Median (Range)	99.3 (-263.5, 834.5)	109.5 (-277.0, 536.5)	95.5 (-301.0, 452.5)

[a] Number of patients in treatment group.
[b] Number of patients contributing to summary statistic, which were patients with valid values for baseline and on treatment. Last Observation Carried Forward (LOCF) was used to impute missing values.
The baseline CD4 cell count was calculated as the average of the pre-dose measurements collected at the screening and baseline visits.
QD = Once daily dosing; BID = Twice daily dosing; SD = Standard deviation.

For all treatment groups a higher CD4 cell count at baseline was generally associated with greater increases in CD4 cell count from baseline to Week 24. There was no difference between maraviroc dose groups for any CD4 cell count group. However, in all CD4 count strata groups both maraviroc doses demonstrated a much higher increase in CD4 cell count from baseline compared with placebo.

7.1.4.4.3. Genotypic, Phenotypic and Overall Susceptibility Score

The primary and secondary efficacy endpoints were analysed for the combined A4001027 and A4001028 results by genotypic (GSS), phenotypic (PSS) and the calculated overall susceptibility score (OSS) (as described in Appendix 1.2) at screening in order to assess whether the response to treatment with maraviroc was affected by the number of potentially active agents present in the OBT regimen selected by the Investigator. GSS, PSS and OSS were divided into scores of 0, 1, 2 and ≥3, which indicated the total number of drugs in the OBT to which a patient's virus isolate showed wild-type genotypic and/or phenotypic sensitivity. Any new drugs were scored as active (e.g., tipranavir) if a test was not available at the time of screening. Gp41 sequencing was used to score sensitivity to enfuvirtide, as described in Appendix 1.2.

The numbers of patients within each category for GSS, PSS and OSS were approximately even between treatment groups, with no difference in the median scores. The numbers of patients within each category for each score are presented in Table 30 below.

Table 30. Summary of Genotypic (GSS), Phenotypic (PSS) and Overall Susceptibility Scores (OSS) at Screening (Combined Studies A4001027 and A4001028)

Susceptibility Scores		Maraviroc QD (N= 414) n (%)	Maraviroc BID (N= 426) n (%)	Placebo (N= 209) n (%)
Genotypic (GSS)	0	91 (22.0)	102 (23.9)	51 (24.4)
	1	146 (35.3)	138 (32.4)	53 (25.4)
	2	63 (15.2)	80 (18.8)	41 (19.6)
	≥3	109 (26.3)	104 (24.4)	59 (28.2)
	Median	1.0	1.0	1.0
Phenotypic (PSS)	0	45 (10.9)	50 (11.7)	29 (13.9)
	1	116 (28.0)	115 (27.0)	38 (18.2)
	2	93 (23.5)	107 (25.1)	58 (27.8)
	≥3	154 (37.2)	150 (35.2)	79 (37.8)
	Median	2.0	2.0	2.0
Overall (OSS)	0	52 (12.6)	57 (13.4)	35 (16.7)
	1	133 (32.1)	136 (31.9)	44 (21.1)
	2	88 (21.3)	104 (24.4)	59 (28.2)
	≥3	134 (32.4)	125 (29.3)	66 (31.6)
	Median	2.0	2.0	2.0

QD = Once daily dosing; BID = Twice daily dosing.

This section provides the primary and selected secondary efficacy results for the OSS. Similar results were obtained for both the GSS and PSS (see Appendix 2 for details).

Greater than 67% of the patients in 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. A treatment benefit for maraviroc for all endpoints was observed for each OSS group (Table 31).

Table 31. Summary of Change in HIV-1 RNA from Baseline to Week 24 Split by OSS at Baseline (Combined Studies A4001027 and A4001028)

OSS		Change from Baseline in HIV-1 RNA (log_{10} copies/mL) Maraviroc QD (N= 414)[a]	Maraviroc BID (N= 426)[a]	Placebo (N= 209)[a]
0	N[b]	51	56	35
	Mean (SD)	-1.280 (1.035)	-1.372 (1.308)	-0.166 (0.694)
	Median (Range)	-0.989 (-3.395, 0.080)	-1.057 (-3.524, 1.317)	-0.045 (-2.817, 0.641)
1	N[b]	130	134	44
	Mean (SD)	-1.874 (1.215)	-1.951 (1.321)	-0.507 (0.892)
	Median (Range)	-2.124 (-3.907, 1.080)	-2.325 (-4.504, 0.780)	-0.272 (-3.428, 0.512)
2	N[b]	88	104	59
	Mean (SD)	-2.115 (1.360)	-2.331 (1.004)	-1.023 (1.080)
	Median (Range)	-2.411 (-4.295, 2.039)	-2.580 (-4.547, -0.030)	-0.629 (-3.181, 0.965)
≥3	N[b]	132	121	64
	Mean (SD)	-2.594 (1.146)	-2.592 (1.230)	-2.307 (1.140)
	Median (Range)	-2.954 (-4.492, 0.822)	-2.907 (-4.410, 1.200)	-2.641 (-4.148, 0.442)

[a] Number of patients in treatment group.
[b] Number of patients contributing to summary statistics.
Last Observation Carried Forward (LOCF) has been used to impute missing values.
QD = Once daily dosing; BID = Twice daily dosing; SD = Standard deviation.

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).

Table 32 and Table 33 present the results for the percentage of patients achieving <50 and <400 copies/mL at Week 24 by OSS.

Table 32. Percentage of Patients with an HIV-1 RNA <50 copies/mL at Week 24 by OSS (Combined Studies A4001027 and A4001028)

OSS	Percentage of Patients with HIV-1 RNA <50 copies/mL					
	Maraviroc QD (N= 414)[a]		Maraviroc BID (N= 426)[a]		Placebo (N= 209)[a]	
	N	N (%)	N	n (%)	N	n (%)
0	51	9 (17.7)	56	16 (28.6)	35	1 (2.9)
1	130	56 (43.1)	134	58 (43.3)	44	4 (9.1)
2	88	46 (52.3)	104	55 (52.9)	59	11 (18.6)
≥3	132	81 (61.4)	121	70 (57.9)	64	35 (54.7)

[a] Number of patients in treatment group.
[b] Number of patients with a post-baseline observation used to calculate the percentage.
QD = Once daily dosing; BID = Twice daily dosing.

Table 33. Percentage of Patients with an HIV-1 RNA <400 copies/mL at Week 24 by OSS (Combined Studies A4001027 and A4001028)

OSS	Percentage of Patients with HIV-1 RNA <400 copies/mL					
	Maraviroc QD (N= 414)[a]		Maraviroc BID (N= 426)[a]		Placebo (N= 209)[a]	
	N	N (%)	N	n (%)	N	n (%)
0	51	13 (25.5)	56	23 (41.1)	35	2 (5.7)
1	130	74 (56.9)	134	77 (57.5)	44	5 (11.4)
2	88	55 (62.5)	104	75 (72.1)	59	14 (23.7)
≥3	132	102 (77.3)	121	95 (78.5)	64	41 (64.1)

[a] Number of patients in treatment group.
[b] Number of patients with a post-baseline observation used to calculate the percentage.
QD = Once daily dosing; BID = Twice daily dosing.

Fewer patients with an OSS of 0 achieved viral loads of <50 and <400 copies/mL compared with patients with a higher OSS. For each treatment group the percentage of patients with a viral load of <50 and <400 copies/mL increased as OSS increased. For both secondary endpoints of viral load <50 and <400 copies/mL, both doses of maraviroc were superior to placebo at each category of OSS. Overall, more patients achieved a viral load <400 copies/mL compared with <50 copies/mL for all treatment groups, however, the pattern between treatment groups remained the same for each endpoint.

For both secondary endpoints, patients with an OSS of 0 appeared to respond better to treatment with maraviroc BID than QD, although both doses had a higher percentage of patients achieving these secondary endpoints than placebo (17.7% and 28.6% versus 2.9% patients receiving maraviroc QD, BID and placebo respectively achieved <50 copies/mL and 25.5% and 41.1% versus 5.7% patients receiving maraviroc QD, BID and placebo respectively achieved <400 copies/mL). This pattern was not observed for the other categories of OSS.

7.1.4.4.4. Enfuvirtide Use in OBT

Enfuvirtide use in OBT was one of the stratification factors incorporated into randomization. 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). In addition, in vitro synergy between enfuvirtide and another CCR5 antagonist has been reported (Tremblay CL, 2002). However, only additivity (1 experiment) and slight synergy (second experiment) has been seen in vitro with maraviroc and enfuvirtide in pre-clinical studies.

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 (Table 34).

Table 34. Summary of Change from Baseline to Week 24 in HIV-1 RNA Split by Enfuvirtide use in OBT (Combined Studies A4001027 and A4001028)

Enfuvirtide Use in OBT		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]
Yes	N[b]	165	180	90
	Mean (SD)	-2.136 (1.284)	-2.228 (1.331)	-1.155 (1.275)
	Median (Range)	-2.405 (-4.492, 1.080)	-2.587 (-4.547, 1.317)	-0.744 (-3.650, 0.965)
No	N[b]	243	239	117
	Mean (SD)	-2.062 (1.265)	-2.105 (1.238)	-1.164 (1.312)
	Median (Range)	-2.382 (-4.428, 2.039)	-2.453 (-4.407, 1.200)	-0.598 (-4.148, 0.619)

[a] Number of patients in the treatment group.
[b] Number of patients contributing to the summary statistics, which were patients with valid values for baseline and on treatment.
Last Observation Carried Forward (LOCF) was imputed for missing values.
QD = Once daily dosing; BID = Twice daily dosing; SD = Standard deviation.

Table 35 and Table 36 present the results for the percentage of patients achieving <50 and <400 copies/mL at Week 24 by enfuvirtide use in OBT. Enfuvirtide use in OBT had no impact on response to treatment in any of the treatment groups. Both maraviroc treatment groups demonstrated superior efficacy over placebo whether enfuvirtide was included in a patient's OBT or not.

Table 35. Percentage of Patients with an HIV-1 RNA <50 copies/mL at Week 24 by Enfuvirtide Use in OBT (Combined Studies A4001027 and A4001028)

Enfuvirtide Use in OBT	Percentage of Patients with HIV-1 RNA <50 copies/mL					
	Maraviroc QD (N= 414)[a]		Maraviroc BID (N= 426)[a]		Placebo (N= 209)[a]	
	N[b]	N (%)	N[b]	n (%)	N[b]	n (%)
Yes	165	81 (49.1)	180	82 (45.6)	90	23 (25.6)
No	243	113 (46.5)	239	119 (49.8)	117	28 (23.9)

[a] Number of patients in treatment group.
[b] Number of patients with a post-baseline observation used to calculate the percentage.
QD = Once daily dosing; BID = Twice daily dosing.

Table 36. Percentage of Patients with an HIV-1 RNA <400 copies/mL at Week 24 by Enfuvirtide Use in OBT (Combined Studies A4001027 and A4001028)

Enfuvirtide Use in OBT	Percentage of Patients with HIV-1 RNA <400 copies/mL					
	Maraviroc QD (N= 414)[a]		Maraviroc BID (N= 426)[a]		Placebo (N= 209)[a]	
	N[b]	N (%)	N[b]	n (%)	N[b]	n (%)
Yes	165	97 (58.8)	180	117 (65.0)	90	26 (28.9)
No	243	151 (62.1)	239	156 (65.3)	117	37 (31.6)

[a] Number of patients in treatment group.
[b] Number of patients with a post-baseline observation used to calculate the percentage.
QD = Once daily dosing; BID = Twice daily dosing.

A similar pattern was observed for change in CD4 cell count from baseline by enfuvirtide use in OBT.

The data have not revealed any evidence of an in vivo synergy between two different HIV-1 entry inhibitors, however, the stratification analysis presented above did not take into account previous use of enfuvirtide or baseline resistance to enfuvirtide in patients using enfuvirtide as part of their OBT. A subset analysis of change from baseline in HIV-1 RNA at Week 24 by enfuvitide use in OBT by history of previous enfuvirtide use or evidence of resistance mutations at screening is presented in Table 37.

Table 37. Summary of Change from Baseline in HIV-1 RNA at Week 24 by Enfuvirtide Use in OBT, History of Enfuvirtide Use or Resistance to Enfuvirtide at Screening (Studies A4001027 and A4001028)

		Change from Baseline to Week 24 in HIV-1 RNA (log_{10} copies/mL)		
		Maraviroc QD (N=414)[a]	Maraviroc BID (N=426)[a]	Placebo (N=209)[a]
Total Population	N[b]	408	419	207
	Mean (sd)	-2.092 (1.272)	-2.158 (1.279)	-1.160 (1.293)
	Median (min, max)	-2.385 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
Enfuvirtide Use in OBT - Yes				
History of Use – Yes	N[b]	74	71	32
Resistance - Yes	Mean (sd)	-1.703 (1.289)	-1.799 (1.445)	-0.500 (1.047)
	Median (min, max)	-1.916 (-4.231, 1.080)	-2.083 (-4.547, 1.317)	-0.164 (-3.210, 0.641)
History of Use – No	N[b]	91	109	58
Resistance - No	Mean (sd)	-2.488 (1.174)	-2.508 (1.175)	-1.516 (1.254)
	Median (min, max)	-2.790 (-4.492, 0.184)	-2.799 (-4.504, 0.459)	-1.210 (-3.650, 0.965)
Enfuvirtide Use in OBT - No				
History of Use – Yes	N[b]	67	69	34
Resistance - Yes	Mean (sd)	-1.412 (1.244)	-1.668 (1.343)	-0.463 (1.001)
	Median (min, max)	-1.305 (-3.499, 0.392)	-2.035 (-4.333, 0.602)	-0.236 (-3.463, 0.619)
History of Use – No	N[b]	176	170	83
Resistance - No	Mean (sd)	-2.310 (1.186)	-2.282 (1.151)	-1.451 (1.319)
	Median (min, max)	-2.535 (-4.428, 2.039)	-2.556 (4.407, 1.200)	-1.176 (-4.148, 0.512)

[a] Number of patients in treatment group.
[b] Number of patients contributing to summary statistics.
Last Observation Carried Forward (LOCF) has been used to impute missing values.
Baseline value is the average of the pre-dose measurements collected at screening, randomization and baseline visits.

This analysis demonstrates that for the subgroup of patients who received enfuvirtide for the first time and with no evidence of resistance mutations detected, a greater decrease in HIV-1 RNA from baseline was seen in all three treatment groups, as compared with those patients who were enfuvirtide-experienced, with or without enfuvirtide resistance mutations. However the addition of maraviroc to the enfuvirtide containing OBT provided the same additional treatment benefit compared to placebo, regardless of previous enfuvirtide use/resistance. These results are consistent with an additive effect of enfuvirtide with maraviroc.

7.1.4.4.5. Protease Inhibitors and/or Delavirdine Use in OBT

These analyses were conducted to determine whether the additional antiviral efficacy observed in the maraviroc treatment groups was dependent on maraviroc dose and/or coadministered antiretrovirals. The results demonstrate that the difference between either maraviroc group and the placebo group in change from baseline to Week 24 in HIV-1 RNA was similar regardless of maraviroc unit dose administered (150 mg versus 300 mg), the use or non-use of any PI as part of OBT, or the use or non-use of tipranavir/ritonavir as part of OBT.

Approximately 80% of patients enrolled into Studies A4001027 and A4001028 were receiving a PI (except for tipranavir/ritonavir) 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 300 mg 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 38).

Table 38. 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

[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

7.1.4.4.6. Efficacy in Subgroups Based on Race

The majority of patients participating in Studies A4001027 and A4001028 were white (83.9%); 14.0% were black, 0.9% Asian and 1.4% were designated other (one patient was unspecified).

Table 39 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 39. 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)	-0.801 (-3.519, 0.512)

[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.

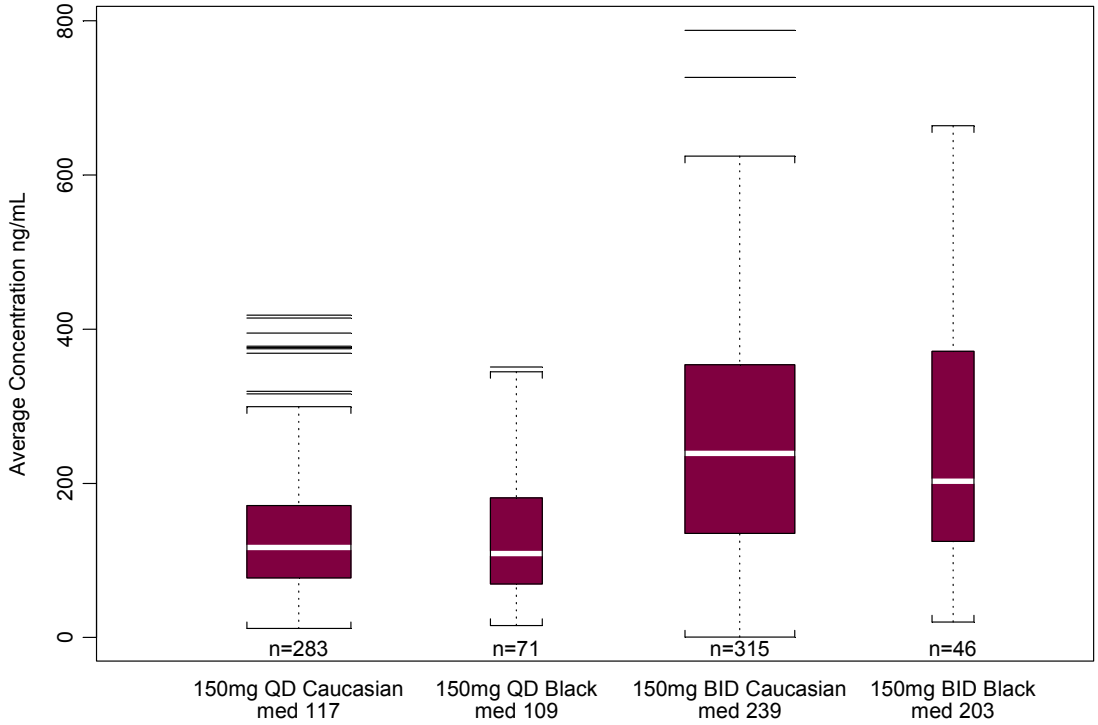
The summary of change from baseline in viral load at Week 24 by race indicated that the black placebo subgroup had an unusually high mean change from baseline (-1.515 log_{10} copies/mL) compared with the white placebo subgroup (-1.132 log_{10} copies/mL). This may be explained by the small number of 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).

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 groups. 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 13 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 13. 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 Sponsor concludes that the most likely rationale for these apparent differences in response in black patients may be due to small patient numbers with chance imbalances.

Safety data indicated that black patients had a similar adverse events profile to other racial groups.

7.2. Efficacy Results from Phase 2b Study in Patients Infected with Non-CCR5 Tropic HIV-1 (A4001029)

As previously discussed the objective of this smaller, Phase 2b safety study was to demonstrate that maraviroc co-administered with other antiretroviral agents would do no harm in treatment-experienced patients infected with non-CCR5 tropic (dual/mixed, CXCR4-tropic or non-phenotypable) HIV-1.

7.2.1. Study Populations

The study population was predominantly white males. The range of age, gender and racial mix was similar for all treatment groups (Table 40). This was an extremely advanced patient population, with a median CD4 cell count of <50 cells/μL in each treatment group. A similar number of patients prematurely discontinued from treatment from the maraviroc QD and placebo treatment groups, which was greater than for the maraviroc BID treatment group.

Table 40. Patient Demographics and Evaluation Groups for Study A4001029

Number of Patients	Maraviroc QD (N= 63)	Maraviroc BID (N= 61)	Placebo (N= 62)
Mean Age (Range), years	43 (16-59)	43 (16-62)	45 (23-65)
Gender (M/F)	53/10	55/6	53/9
Race (W/B/A/O)	46/17/0/0	44/13/1/3	40/18/3/1
Mean (Range) Years Since Diagnosis	14 (6-21)	14 (5-24)	13 (2-20)
Baseline HIV-1 RNA[a] (log_{10}copies/mL)			
Mean	5.031	5.103	5.008
Median (Range)	5.098 (3.429-5.938)	5.174 (3.609-6.672)	5.104 (3.648-6.150)
Baseline CD4 Cell Count[a] (cells/μL)			
Mean	85.0	96.7	98.9
Median (Range)	39.5 (1.0-442.0)	43.1 (0-615.0)	41.4 (1.5-650.0)
CCR5 Δ32 Genotype			
WT/WT	44	54	46
WT/Δ32	12	5	9
Screening Genotypic Sensitivity Score[b]			
0-1	35	24	23
2-4	21	23	34
≥4	0	4	0
Median	1.0	2.0	2.0
Screening Phenotypic Sensitivity Score[b]			
0-1	13	7	15
2-4	43	40	42
≥4	0	4	0
Median	2.0	3.0	3.0
Screening Overall Sensitivity Score[b]			
0-1	21	12	17
2-4	35	35	40
≥4	0	4	0
Median	2.0	2.0	2.0
Number Treated, n (%)	63	61	62
Discontinuations, n (%)	38 (60.3)	32 (52.5)	38 (61.3)
Ongoing at Week 24, n (%)	25 (39.7)	29 (47.5)	24 (38.7)
Evaluated for Efficacy[c], n (%)	63 (100.0)	61 (100.0)	62 (100.0)

[a] Baseline values were calculated as the average of three pre-dose assessments taken at screening, randomization and baseline visits.
[b] For patients infected with dual/mixed tropic HIV-1.
[c] Full Analysis Set.
QD = Once daily dosing; BID = Twice daily dosing; W = White, B = Black, A = Asian, O = Other.

7.2.2. Primary Efficacy Endpoint

The following Table 41 shows the statistical analysis of change in viral load (log_{10} copies/mL) from baseline to Week 24 for the 'As Treated' population infected with dual/mixed tropic HIV-1. The point estimates for the change from baseline in HIV-1 RNA

level to week 24 was similar between the three treatment groups, however as the upper limit of each 97.5% CI was >0.25 $\log_{10}$ copies/ml (the pre-defined non-inferiority margin), neither maraviroc dose demonstrated non-inferiority to placebo. The sample size calculation for the non-inferiority analysis had assumed a 0.25 $\log_{10}$ copies/mL advantage of each maraviroc dose versus placebo.

Table 41. Summary of Mean Change from Baseline to Week 24 in HIV-1 RNA (Study A4001029)

Treatment	N	Plasma HIV-1 RNA ($\log_{10}$ copies/mL)				
		Change from Baseline to Week 24			Treatment Difference Maraviroc-Placebo	
		Raw Mean (se)	Median	Adjusted Mean (se)	Estimate (se)	97.5% CI
Maraviroc QD	57	-0.890 (0.171)	0.000	-0.913 (0.185)	0.055 (0.258)	-0.528, 0.638
Maraviroc BID	52	-1.194 (0.206)	0.000	-1.200 (0.192)	-0.232 (0.264)	-0.829, 0.364
Placebo	58	-0.953 (0.180)	0.000	-0.968 (0.182)	N/C	N/C

Missing values have been imputed as the baseline value for patients who discontinued from blinded study drug.
QD = Once daily dosing; BID = Twice daily dosing; CI = Confidence interval; se = Standard error; N/C = Not calculated.

7.2.3. Secondary Efficacy Endpoints

There was a slightly higher proportion of patients receiving maraviroc BID with an HIV-1 RNA level <400 copies/mL, <50 copies/mL, <400 copies/mL or ≥1.0 $\log_{10}$ viral load decrease and <400 copies/mL or ≥0.5 $\log_{10}$ viral load decrease compared with those receiving maraviroc QD or placebo (Table 42).

Table 42. Overview of Patients[a] with an Undetectable Viral Load at Week 24 (Study A4001029)

Parameter (HIV-1 RNA)	Maraviroc QD (N=57)	Maraviroc BID (N=52)	Placebo (N=58)
<400 copies/mL, n (%)	14 (24.6)	16 (30.8)	14 (24.1)
<50 copies/mL, n (%)	12 (21.1)	14 (26.9)	9 (15.5)
≥0.5 $\log_{10}$ Viral Load Decrease, n (%)	24 (42.1)	25 (48.1)	23 (39.7)
≥1.0 $\log_{10}$ Viral Load Decrease, n (%)	18 (31.6)	23 (44.2)	21 (36.2)

[a] Includes patients infected with dual/mixed tropic HIV-1.
QD = Once daily dosing; BID = Twice daily dosing.

Change in CD4 cell count from baseline was higher for both doses of maraviroc compared with placebo, reaching statistical significance for the BID dose compared with placebo (no adjustments were made for multiple comparisons). The change in CD8 cell count from baseline was statistically significantly higher for both doses of maraviroc compared with placebo. Table 43 presents the change in CD4 and CD8 cell counts from baseline to Week 24 for all treatment groups.

Table 43. Statistical Analysis of Change from Baseline to Week 24 in CD4 and CD8 Cell Count[a] (Study A4001029)

Treatment Group	CD4 Cell Count (cells/μL)			CD8 Cell Count (cells/μL)		
	Adjusted Mean	Difference[b] (95% CI)	P-Value	Adjusted Mean (se)	Difference[b] (95% CI)	P-Value
Maraviroc QD	59.6	23.9 (-1.4, 49.2)	0.0635	384	234 (75, 394)	0.0042
Maraviroc BID	62.4	26.7 (0.9, 52.5)	0.0429	339	189 (24, 354)	0.0250
Placebo	35.7	N/C	N/C	150	N/C	N/C

[a] Includes patients infected with dual/mixed tropic HIV-1.
[b] Compared with Placebo.
QD = Once daily dosing; BID = Twice daily dosing; N/C = Not calculated.

By Week 24, 27 (out of 167 patients) infected with dual/mixed tropic HIV-1 at screening had a valid tropism result and were on study drug. Of these, 7 had a different tropism result compared to their screening result; 5/7 patients had a CXCR4 tropism result, 4 of whom were in the maraviroc treatment groups. Of 75 patients who failed treatment, 31 (41%) had a different tropism result from that at screening; the majority (26 out of 31) had a CXCR4 tropism result, with 24 of these being in the maraviroc treatment groups. The virological endpoint analysis for these patients is included in Section 8 below.

7.2.4. Conclusions

The primary objective of 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 selective suppression of CCR5 variants by maraviroc, when given as part of a failing regimen, in a dual/mixed virus population would result in a shift to a predominantly CXCR4 phenotype, and that this would result in an adverse virological and immunological outcome.

Statistical analysis of the primary endpoint, change from baseline to Week 24 in viral load, showed that neither dose of maraviroc was superior or non-inferior to placebo, the latter likely due to assumptions made of a small benefit for maraviroc (0.25 $\log_{10}$ superiority to placebo) when powering the study. There was no evidence of virologic harm and there was an increase in CD4 cell count that was statistically significantly higher for the maraviroc BID treatment group compared with placebo (unadjusted for multiple comparisons).

The increase in CD4 cell count was statistically significantly higher for the maraviroc BID treatment group compared with placebo and was particularly notable for patients with an OSS of 0-1. The increase in CD8 cell count was statistically significantly higher for both doses of maraviroc compared with placebo.

Since submission of the maraviroc NDA 22-218, Week 48 analysis has been completed. There are no substantial differences from the results and conclusions from the Week 24 analysis presented above.

7.3. Overall Efficacy Conclusions

- Maraviroc is the first NDA submission for a class of new antiretroviral agents designed to inhibit binding of HIV-1 to the CCR5 receptor, thereby blocking an essential step in viral replication.

- In Phase 3 registrational studies, 1049 highly treatment-experienced patients were treated with at least one dose of active study drug or placebo in combination with OBT.

    - Maraviroc demonstrated statistically significant differences in viral load reduction compared with placebo (OBT alone) as indicated by the estimates of the treatment difference for maraviroc QD:, -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 statistical superiority of maraviroc QD and maraviroc BID compared with placebo.

    - 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 $\log_{10}$ copies is recognized as clinically significant.

- Maraviroc demonstrated statistically superior efficacy compared with placebo (OBT alone) when considering the secondary efficacy endpoints of percentage of patients achieving an HIV-1 RNA <50 and <400 copies/mL at Week 24; 44.0%, 45.3% and 23.0% of patients achieved <400 copies/mL in the maraviroc QD, maraviroc BID and placebo treatment groups respectively and 55.1%, 61.0% and 27.8% achieved <400 copies/mL in the maraviroc QD, maraviroc BID and placebo groups respectively.

- All additional secondary endpoint results at Week 24 (patients with at least a 1.0 $\log_{10}$ reduction from baseline or <400 copies/mL, and at least a 0.5 $\log_{10}$ reduction from baseline or <400 copies/mL, CD4 and CD8 cell count change from baseline to Week 24, TAD and time to treatment failure) were consistent with the primary endpoint and support the apparent greater efficacy of both maraviroc treatment groups over placebo.

- The mean change in CD4 cell count (cells/μL) was greater for the maraviroc treatment groups than placebo. The adjusted mean CD4 cell count increases observed in patients receiving maraviroc QD and BID were 108.6 cells/μL and 106.3 cells/μL, respectively, compared with placebo where an increase of 57.4 cells/μL was demonstrated.

- 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 analyses.

- The 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.

- 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, which led to discontinuation of the maraviroc QD treatment arm.

    - 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, probably due to the small size of this subgroup of patients.

8. CHANGES IN VIRAL TROPISM AND CHARACTERIZATION OF MARAVIROC RESISTANCE

8.1. Introduction

The following considerations were made in designing studies to characterize changes in viral tropism and the selection of maraviroc resistant virus during the pre-clinical and clinical phases of the program:

- Maraviroc is representative of a new class of antiretrovirals, called CCR5 antagonists, which target the entry stage of the HIV-1 life cycle.

- Maraviroc is selective for CCR5-tropic virus strains and has no antiviral activity against CXCR4-tropic or dual tropic strains (collectively termed 'CXCR4-using').

- Maraviroc exerts its antiviral activity through binding to a host cell protein (CCR5) rather than a viral protein.

- The viral envelope (gp120) is the relevant viral protein to study with respect to maraviroc resistance and viral tropism because it is the protein that binds to CCR5.

- Drug susceptibility assays that can phenotypically characterize drug resistance to entry inhibitors are less well advanced than those that target the viral polymerase and protease.

There are two possible pathways of viral escape from maraviroc: firstly, the selection of viruses that can use CXCR4 as their entry co-receptor ('change in viral tropism'); secondly, the selection of viruses that continue to use CCR5 but can recognize the receptor even when maraviroc is bound ('maraviroc resistance'). The relevance of each of these pathways was investigated both pre-clinically and in virus from patients failing maraviroc-containing regimens.

8.2. Strategy for Selecting Virus Resistant to Maraviroc and Monitoring Changes in Viral Tropism In Vitro

In vitro resistance studies are typically conducted by serial passage of lab adapted strains of HIV-1 in immortalized cell lines, with compound concentrations being raised incrementally (from ~IC_{50}) during the course of the experiment. This method has been successfully applied to generate in vitro resistance against many licensed antiretrovirals (e.g. Jacobsen et al., 1995, Rimsky et al., 1998). It was not possible to use this experimental strategy for generating maraviroc resistant virus in vitro. Most common lab-adapted strains are CXCR4-tropic (e.g. IIIB/LAV, HXB2, NL4-3) and most immortalized human cell lines that support HIV-1 infection co-express CD4 and CXCR4 but not CCR5. Serial passaging was therefore performed in mitogen-stimulated peripheral blood lymphocytes (PBL) and the PM-1 cell line. PBL were chosen since they are a relevant in vivo target cell for HIV-1 replication and, upon stimulation with phytohaemagglutinin (PHA), a subset of PBL co-express CD4, CCR5 and/or CXCR4. This cell system also supports the replication in vitro of both HIV-1 lab adapted strains and primary isolates. PM-1 cells are an immortalized human cell line that naturally expresses CD4, CXCR4 and CCR5 and therefore support the replication of CCR5-tropic lab strains.

8.3. Strategy for Assessing the Selection of Virus Resistant to Maraviroc and Monitoring Changes in Viral Tropism in the Clinical Program

The treatment of HIV-1 infection involves the co-administration of three or more antiretroviral agents to reduce viral replication and thus slow/prevent further disease progression. Drug-resistant variants may be selected in patients whose virus is not completely suppressed during anti-retroviral therapy; this often leads to virological failure in clinical studies. Since maraviroc has no activity against CXCR4-using viruses, viral tropism was measured throughout the clinical program to identify changes in tropism that occurred during active treatment. Exploratory virological analyses were performed on emergent CXCR4-using virus that was detected in some patients in order to understand whether this virus emerged from a pre-treatment CXCR4-using reservoir that was not detected at baseline or was as a result of mutation from a CCR5-tropic progenitor.

Exploratory in vitro analyses were conducted on viruses from a representative group of patients who failed therapy but still carried a CCR5 tropic virus. This allowed characterization of resistance to maraviroc for viruses that still used CCR5 as their entry co-receptor. These analyses employed genotypic (DNA sequencing) and phenotypic (in vitro drug susceptibility) assay technologies that are specific for the HIV-1 envelope (gp120/gp41).

8.4. Changes in Viral Tropism Observed In Vitro

Maraviroc did not select for CXCR4-using variants during weekly serial passage of CCR5-tropic primary isolates through peripheral blood lymphocytes (PBL) for up to 20 weeks, or the lab adapted strain, Ba-L, through PBL and PM-1 cells (an immortalized human cell line that naturally expresses CD4, CCR5 and CXCR4) for up to 32 weeks (Westby et al, 2007). CXCR4-using variants did emerge during serial passage of the HIV-1 strain, SF162 (Clade B), through PBL. This occurred both in the cultures containing maraviroc and in untreated control virus passaged in parallel, indicating that its appearance was not a result of selective pressure by maraviroc. The selection of CXCR4-using variants of the SF162 strain has been described previously, after its serial passage through cells with low CCR5 expression (Dejucq et al., 2000, Harrowe and Cheng-Mayer, 1995).

8.5. Changes in Viral Tropism Observed in the Clinical Program

8.5.1. Introduction

Viral co-receptor tropism was determined throughout the clinical program using an in vitro phenotypic assay (Trofile™, Monogram Biosciences, San Francisco; see Appendix 1.1 for details). The Trofile™ assay results are reported as 'R5-tropic' (CCR5-tropic virus only detected), 'X4-tropic' (CXCR4-tropic virus only detected) or 'D/M-tropic' (dual/mixed tropism, i.e. a signal on both CCR5-expressing and CXCR4-expressing cells). The D/M-tropic classification reflects the fact that patients may be infected with a population of related but genetically distinct viruses that each have their own co-receptor specificities: thus the assay does not distinguish between mixed populations of CCR5 + CXCR4 viruses, CCR5 + CCR5CXCR4 + CXCR4 viruses, or a pure population of CCR5CXCR4 viruses (Figure 14).

Figure 14. Relationship Between Viral Composition of Pure/Mixed Virus Populations

PANEL A **PANEL B**

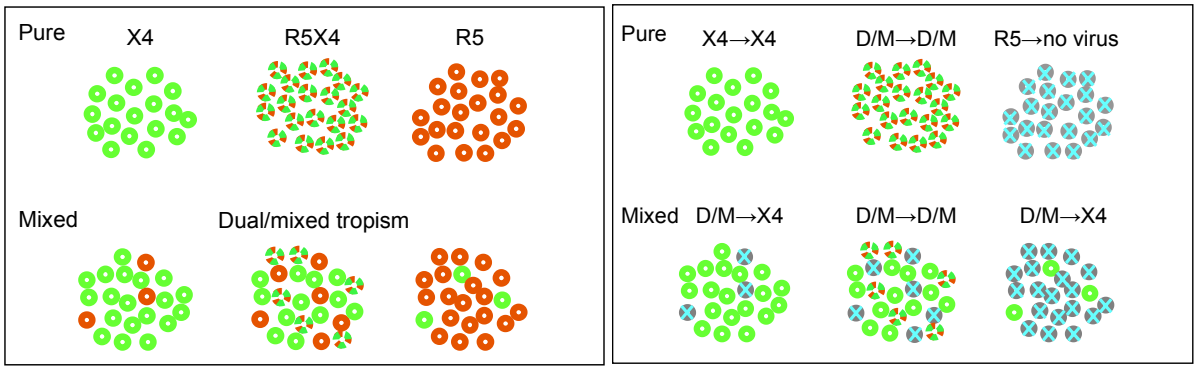


Figure legend. Within a patient, the circulating virus population is composed of various mixtures of closely related but genetically distinct viruses ('quasispecies'). These quasispecies may comprise a pure population that all share the same tropism (Panel A, upper line). Alternatively, quasispecies with different tropisms may co-exist in a mixed population (Panel A, lower line). Maraviroc selectively inhibits CCR5 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).
X4 = CXCR4-Tropic Virus; R5X4 = CCR5CXCR4 (Dual)-Tropic Viruses; R5 = CCR5 Tropic Virus.

The output of the assay is a reflection of the relative sizes of the CCR5-using and CXCR4-using virus populations in the patient sample and is neither quantitative, nor absolute. In mixing experiments conducted in vitro, a 10% minority population of CXCR4-using clones could be detected with 100% sensitivity, while the presence of a 5% CXCR4- using population could be detected with 83% sensitivity (Whitcomb JM, 2007). The assay has been technically validated with a lower limit of sensitivity of 1000 copies of HIV-1 RNA/mL for amplification. In the clinical program, a lower limit in plasma viral load of 500 HIV-1 RNA copies/mL was used in order to increase the number of samples with low viral load for which tropism was determined. If viral load was <500 RNA copies/mL at a study timepoint, the tropism test was either cancelled or the result was censored.

8.5.2. Assessment of Viral Tropism in Patients Infected with non-R5 tropic virus (A4001029)

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 D/M-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.

A change in tropism result was observed in 18/167 (11%) patients between the screening and baseline study visits; 16 patients had a change in tropism result from D/M to R5-tropic, while 2 had a change in tropism result from D/M to X4-tropic.

Of all the patients who failed treatment (across the maraviroc and placebo arms) and for whom a valid tropism test result was available, 31 of 75 patients (41%) had a different viral tropism result at failure (Table 44). A total of 25 of 53 patients (47%) in the maraviroc treatment groups had a different tropism result at time of treatment failure compared to 6 of 22 patients (27%) receiving placebo. Specifically, 24 of 53 patients (45%) had an X4 tropism result at failure in the maraviroc arms (consistent with selective suppression by maraviroc of CCR5 tropic virus strains in these patients), compared with 2 of out 22 (9%) patients in the placebo group.

Table 44. Tropism Status at Failure for Patients with Dual/Mixed Status at Screening who Discontinued due to Treatment Failure (A4001029)

		Tropism Status			
Treatment arm	**N**	**R5**	**X4**	**D/M**	**NR/BLQ**
Maraviroc QD	33	1	12	19	1 [a]
Maraviroc BID	21		12	9	0
Placebo	23	4	2	16	1

[a] Viral load was <500 copies/ml at planned tropism date nearest to treatment failure time point; patient had a dual/mixed tropism result at Early Termination (17 days after last dose).
NR = Non-phenotypable/no result; BLQ below level of quantification (tropism test cancelled or result censored due to viral load <500 copies/ml)

Both maraviroc treatment groups had a higher CD4 cell count increase compared with placebo, irrespective of virological response, indicating that CD4 cell count increases observed in the maraviroc treatment arms were not restricted to patients that were on study drug at Week 24 (Table 45).

Table 45. Mean Change (Range) in CD4 Cell Count (cells/μL) from Baseline to Week 24 (A4001029)

	Maraviroc QD + OBT	**Maraviroc BID + OBT**	**Placebo + OBT**
All Patients with Dual/Mixed Virus at Screening (n=163)	**+59.6** [a] (n=57)	**+62.4** [a,b] (n=52)	**+35.7** [a] (n=54)
Patients with an On-treatment Assessment at Week 24 (n=73)	**+90.9** (range -29 to +255) (n=23)	**+99.3** (range -22 to +303) (n=26)	**+79.9** (range -49 to +212) (n=24)
Patients Discontinuing due to Treatment Failure[c] (n=77)	**+37.5** (-7 to +237) (n=33)	**+24.8** (-11 to +140) (n=21)	**+3.7** (-118 to +76) (n=23)

Fifteen patients discontinued treatment prior to week 24 for reasons other than treatment failure. Data shown are for patients for whom CD4 values were available.
[a] Adjusted mean from ANCOVA model, adjusting for randomization strata.
[b] P<0.05 compared with placebo arm.
[c] Mean time (days) to treatment failure in patients was; placebo 68; maraviroc QD 69; maraviroc BID 82.

Changes in CD4 cell count from baseline to the time of treatment failure were the same for patients on maraviroc who had a X4 tropism result at failure and those whose tropism result remained dual/mixed (Table 46), confirming that a X4 tropism result was not associated with an adverse CD4 cell count outcome in this patient population.

Table 46. Change In CD4 Cell Count for Patients whose Virus was Classified as Dual/Mixed at Screening and who Discontinue due to Treatment Failure by Tropism Result at Time of Failure (A4001029)

Treatment arm	Tropism BL to TOF	Change from baseline			
		N	Mean	Median	Range
Maraviroc QD	D/M to R5	1	-3	-3	N/A
	D/M to D/M	19	+34	+15	-7 to +237
	D/M to X4	12	+48	+36	+2 to +164
	D/M to other[a]	1	+19	+19	N/A
Maraviroc BID	D/M to D/M	9	+14	+6	-11 to +56
	DM to X4	12	+33	+29	-9 to +140
Placebo	D/M to R5	4	+18	+21	+3 to +30
	D/M to D/M	16	+12	+2	-18 to +76
	D/M to X4	2[c]	-104	-104	-118 to -89
	D/M to other[b]	1	+29	+29	N/A

[a] BLQ
[b] Non phenotypable/no result
[c] These 2 patients had outlying baseline CD4 cell counts and therefore any change from baseline cannot be taken as representative.
BL = baseline (Day 1 pre-dose); BLQ = Viral load <500 copies/mL; TOF = protocol defined treatment failure.

8.5.3. Assessment of Viral Tropism in Phase 3 Studies for Patients Infected with CCR5 Tropic Virus (Analysis of combined data from studies A4001027 and A4001028)

8.5.3.1. Introduction

Studies A4001027 and A4001028 are two independent, multicentre, randomized, double-blind, placebo-controlled studies of maraviroc in combination with OBT versus OBT alone (placebo) for the treatment of antiretroviral experienced patients infected with CCR5 tropic HIV-1 only. These studies are identical in study design except for overlapping geographic region; A4001027 is being conducted in North America and A4001028 is being conducted in Europe, Australia and USA. More than 1,000 patients have been treated with blinded study drug, of which 840 have received maraviroc either once daily (QD) or twice daily (BID) in combination with OBT. An additional 209 patients have received placebo in combination with OBT.

The primary objective for the Phase 3 pivotal efficacy studies was to confirm the hypothesis that maraviroc in combination with OBT provided an additional reduction in plasma HIV-1 RNA level compared with OBT alone, as measured by the difference between each of the two maraviroc dosing regimens (QD and BID) versus the placebo regimen in the mean changes from baseline in $\log_{10}$ plasma HIV-1 RNA level at Week 24. These studies are currently ongoing to the 48-week endpoint.

A pre-planned combined analysis for efficacy was conducted, which included the analysis of primary and secondary endpoints in sub-populations from Studies A4001027 and A4001028. The following analyses of viral tropism are presented on these combined data.

Viral tropism was assessed in the Phase 3 studies at screening and subsequent study visits when viral load was >500 copies/ml. However, by Week 4 more than 40% of patients across the two studies already had a plasma viral load <500 copies/mL and therefore had no valid on-treatment tropism result. Furthermore, at Week 24, only 124 patients had a valid tropism result. Two reasons largely accounted for this: the high proportion of virologic responders who had a viral load <500 copies/mL at Week 24 (557 patients) whose tropism test was therefore either cancelled or censored, and the 315 patients who discontinued prior to Week 24. Therefore, assessment of tropism in patients who remained on blinded study drug at Week 24 is not informative.

8.5.3.2. Changes in Tropism Assignment between screening and baseline

Of the 1042 patients with a R5 tropism result at screening, 79 (7.6%) patients had a different tropism result at baseline; all of these were assigned as dual/mixed. These data are consistent with the results of the ACTG study A5211, where 10% of patients had a different tropism result between screening and baseline (Wilkin et al, 2007). This illustrates the background change in tropism result over a 4 to 6 week period in treatment-experienced patients, prior to a change in antiretroviral regimen or administration of a CCR5 antagonist.

Since the majority of patients enrolled into Studies A4001027 and A4001028 had exclusively R5-tropic virus detected at baseline, the decrease from baseline in viral load at Week 24 in this subset reflects that of the overall population (Table 47). In patients with D/M-tropic HIV-1 at baseline the mean change in HIV-1 RNA from baseline to Week 24 was comparable between the maraviroc QD and placebo groups and lower for the maraviroc BID group (Table 47). In general, these results confirm the findings in Study A4001029 in patients infected with non-CCR5 tropic HIV-1.

Table 47. Summary of Change from Baseline in HIV-1 RNA at Week 24 by Tropism Status at Baseline (Combined Studies A4001027 and A4001028)

Tropism Status at Baseline		Change from Baseline to Week 24 in HIV-1 RNA (log_{10} copies/mL) Maraviroc QD (N= 414)[a]	Maraviroc BID (N= 426)[a]	Placebo (N= 209)[a]
Total Population	N[b]	406	417	207
	Mean (SD)	**-2.099** (1.271)	**-2.162** (1.274)	**-1.160** (1.293)
	Median (Range)	-2.387 (-4.492, 2.039)	-2.468 (-4.547, 1.317)	-0.614 (-4.148, 0.365)
R5	N[b]	362	377	187
	Mean (SD)	**-2.168** (1.238)	**-2.254** (1.241)	**-1.149** (1.290)
	Median (Range)	-2.484 (-4.492, 2.039)	-2.571 (-4.547, 1.317)	-0.614 (-4.148, 0.365)
Dual/Mixed	N[b]	33	33	17
	Mean (SD)	**-1.510** (1.540)	**-1.073** (1.255)	**-1.450** (1.375)
	Median (Range)	-1.002 (-4.303, 0.597)	-0.392 (-4.504, 0.326)	-1.176 (-3.398, 0.483)

[a] Number of patients in the treatment group
[b] Number of patients contributing to the summary statistics, which were patients with valid values for baseline and on treatment.

8.5.3.3. Changes in Tropism Result at Time of Treatment Failure

Of the 204 patients with a R5 tropism result at baseline, and who experienced treatment failure, 67 (32.8%) had a change in tropism result to X4 or D/M at time of treatment failure (Table 48). All but 4 of these patients were in the maraviroc treatment arms.

Table 48. Percentage of Patients with a Change in Tropism Result from R5 to X4 or D/M Tropic Between Baseline and Time of Treatment Failure (Combined Studies A4001027 and A4001028)

Parameter	Maraviroc QD N=57	Maraviroc BID N=58	Placebo N=89
n (%)	31 (54.4%)	32 (55.2%)	4 (4.5%)
Difference[a]	**27 (49.9%)**	**28 (50.7%)**	N/C
95% CI	(36.3, 63.5)	(37.2, 64.2)	N/C

N = number of patients with CCR5 virus at baseline and who had treatment failure due to insufficient clinical response.
n = number of patients with a change in tropism result from R5 to X4 or D/M.
[a] Difference between maraviroc and placebo.
CI = Confidence interval; N/C = Not calculated.

The change in tropism result between baseline and time of treatment failure is summarised in Table 49. Of the 28 patients who had a dual/mixed tropism result at baseline and who failed treatment with maraviroc, only one patient had exclusively R5-tropic virus detected at time of failure. In contrast of the 4 patients who had a D/M tropism result at baseline and who failed treatment on placebo, 3 patients had exclusively R5-tropic virus detected at time of failure.

Table 49. Change in Tropism Result Between Baseline and Time of Treatment Failure (Combined Studies A4001027 and A4001028)

Treatment Group	Tropism at Baseline	Tropism at Time of Failure[a]			
		R5	X4	D/M	NR/NP
Total Population, N=1045	R5	115 (11.0%)	15 (1.4%)	52 (5.0%)	20 (1.9%)
Failures, n=242	D/M	4 (0.4%)	8 (0.8%)	18 (1.7%)	3 (0.3%)
Maraviroc QD, N=412	R5	18 (4.3%)	8 (1.5%)	23 (5.6%)	7 (1.7%)
Failures, n=68	D/M	1 (0.2%)	1 (0.2%)	6 (1.5%)	1 (0.2%)
Maraviroc BID, N=424	R5	17 (4.0%)	7 (1.7%)	25 (5.9%)	8 (1.9%)
Failures, n=77	D/M	0	6 (1.4%)	11 (2.6%)	2 (0.5%)
Placebo, N=209	R5	80 (38.2%)	0	4 (1.9%)	5 (2.4%)
Failures, n=97	D/M	3 (1.4%)	1 (0.5%)	1 (0.5%)	0

[a] The assessment for time of treatment failure is defined as the last on treatment assessment.
N = number of patients with a tropism result at baseline (used to calculate the percentages in this table)
n = number of patients with a tropism result at baseline and who had treatment failure due to insufficient clinical response.
NR/NP = non-reportable/non-phenotypable.

8.5.3.4. Change in CD4 at time of treatment failure by tropism result at failure

There was a greater mean increase in CD4 cell count for patients who failed therapy with maraviroc, compared to placebo (Table 50).

Table 50. Summary of Change from Baseline in CD4 Cell Count at Week 24 (Using LOCF) by Tropism Status at Baseline and Failure (Combined Studies A4001027 and A4001028)

Tropism Status Baseline - Failure		Change in CD4 Cell Count from Baseline to Week 24 (cells/μL) Maraviroc QD (N= 414)[a]	Maraviroc BID (N= 426)[a]	Placebo (N= 209)[a]
Total Population	N[b]	68	77	97
	Mean (SD)	**+49.4** (72.0)	**+71.1** (86.1)	**+13.8** (69.3)
	Median (Range)	32.8 (-193.0, 263.5)	47.0 (-131.0, 319.5)	3.0 (-301.0, 187.0)
R5 to R5	N[b]	18	17	80
	Mean (SD)	**+60.8** (106.3)	**+137.6** (85.5)	**+14.5** (67.2)
	Median (Range)	35.3 (-193.0, 263.5)	164.5 (0.5, 319.5)	2.5 (-301.0, 187.0)
R5 to DM/X4	N[b]	31	32	4
	Mean (SD)	**+37.0** (42.8)	**+56.0** (81.9)	**+67.1** (78.5)
	Median (Range)	25.0 (-49.0, 122.0)	36.3 (-131.0, 317.0)	54.3 (-11.0, 171.0)
R5 to	N[b]	8	9	5
NR/NP/BLQ/Missing	Mean (SD)	**+65.4** (99.0)	**+95.0** (79.6)	**-42** (84.6)
	Median (Range)	29.8 (-63.5, 205.5)	123.5 (-1.0, 227.5)	-24.0 (-184.5, 41.5)
Non-R5 to All	N[b]	11	19	8
	Mean (SD)	**+53.8** (47.6)	**+25.6** (58.4)	**+14.5** (64.7)
	Median (Range)	63.0 (-31.0, 116.0)	15.5 (-93.5, 178.0)	13.3 (-76.0, 149.0)

Baseline CD4 cell count is calculated from an average of the screening and baseline values.
[a] Number of patients in the treatment group.
[b] Number of patients contributing to the summary statistics.
QD = Once daily dosing; BID = Twice daily dosing; SD = Standard deviation. NR/NP = Non-reportable/non-phenotypable; BLQ = Viral load <500 copies/mL.

For those patients with a R5 tropism result at baseline, approximately twice as many patients who received maraviroc and failed therapy had a D/M or X4 tropism result at failure (n=63) compared to a R5-tropism result (n=35). The mean increase in CD4 cell count from baseline in patients who failed with a change in tropism to D/M tropic or X4, in both the maraviroc QD (37 cells/μL) and BID (56 cells/μL) groups was greater than that seen in the total placebo group who failed (13.8 cells/μL). In patients with a R5 tropism result at failure who either received maraviroc QD or BID, the increase in mean CD4 cell counts at failure was much greater than that of patients with a D/M or X4-tropism result at failure who received maraviroc QD or BID (Table 50).

Increases of mean changes in CD4 cell counts for the maraviroc treatment groups were also seen for 30 patients with a non-R5 tropism result at baseline (D/M, X4 or non-phenotypable), and for 17 patients with a R5-tropism result at baseline but who had no tropism assignment at failure (Table 50).

The numbers of patients on the placebo arm with a non-R5 tropism result at failure were too low to draw any conclusions from the data (n=4, 5 and 8 respectively for R5 to D/M/X4, R5 to non-reportable/non-phenotypable/BLQ/missing and non-R5). However, all of the results were within the range of changes seen in the placebo group with a CCR5 tropism result at failure (Table 50).

8.5.3.5. Origin of CXCR4-Using Virus Identified in Patients on Blinded Study Drug in Phase 3 Studies (Combined Studies A4001027 and A4001028)

Detailed virology studies were conducted on samples from 20 patients from the Phase 3 clinical program, whose virus was assigned as R5-tropic at study entry and in whom X4-using virus was detected whilst on blinded treatment. The objective of these investigational in vitro analyses was to understand whether the CXCR4-using virus emerged from a pre-treatment CXCR4-using reservoir that was not detected at baseline or as a result of mutation from a CCR5-tropic progenitor ('tropism switch').

There was no difference in the origin of CXCR4-using virus that was detected on treatment in 16 patients who received maraviroc + OBT and 4 patients who received placebo + OBT. In all cases the on-treatment CXCR4-using virus either emerged from a subsequently-identified pre-treatment CXCR4-using clone(s) or was shown to be phylogenetically very distant from the CCR5-tropic baseline virus such that emergence of pre-treatment archived CXCR4-using virus was by far the most likely explanation. This was true for patients who failed therapy within the first 8 weeks ('early' failures), who failed after week 8 ('late' failures) and those who were still on study drug at week 24 ('responders'). Clonal analyses comparing pre-treatment and on-treatment samples from patients who received maraviroc and in whom CXCR4-using virus was detected at baseline indicate a large decrease in the relative proportion of CCR5-tropic versus CXCR4-using viruses upon therapy with maraviroc. These data are consistent with maraviroc's mechanism of action, as a CCR5 antagonist that selectively inhibits CCR5 tropic virus in a mixed population, and are also consistent with the results of a clonal analysis of virus obtained from two patients in the Phase 2a studies in whom CXCR4-using virus was detected following 10days of maraviroc monotherapy (Westby et al. 2006). Importantly, there was no evidence of a switch in co-receptor usage of a CCR5-tropic virus in any of the studies conducted.

8.6. Selection of Virus Resistant to Maraviroc In Vitro

Resistance to maraviroc did not rapidly emerge during weekly serial passage of CCR5-tropic primary isolates through PBL for up to 20 weeks, or the lab adapted strain, Ba-L, through PBL and PM-1 cells for up to 32 weeks (Westby et al, 2007). As discussed above, the selection of maraviroc-resistant variants by serial passage of primary isolates in the presence of maraviroc was not associated with a switch in co-receptor tropism, except where this also occurred in untreated control virus passaged in parallel. Instead, maraviroc resistance is associated with continued use of CCR5 and dose response curves in drug susceptibility assays that are characterized by plateaus in maximal percentage inhibition (MPI) rather than a shift in IC_{50} (Figure 15).

Figure 15. Susceptibility of Env Pseudotyped Viruses Derived from CC1/85 to Maraviroc (panel A) and Enfuvirtide (panel B) in the PhenoSense HIV Entry Assay (U87CD4+ Cells Expressing CCR5).

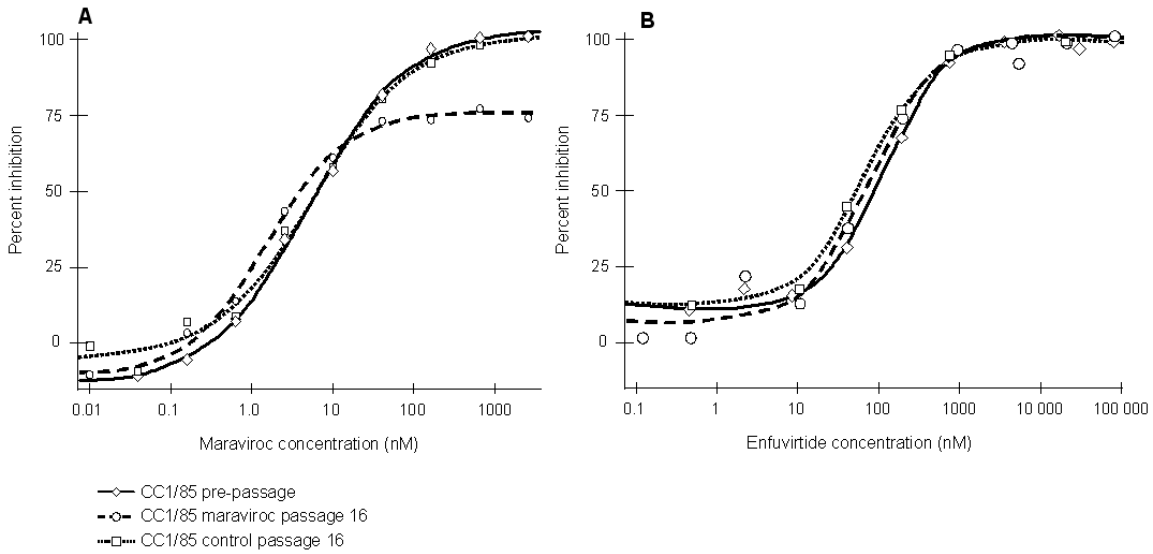


Figure legend. Maraviroc-resistant viruses are characterized phenotypically by plateaus in maximum percentage inhibition (MPI). The HIV-1 Envelope (Env) gene, encoding the entire gp120/gp41 (gp160) region, was amplified from different cultures of the CC1/85 strain: either a pre-passage stock (solid line), or virus serially passaged weekly through mitogen-stimulated PBL for 16 weeks in the presence (dashed line) or absence (dotted line) of maraviroc at increasing concentrations. The Env amplicons were used to build replication-defective pseudovirus particles which encoded a luciferase reporter gene. Luciferase activity was measured to quantify infection of U87CD4+CCR5+ cells by pseudoviruses in the presence of various concentrations of maraviroc (panel A) or enfuvirtide (panel B). Note that the maraviroc passaged virus gives a plateau in MPI of approximately 70% in response to maraviroc (dashed line, panel A). In contrast the passage control and the pre-passage viruses give normal dose response curves, as do all three viruses in panel B, indicating a lack of cross-resistance to enfuvirtide. Data points represent the mean of duplicate wells from a single experiment. Testing performed at Monogram Biosciences.

The observation that dose inhibition curves from maraviroc-resistant viruses are characterized by plateaus in MPI (rather than shifts in IC_{50}) is consistent with maraviroc's mechanism of action as a non-competitive inhibitor. The incomplete inhibition of viral replication even at high compound concentrations reflects the ability of the maraviroc-resistant viruses to use both maraviroc-bound and free CCR5 molecules to infect target cells (Figure 16).

Figure 16. Model of maraviroc resistance through recognition by the virus of compound-occupied receptors

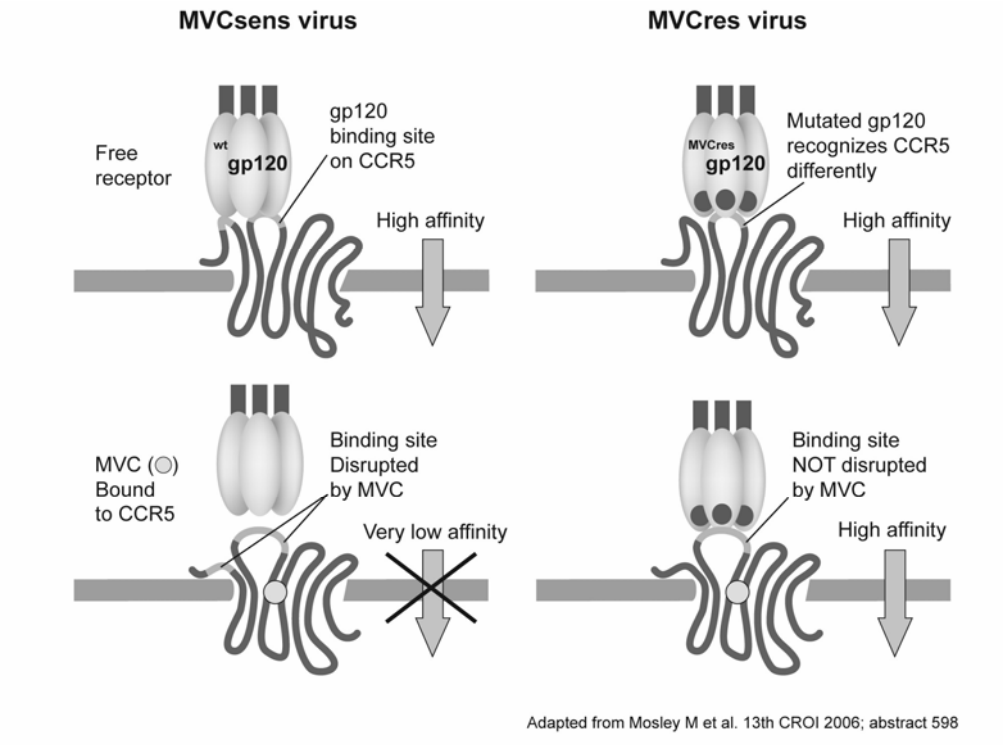


Figure legend. CCR5 antagonists, such as maraviroc, are non-competitive inhibitors of virus entry. Instead of directly blocking the interaction between CCR5 and gp120, they bind to a pocket in the transmembrane region of CCR5, thus causing conformational changes in CCR5 such that gp120 is no longer able to bind. However, resistant HIV-1 can acquire the ability to also recognize receptor conformations stabilized by maraviroc and therefore can no longer be inhibited even at high compound concentrations. In a particular drug susceptibility (phenotypic) assay, maraviroc-resistant viruses will thus be characterized by plateaus in maximum percentage inhibition (MPI); the plateau height will depend upon how efficiently the maraviroc-resistant virus can use the bound receptor compared to the free receptor (the more efficiently the bound receptor is used the lower the plateau). MVC=maraviroc; MVCsens=maraviroc sensitive virus; MVCres=maraviroc resistant virus; ^{wt}gp120 = gp120 envelope from wild type (sensitive) virus; ^{MVCres}gp120=gp120 envelope from maraviroc resistant virus.

Maraviroc-resistant viruses that emerged in vitro contained amino acid substitutions/deletions in the V3 loop of the HIV-1 envelope (gp120). Resistant variants of the primary isolate, CC1/85 (Clade B), contained the V3 loop substitutions, A19T and I26V. The importance of these V3 loop amino acid mutations in conferring the maraviroc-resistant phenotype was confirmed by site directed mutagenesis. In contrast maraviroc resistance of the primary isolate, RU570 (Clade G), was associated with a 3 amino acid deletion in the V3 loop, ΔQAI (18-20). Serial passage of the maraviroc-resistant variants in the absence of maraviroc selected for variants with sensitivities increased towards wild type maraviroc susceptibility; this correlated with loss of some or all of the mutations in the V3 loop. Maraviroc-resistant variants remained susceptible to other investigational CCR5 antagonists, enfuvirtide (HIV fusion inhibitor) and saquinavir (PI).

8.7. Selection of Viruses Resistant to Maraviroc in Patients Failing Blinded Therapy (Combined Studies A4001027 and A4001028)

From the combined Phase 3 studies, the majority of patients who failed on maraviroc had a D/M or X4 tropism result at failure, indicating that selection for CXCR4-using variants is the most common virological outcome at the time of failure (Table 48). Notwithstanding this fact, an exploratory in vitro analysis was conducted on virus from 38 patients enrolled in clinical studies A4001027 and A4001028, who failed blinded therapy with a CCR5-tropic virus. The objective was to identify phenotypic and genotypic markers associated with maraviroc resistance in vivo. The testing strategy was designed with consideration to the understanding of maraviroc resistance obtained during the pre-clinical phase of the program (see Section 8.6 above). This exploratory study was conducted on blinded samples, using a pre-defined testing protocol to avoid possible bias during the study. Additional samples from 4 of the 38 patients, who went on to receive open label maraviroc, were also included in the analysis. Of the 38 patients, 13 were subsequently shown to be on maraviroc treatment arms, the remainder received placebo.

Of the 79 plasma-derived viruses analyzed for susceptibility to maraviroc, 7 viruses (from 5 patients) showed evidence of a plateau in MPI <95%. All of these plateaus in MPI were observed following failure of a maraviroc-containing regimen. Four patients had a virus which gave a plateau following treatment failure in the blinded study period. One of these patients subsequently received open label maraviroc and virus from this patient continued to plateau (Patient 04). Virus from the fifth patient, who failed the OBT + placebo arm (Patient 01), developed a plateau during the open label maraviroc treatment phase. No plateaus in MPI <95% to maraviroc were observed in any of the baseline samples from the 37 patients studied, nor in the failure samples from the 25 patients on placebo.

In contrast shifts in IC_{50} to maraviroc were not generally identified as being associated with treatment failure (Table 51). Virus from one patient who failed a maraviroc containing regimen did show a 3-5-fold shift in IC_{50} between screening and baseline. The clinical and virological significance of this is not clear but the data indicate that this in vitro approach is also suitable for identifying these types of phenotypic changes.

Table 51. Summary of Maraviroc IC_{50} FC and Maximum Percentage Inhibition (MPI) for CCR5-Tropic Virus from Patients Failing Blinded Therapy in Studies A4001027 and A4001028

	IC_{50} Δ Resist. FC JRCSF[a]		MPI <95 (number of patients)	
	BL	**Fail**	**BL**	**Fail**
	Maraviroc Group (N=11[b])			
Value	0.84	1.00	0	4
Range (Min-max)	0.32-1.58	0.38-2.42	-	-
	Placebo Group (N=25)			
Value	0.67	0.65	0	0
Range (Min-Max)	0.22-2.65	0.22-2.82	96-100	97-100
p-value [c]		**0.13**		

[a] IC_{50} Δ Resist. JRCSF = fold change in IC_{50} between patient-derived virus and the reference strain, JRCSF, tested in the same assay and is reported as geometric mean values; [b] Excludes 2 of the 13 patients on maraviroc: 1 patient who had a plateau in inhibition <50% at failure (therefore no IC_{50} was reached) and 1 patient is excluded as no valid PhenoSense™ Susceptibility data was obtained.; [c]Analysis of covariance at failure (using the baseline response as a covariate) between treatment arm and placebo, mean fold difference between treatment groups = 0.82 (95% CI range 0.63-1.07). BL = baseline sample; Fail = sample taken following treatment failure. Table excludes data from unblinded treatment phase of 4 patients.

The 5 patients whose virus showed plateaus in MPI with maraviroc in the PhenoSense™ assay all had amino acid changes in the V3 loop which were present at failure time-points but were not present at baseline. The V3 loop sequences and mutations were different for each patient virus and reflect the heterogeneity associated with the V3 region of gp120.

No specific V3 amino acid changes were seen at treatment failure for the patient whose virus had shown a small 3 fold-shift in IC_{50}. Neither were any amino acid changes consistently observed in clones at failure timepoints from the 3 patients who had received placebo as part of their blinded treatment regimen and for whom a clonal analysis was performed. Patient 01, who also received placebo during the blinded study phase, only demonstrated V3 loop amino acid changes after receiving maraviroc as open label.

In order to understand the significance of the V3 amino acid changes in conferring in vivo resistance to maraviroc, site directed mutagenesis (SDM) was performed on representative Env clones from the start and failure timepoints from 4 of the 5 patients. These results are summarized in Table 52.

Table 52. Maraviroc susceptibility of SDM Env clones from patients failing maraviroc with CCR5 tropic virus (Combined Studies A4001027 and A4001028).

Patient (Study code)	Clone ID	Study visit	Maraviroc plateau in MPI (%)	V3 sequence 10 20 30 ....|....|....|....|....|....|....|.
Patient 08 (A4001027)	START	Baseline	100	CTRPNNNTRKSIPIG-PGRAFYATGDIIGDIRQAHC
	START(SDM V3 Fail)		**41**	...........S..A..................
	FAIL	E_TERM	**51**	...........S..A..................
	FAIL (SDM V3 Start)	(Week 24)	98	....
Patient 04 (A4001028)	START	Baseline	100	CTRPNNNTRKGIHIGPGRSFYATGDIIGDIRQVHC
	START (SDM V3 Fail)		100	.........S.............V........
	FAIL	Week 8	**55**	.I.......S.............V......A..
	FAIL (SDM V3 Start)		99	.I............................A..
Patient 14 (A4001027)	START	Baseline	100	CTRPGNNTRKSIHMGPGSSIYATGAIIGDIRQAHC
	START (SDM V3 Fail)		**85**	..................F....DV........
	FAIL	Week 24	**63**	..................F....DV........
	FAIL (SDM V3 Start)		99	....
Patient 01 (A4001027)	START	Baseline	96	CIRPNNNTRKSINIGPGRAWYTTGDIIGDIRQAHC
	START (SDM V3 Fail)		**66**	...........H.....................
	FAIL	Week 8	**50**	.T.........H....K...A............
	FAIL (SDM V3 Start)		**91**	.T..............K...A............

For each patient a representative Env clone from Baseline ('Start') and Failure ('Fail') was selected. Mutations were introduced into the Start clone to resemble the consensus V3 sequence at failure ('Start (SDM V3 Fail)') and into the Fail clone to resemble the consensus V3 sequence at baseline ('Fail (SDM V3 Start)'). Amino acids shown in grey-highlight indicate unique changes common to all 12 treatment-failure clones. The treatment-failure clones from Patient 08 all had an alanine insertion at position 16; hence in the alignment above the Start clone has a dash (-) at this position. 'E_TERM' = early termination visit. MPI = maximum percentage inhibition (PhenoSense™ HIV Entry Assay). MPI values shown in bold fall below the 95% cutoff and these clones are considered to be resistant to maraviroc.

For all four patients the V3 loop amino acids which were mutated played an important role in the maraviroc resistance phenotype. For two of the four patients (patients 08 and 14) the Env V3 amino acid mutations (P13S/A16$_{insertion}$ and I20F/A25D/I26V respectively) were both necessary and sufficient for maraviroc resistance, i.e., mutations of the V3 loop from the baseline clones resulted in a maraviroc-resistant phenotype, and back-mutation of the V3 loop from the maraviroc-resistant clones resulted in a maraviroc-sensitive phenotype (Table 52).

For one of the four patients (patient 01) mutation of the V3 amino acid (N13H) was sufficient to alter the maraviroc-sensitive phenotype of the baseline Env clone to a maraviroc-resistant one. However, the reverse mutation of this amino acid in the maraviroc-resistant Env clone (which had an MPI of 50%) did not fully restore the maraviroc-sensitive phenotype (although it did exhibit an MPI of 91%).

For one of the four patients (patient 04) mutation of the V3 amino acids (G11S/I26V) were necessary, but not sufficient, for maraviroc resistance. Mutation of the amino acids in the maraviroc-sensitive Env clone had no effect on the phenotype. However, reverse mutation of these amino acids in the maraviroc-resistant Env clone did restore the maraviroc-sensitive phenotype.

Resistance to maraviroc was not associated with changes in maraviroc IC_{50} values, and altering the genotype of Env clones by SDM had no apparent effect on these values (i.e. all changes in IC_{50} values were <2-fold).

Resistance to maraviroc was not associated with cross-resistance to enfuvirtide. Altering the specific amino acid residues in the Env V3 loop that were associated with resistance to maraviroc in vivo, had no effect on the susceptibility of the Env clones to enfuvirtide. This is consistent with the data obtained from maraviroc-resistant virus generated in vitro (see Figure 15).

8.8. Conclusions

Both pre-clinical selection experiments and exploratory in vitro studies conducted on pre- and post-treatment viruses from patients enrolled in the Phase 2a and Phase 2b/3 maraviroc clinical program have found:

- The data presented are consistent with maraviroc acting as a highly selective and potent inhibitor of CCR5-tropic viruses.

- There is a background change in tropism result from CCR5 to dual/mixed tropic between screening and baseline in approximately 8% of patients. The clinical outcome in these patients was similar to that of patients with non-CCR5 tropic virus in Study A4001029.

- In patients with a CCR5 tropism result at screening/baseline and who fail a maraviroc containing regimen, emergence of CXCR4-using virus is seen in the majority of cases.

- However, the emergence of CXCR4-using virus is not associated with a decrease in CD4 count, as patients failing on a maraviroc containing regimen had a larger mean increase in CD4 from baseline compared to placebo, irrespective of tropism result at time of failure.

- There is no evidence to suggest that changes in tropism result which occur in the circulating virus from patients on maraviroc-containing regimens are caused by mutation of a CCR5-tropic virus to a CXCR4-using virus (i.e. no evidence of tropism switch).

- In most cases, screening of large numbers of Env clones from baseline samples identified a low frequency of CXCR4-using clones that pre-existed maraviroc treatment and which were phylogenetically highly related to the on-treatment CXCR4-using virus. Where no CXCR4-using clones could be identified in the pre-treatment sample from a patient, the on-treatment CXCR4-using virus was shown to be phylogenetically very distant from the CCR5 tropic baseline virus such that emergence of a pre-treatment CXCR4-using virus (present at baseline but not detected) was by far the most likely explanation.

- The pre-clinical studies of maraviroc resistance (with continued CCR5-tropism) were predictive of what was seen in the clinic.

- Dose response inhibition curves with plateaus in MPI are predictive of resistance to maraviroc, consistent with its mechanism of action as a non-competitive inhibitor of viral entry.

- The in vitro susceptibility data obtained in the PhenoSense™ HIV Entry Assay is in good agreement with the data from testing the same patient-derived viral envelopes in PBL, suggesting that the former can be used as a primary screen for testing patient samples for resistance to maraviroc.

- Virus from one patient did demonstrate a small (3 to 5-fold) shift in IC_{50} between baseline and failure and this was detected in both assay systems. The clinical and virological significance of this is not clear but the data presented indicate that this in vitro approach is also suitable for identifying these types of phenotypic changes.

- Preliminary sequence data of maraviroc-resistant viruses from 5 patients failing maraviroc-containing regimens in the clinical program is consistent with the pre-clinical findings; namely that the V3 loop plays an important role in conferring resistance. In particular, an I26V mutation in the V3 loop may be a key mutation for some viruses, as may mutations that disturb the structure of the 'GPG' crown.

- Site directed mutagenesis studies on viruses from 4 patients confirmed the importance of V3 loop mutations in conferring resistance to maraviroc. In all cases, specific mutations were necessary and/or sufficient to confer resistance.

- However, it is not possible to propose a genotypic (sequence) algorithm to identify maraviroc resistance. No consistent changes in amino acid sequence between different patients were associated with a maraviroc resistant phenotype.

- There is no evidence that failure on a maraviroc-containing regimen will lead to cross-resistance to enfuvirtide, and no rationale for cross-resistance between maraviroc and other drug classes. Similarly, viruses with reduced susceptibility to enfuvirtide were susceptible to maraviroc.

9. SAFETY

Although maraviroc is the first CCR5 antagonist to be submitted for marketing authorization, other experimental agents in this new class of antiretroviral agents have undergone clinical development and have been associated with significant safety issues. Aplaviroc (Glaxo-Smith-Kline [GSK]) was discontinued from Phase 2b/3 development for severe hepatic toxicity. In a recent placebo-controlled clinical trial with another CCR5 antagonist, vicriviroc (Schering Plough), 4 cases of lymphoma and 1 of gastric adenocarcinoma were reported in patients treated with active drug. There was no clear evidence that these malignancies were linked to drug. Small numbers in the study, especially in the placebo group (90/118 received vicriviroc), confound assessment of a causal relationship between vicriviroc and development of malignancies. The data presented in this document do not indicate that maraviroc is associated with hepatotoxicity or carcinogenicity relative to placebo.

Safety concerns raised by pre-clinical models and the Phase 1/2a studies of maraviroc include postural hypotension and the potential to cause QT prolongation. Theoretical concerns based on the drug's mechanism of action include an increased risk for infection and development of malignancy. However, there is no evidence from the Phase 2b/3 studies that maraviroc, administered at a dose equivalent of 300 mg (QD or BID), is associated with an increased frequency relative to placebo of symptomatic postural hypotension, QTc interval prolongation, infections or malignancies.

The all-causality adverse event profile of maraviroc was similar for both the QD and BID dosing arms in treatment-experienced patients up to and beyond 24 weeks of treatment. Furthermore, most treatment-related events associated with maraviroc occurred at similar incidences to placebo. There were no age-, gender- or race-related differences in the safety profile of the maraviroc treatment groups versus placebo. There was no significant difference in the safety profile of maraviroc plus OBT compared with placebo plus OBT.

Safety data from the maraviroc submission, with a database cut off of 11 September 2006 are summarised below. Since the date of the NDA submission a 3-month safety update, with a database cut off of 30 November 2006, has been conducted by the Sponsor. There are no differences in the overall adverse event profile from the safety presented below and therefore no impact on the benefit-risk of maraviroc as discussed in Section 10.2. An updated presentation of deaths and lymphomas from this safety update are included in Section 9.10.

9.1. Overview of Maraviroc Safety Database

Phase 1/2a Clinical Studies

The maraviroc clinical safety database consisted of 674 subjects participating in Phase 1 single and multiple dose studies (including 37 HIV-1 infected patients) who received single doses of

maraviroc ranging from 1-1200 mg, or multiple doses of maraviroc ranging from 3 to 900 mg BID and 1200 mg QD, for periods ranging from 7-28 days. At the time of the submission of the NDA, 28 Phase 1 clinical studies had been completed, including 14 single dose and 14 multiple dose studies. Since this submission a further 2 Phase 1 clinical studies have been completed (A4001023 an hepatic impairment study and A4001052 a drug-drug interaction study with darunavir [TMC-114]).

During the Phase 2a studies a total of 66 asymptomatic HIV-1 infected patients received maraviroc for 10 days as monotherapy in doses ranging from 50 to 300 mg BID or 25 to 300 mg QD.

Phase 2b/3 Clinical Studies

A total of 1049 patients infected with CCR5 tropic HIV-1 participated in the Phase 3 treatment-experienced studies and were analysed for safety for the 24-week interim analysis.

The duration of treatment with maraviroc QD and BID was much greater than that with placebo in the Phase 3 Studies A4001027 and A4001028 conducted in treatment-experienced patients infected with CCR5-tropic HIV-1. In contrast, the duration of exposure in Study A4001029, conducted in treatment-experienced patients infected with non-CCR5-tropic (dual/mixed, CXCR4-tropic or non-phenotypable) HIV-1 was similar for the 3 treatment groups (Table 53).

Table 53. Exposure to Maraviroc during the Phase 2b/3 Studies in Treatment-Experienced Patients (Studies A4001027, A4001028 and A4001029)

Duration Categories (Days)	Maraviroc QD		Maraviroc BID		Placebo	
	A4001027/ A4001028	A4001029	A4001027/ A4001028	A4001029	A4001027/ A4001028	A4001029
N	**414**	**63**	**426**	**61**	**209**	**62**
≤1	0	0	1	0	0	1
2-14	5	0	5	1	2	2
15-28	1	0	11	2	2	1
29-90	51	19	53	12	64	20
91-180	104	19	92	17	60	14
181-364	248	25	262	29	80	24
≥365	5	0	2	0	1	0
Median (Days)	235.5	119.0	238.5	176.0	145	127.0
Range (Days)	2-381	64-317	1-366	11-326	7-427	1-318
Total Exposure (patient-years)[a]	**258.7**	**26.4**	**266.8**	**27.9**	**99.3**	**25.0**

[a] The sum of all subjects' duration of treatment, expressed in years.

More than 75% of patients dosed with maraviroc in these studies received unit doses of 150 mg, because their OBT included a PI (other than tipranavir/ritonavir) or delavirdine. The calculation of duration of therapy represents data collected to the patient's Week 24 visit and any subsequent exposure to a maximum of 48 weeks for each individual.

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. 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 and 129 patients respectively). In addition, serious adverse events and deaths that occurred more than 28 days after cessation of study drug were reported in patients who did not go on to receive open label maraviroc but who remained in study; these subjects are designated as belonging to an 'In-Study-Off-Drug' (ISOD) treatment group.

As of 11 September 2006, 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 15 September 2006 and include reports from all patients to a maximum of 22 months follow-up following screening. Integrated analyses primarily focused 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.

9.2. Safety Data from Early Phase 1/2a Clinical Studies

The adverse event profile for maraviroc unit doses ≤300 mg in the Phase 1 development program 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.

The adverse event profile was similar for single and multiple dose studies and no difference were observed between males and females. The most frequent (≥5%) treatment-emergent, treatment-related adverse events occurring in maraviroc-treated subjects from the Phase 1 multiple-dose studies were: headache (18.2%), dizziness (10.1%), fatigue (8.1%), nausea (7.4%), flatulence (7.4%), vision blurred (4.7%) and postural hypotension (4.7%). Some adverse events were reported exclusively or more frequently at higher doses (irrespective of relatedness), suggesting a dose-response relationship (although often the total number of events was small). Postural hypotension, ocular hyperemia and blurred vision (thought to be related to vasodilatation) showed a clear dose-response, with a distinct threshold above which they occur more frequently than with placebo. Though this threshold differed among these adverse events, in all cases it was above the proposed clinical dose of 300 mg BID. Other adverse events that showed some evidence for a dose-response relationship include dry mouth, nausea, fatigue, dizziness, headache and nasal congestion.

The adverse event profile for the Phase 2a studies was similar to that seen in the Phase 1 studies. The most frequently reported all-causality events were: headache (25.8%, 17/66), dizziness (10.6%, 7/66) fatigue (10.6%, 7/66), nausea (7.6%, 5/66) and flatulence (6.1%,

4/66). The adverse event profile for all treatment groups (including placebo) was similar, with no evidence of a dose relationship for any event at the doses studied (25 mg QD – 300 mg BID) in the Phase 2a population; however, the doses studied are below the threshold at which dose relationships became apparent in the healthy volunteer Phase 1 database (i.e., unit doses of 600 mg). The most frequently reported treatment-related adverse events were headache, dizziness and fatigue.

9.3. Overall Adverse Event Profile from Phase 2b/3 Clinical Studies

A similar proportion of patients from each treatment group in the Phase 3 registrational studies (A4001027 and A4001028) reported an adverse event whilst receiving blinded study drug. The most commonly reported all-causality adverse events during are presented in Table 54.

Table 54. All-Causality Adverse Events Reported in ≥2% of Patients in the Phase 3 Studies A4001027 and A4001028

System Organ Class MedDRA Preferred Term	Maraviroc QD N (%)	Maraviroc BID N (%)*	Placebo N (%)	Combined Maraviroc Doses N (%)
Subjects Evaluable for Adverse Events	**414**	**426**	**209**	**840**
Subjects With Adverse Events	**366 (88.4)**	**383 (89.9)**	**175 (83.7)**	**749 (89.2)**
Blood and Lymphatic System Disorders				
Anemia	9 (2.2)	12 (2.8)	6 (2.9)	21 (2.5)
Gastrointestinal Disorders				
Abdominal distension	14 (3.4)	10 (2.3)	6 (2.9)	24 (2.9)
Abdominal pain	18 (4.3)	19 (4.5)	7 (3.3)	37 (4.4)
Abdominal pain upper	20 (4.8)	14 (3.3)	7 (3.3)	34 (4.0)
Constipation	19 (4.6)	23 (5.4)	6 (2.9)	42 (5.0)
Diarrhea	94 (22.7)	89 (20.9)	45 (21.5)	183 (21.8)
Dyspepsia	10 (2.4)	11 (2.6)	5 (2.4)	21 (2.5)
Flatulence	14 (3.4)	16 (3.8)	9 (4.3)	30 (3.6)
Nausea	75 (18.1)	73 (17.1)	39 (18.7)	148 (17.6)
Vomiting	38 (9.2)	31 (7.3)	20 (9.6)	69 (8.2)
General Disorders and Administration Site Conditions				
Asthenia	16 (3.9)	11 (2.6)	5 (2.4)	27 (3.2)
Fatigue	45 (10.9)	54 (12.7)	31 (14.8)	99 (11.8)
Injection site reaction	28 (6.8)	31 (7.3)	18 (8.6)	59 (7.0)
Edema peripheral	14 (3.4)	9 (2.1)	6 (2.9)	23 (2.7)
Pain	5 (1.2)	9 (2.1)	4 (1.9)	14 (1.7)
Pyrexia	30 (7.2)	51 (12.0)	17 (8.1)	81 (9.6)
Infections and Infestations				
Bronchitis	23 (5.6)	23 (5.4)	8 (3.8)	46 (5.5)
Condyloma acuminatum	6 (1.4)	9 (2.1)	2 (1.0)	15 (1.8)
Folliculitis	7 (1.7)	14 (3.3)	4 (1.9)	21 (2.5)
Herpes simplex	14 (3.4)	26 (6.1)	6 (2.9)	40 (4.8)
Influenza	14 (3.4)	6 (1.4)	0	20 (2.4)
Nasopharyngitis	30 (7.2)	30 (7.0)	9 (4.3)	60 (7.1)
Esophageal candidiasis	12 (2.9)	2 (0.5)	2 (1.0)	14 (1.7)
Oral candidiasis	13 (3.1)	10 (2.3)	7 (3.3)	23 (2.7)
Pneumonia	11 (2.7)	6 (1.4)	7 (3.3)	17 (2.0)
Rhinitis	9 (2.2)	4 (0.9)	2 (1.0)	13 (1.5)
Sinusitis	15 (3.6)	25 (5.9)	7 (3.3)	40 (4.8)
Upper respiratory tract infection	38 (9.2)	44 (10.3)	11 (5.3)	82 (9.8)
Investigations				
Alanine aminotransferase increased	7 (1.7)	10 (2.3)	1 (0.5)	17 (2.0)
Aspartate aminotransferase increased	7 (1.7)	15 (3.5)	1 (0.5)	22 (2.6)
Blood creatine phosphokinase increased	5 (1.2)	9 (2.1)	1 (0.5)	14 (1.7)
Weight decreased	17 (4.1)	13 (3.1)	4 (1.9)	30 (3.6)
Metabolism and Nutrition Disorders				
Anorexia	17 (4.1)	16 (3.8)	8 (3.8)	33 (3.9)
Decreased appetite	10 (2.4)	14 (3.3)	5 (2.4)	24 (2.9)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	18 (4.3)	22 (5.2)	6 (2.9)	40 (4.8)
Back pain	22 (5.3)	21 (4.9)	6 (2.9)	43 (5.1)
Muscle spasms	13 (3.1)	9 (2.1)	9 (4.3)	22 (2.6)
Myalgia	19 (4.6)	12 (2.8)	1 (0.5)	31 (3.7)
Pain in extremity	12 (2.9)	11 (2.6)	5 (2.4)	23 (2.7)
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)				
Skin papilloma	11 (2.7)	8 (1.9)	3 (1.4)	19 (2.3)
Nervous System Disorders				
Dizziness	39 (9.4)	34 (8.0)	14 (6.7)	73 (8.7)
Dysgeusia	3 (0.7)	12 (2.8)	2 (1.0)	15 (1.8)
Headache	61 (14.7)	54 (12.7)	32 (15.3)	115 (13.7)

Table 54. All-Causality Adverse Events Reported in ≥2% of Patients in the Phase 3 Studies A4001027 and A4001028

System Organ Class MedDRA Preferred Term	Maraviroc QD N (%)	Maraviroc BID N (%)*	Placebo N (%)	Combined Maraviroc Doses N (%)
Hypoesthesia	10 (2.4)	11 (2.6)	2 (1.0)	21 (2.5)
Neuropathy peripheral	9 (2.2)	9 (2.1)	4 (1.9)	18 (2.1)
Paresthesia	11 (2.7)	11 (2.6)	5 (2.4)	22 (2.6)
Psychiatric Disorders				
Anxiety	8 (1.9)	12 (2.8)	5 (2.4)	20 (2.4)
Depression	13 (3.1)	14 (3.3)	6 (2.9)	27 (3.2)
Insomnia	23 (5.6)	29 (6.8)	9 (4.3)	52 (6.2)
Sleep disorder	9 (2.2)	6 (1.4)	3 (1.4)	15 (1.8)
Renal and Urinary Disorders				
Dysuria	6 (1.4)	11 (2.6)	1 (0.5)	17 (2.0)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	35 (8.5)	48 (11.3)	10 (4.8)	83 (9.9)
Dyspnea	13 (3.1)	11 (2.6)	2 (1.0)	24 (2.9)
Nasal congestion	10 (2.4)	12 (2.8)	5 (2.4)	22 (2.6)
Pharyngolaryngeal pain	17 (4.1)	10 (2.3)	6 (2.9)	27 (3.2)
Skin and Subcutaneous Tissue Disorders				
Night sweats	13 (3.1)	16 (3.8)	6 (2.9)	29 (3.5)
Pruritus	11 (2.7)	13 (3.1)	3 (1.4)	24 (2.9)
Rash	27 (6.5)	34 (8.0)	8 (3.8)	61 (7.3)
Vascular Disorders				
Hypertension	8 (1.9)	13 (3.1)	3 (1.4)	21 (2.5)

*Does not include adverse events experienced by patients who switched to open label BID treatment.

Adverse events 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, dyspnea, ALT increased, AST increased, blood creatine phosphokinase increased and influenza.

An apparent imbalance in cardiac events related to coronary artery disease was noted, with cardiovascular ischemic events (including myocardial infarctions) occurring infrequently in the maraviroc groups but not at all in the placebo group. Six maraviroc treated patients (4 QD, 2 BID) reported 8 serious adverse events suggestive of coronary artery disease.

After adjusting for differences in duration of exposure (of about 2.5-fold), the disparity between maraviroc treatment groups and the placebo group with respect to frequency of certain adverse events (included in Table 54), already relatively unremarkable, diminishes further and often disappears altogether. Although events of upper respiratory tract infection, influenza, cough, rash, herpes simplex (although when combined with herpes virus, the rate in either maraviroc group does not exceed that in the placebo group by $\geq$ 3%), myalgia, dysuria, dyspnea, AST increased, ALT increased and blood creatine phosphokinase remained more frequent in at least 1 of the maraviroc groups than in the placebo group, the incidences of dizziness, insomnia, arthralgia and back pain become quite similar to placebo (<2-fold different) following adjustment for exposure (Table 55).

Table 55. Adverse Events Reported in Either Maraviroc Treatment Group at ≥2% at a Rate Exceeding that in the Placebo Treatment Group by 3% or 3-Fold, Adjusted for Exposure Per 100 Patient Years (Studies A4001027 And A4001028)

	Incidences per 100 Years of Patient Exposure		
	Maraviroc QD N= 414	**Maraviroc BID N= 426**	**Placebo N= 209**
Upper respiratory tract infection	15.8	17.7	11.6
Cough	14.3	19.4	10.5
Rash	11.1	13.5	8.5
Herpes simplex	5.6	10.2	6.1
AST increased	2.7	5.8	1.0
Myalgia	7.6	4.6	1.0
Dysuria	2.3	4.2	1.0
Dyspnea	5.1	4.2	2.0
ALT increased	2.7	3.8	1.0
Blood creatine phosphokinase increased	1.9	3.4	1.0
Influenza	5.5	2.3	0.0

QD = Once daily dosing; BID = Twice daily dosing.

The most common treatment-related adverse events (occurring in ≥5% of patients in the combined maraviroc treatment group) reported during the Phase 3 studies were diarrhoea, nausea, headache and fatigue. Most treatment-related adverse events reported at incidences of ≥2% in either of the 2 maraviroc regimens were reported at similar incidences in the placebo group.

Adverse events were analysed by racial group. No difference in adverse event profile was observed in any of the subgroups of patients compared with the overall population. However, these results should be interpreted in the context of small numbers for the non-Caucasian patient subgroups.

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.

Patients who experienced protocol-defined treatment failure at any time during therapy but whose virus remained CCR5-tropic had the option of changing to open label treatment with maraviroc BID. One hundred and nine (109) patients have received open label BID treatment with maraviroc in Studies A4001027 and A4001028 (original group). Of these, 64 (58.7%) reported at least 1 AE. Fewer patients reported adverse events whilst on open label therapy for Studies A4001027 and A4001028 than during blinded therapy. However, the spectrum of adverse events reported during open label treatment was similar to that reported on blinded therapy and less than half of the open label adverse events were considered to be treatment-related by the Investigator.

9.4. 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 led to discontinuation, which 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 (including liver enzyme 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.

9.5. Serious Adverse Events

Two serious adverse events were reported in Phase 1 studies, both unrelated to study treatment (Study A4001040, 1 subject - vasovagal syncope, A4001042, 1 subject - severely burned hands in a house fire).

No serious adverse events were reported during the conduct of the Phase 2a studies. However, a case of large B-cell non-Hodgkins lymphoma was diagnosed more than 3 years after completion of 10 days of maraviroc dosing. The Investigator causality was ‘possibly study drug related’; this event was reported following the publication of the vicriviroc data.

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 1.9% (maraviroc QD), 2.1% (maraviroc BID) and 1.0% (placebo) of patients experienced serious adverse events that were considered possibly treatment related by the Investigator. Table 56 provides brief details of these treatment-related serious adverse events.

Table 56. Treatment-Related Serious Adverse Events Reported During Phase 3 Studies A4001027 and A4001028

Study Drug	Study	Serious Adverse Event	Action (Re: Study Drug)
Maraviroc QD	A4001027	Hypersensitivity reaction and acute renal failure	Discontinued
Maraviroc QD	A4001027	Epigastric pain and vomiting	Discontinued
Maraviroc QD	A4001027	Worsening anemia	Discontinued
Maraviroc QD	A4001027	Pancreatitis	Temporarily discontinued; the subject later withdrew
Maraviroc QD	A4001027	Abdominal pain and nausea	Continued dosing and event resolved on therapy
Maraviroc QD	A4001028	Myositis	Discontinued
Maraviroc QD	A4001028	Aplastic anemia	Discontinued
Maraviroc QD	A4001028	Thrombosis (Chest pain)	Discontinued On Day 128 (chest pain Day 43) due to a number of none serious AEs. Thrombosis diagnosed approx 8 months post discontinuation
Maraviroc BID	A4001027	Heat exhaustion with rhabdomyolysis and elevated transaminases	Discontinued
Maraviroc BID	A4001027	Generalized rash	Discontinued
Maraviroc BID	A4001027	Mucormycosis myositis	Continued dosing event resolved
Maraviroc BID	A4001028	Increased nausea and vomiting	Temporary discontinuation No further episodes following recommencing therapy
Maraviroc BID	A4001028	Transaminase elevations	Discontinued
Maraviroc BID	A4001028	Syncope and pancytopenia	Discontinued
Maraviroc BID	A4001028	Diarrhea	Temporary discontinued. Restarted therapy with no further events
Maraviroc BID	A4001028	Syncope and orthostatic hypotension	Discontinued
Maraviroc BID	A4001028	Increased hepatic enzymes	Temporary discontinuation No further episodes after restarting therapy
Placebo	A4001028	Fever, worsening of dyspnea and acute renal failure	Temporary discontinuation. No further episodes after restarting therapy
Placebo	A4001027	Transient ischemic attack	Continued

* Patient subsequently permanently discontinued due to lack of efficacy.

During Study A4001029 there were 30 patients with at least 1 serious adverse event: 10 on maraviroc QD, 9 on maraviroc BID and 11 on placebo. Five patients in this study had serious adverse events which occurred whilst they were still in study but had been off drug for ≥28 days, and their events were assigned to 'In-Study-Off-Drug' (ISOD) as treatment group. There were 2 patients who experienced serious adverse events during the period between screening and initiating maraviroc treatment.

During Study A4001026 there were 21 treatment-naïve patients with serious adverse events in the discontinued maraviroc QD treatment arm. Four were considered treatment-related.

As the number of serious adverse events reported for the Phase 2b/3 clinical programme is modest given the advanced nature of disease in the patient population and the number of all-causality events was similar between treatment groups, no firm conclusions can be drawn as to the nature, likelihood and relationship of serious adverse events reported with maraviroc treatment compared with placebo.

9.6. Deaths

During the maraviroc Phase 2b/3 clinical development program (including Studies A4001026, A4001027, A4001028 and A4001029) there have been a total of 42 deaths reported up to the date of database cut off of 15 September 2006. Of these, 12 were reported during the 4-6 weeks period between the screening and randomization 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 ISOD patient previously randomised to maraviroc BID. Five deaths occurred in treatment naïve patients in Study A4001026 (maraviroc QD 2, maraviroc BID 1, efavirenz 2) and 25 patients died in the treatment experienced studies as discussed below.

Table 57 below provides brief details of deaths that occurred after start of study treatment (post-randomization) for Studies A4001026, A4001027, A4001028 and A4001029. Only 1 death, receiving open label maraviroc in Study A4001027, was considered as possibly related to study drug by the Investigator.

Table 57 Deaths Occurring Post-Randomisation in the Maraviroc Phase 2b/3 Clinical Program

Unblinded Treatment	Cause of Death	Total Days on Therapy	Days Post-Therapy	Related
Study A4001026 – Treatment-Naïve Patients Infected with CCR5 Tropic HIV-1[a]				
Maraviroc QD	Suicide	34	7	No
Maraviroc QD	Non-Hodgkin's lymphoma (confirmed)	*35*	*92*	*No*
Maraviroc BID	Liver failure; pneumonia.	*11*	*120*	*No*
Efavirenz	Castleman's Disease.	30	15	No
Efavirenz	Hodgkin's lymphoma (confirmed).	*11*	*180*	*No*
Study A4001027 – Treatment-Experienced Patients Infected with CCR5 Tropic HIV-1				
Maraviroc QD	Right cerebrovascular accident	11	2	No
Maraviroc QD	Respiratory failure.	84	19	No
Maraviroc BID	Stroke	142	2	No
Maraviroc BID Open Label [Randomised to maraviroc BID]	*HIV disease progression.*	*153 [including 50 days blinded therapy]*	*73*	*No*
Maraviroc BID Open Label [Randomised to placebo]	*Large B cell lymphoma (confirmed)*	*143 [74 days on blinded placebo]*	*39*	*Yes*
ISOD[b] [Randomised to maraviroc BID]	*Treatment-resistant giardiasis and end-stage AIDS.*	*82*	*>6 months*	*No*
Placebo	Pneumonia	88	On Treatment	No
Placebo	*Neck mass (Large Cell lymphoma)*	*298*	*84*	*No*
Study A4001028 – Treatment-Experienced Patients Infected with CCR5 Tropic HIV-1.				
Maraviroc QD	Anorexia	198	26	No
Maraviroc QD	Septic shock	79	2	No
Maraviroc QD	Myocardial infarction/acute heart failure/coronary artery atheroma.	206	On Treatment	No
Maraviroc QD	Bacterial pneumonia.	63	25	No
Maraviroc QD	*End stage HIV-1 disease.*	*56*	*249*	*No*
Maraviroc BID	Death (found dead)	62	1	No
Maraviroc BID	Pneumonia/endocarditis bacterial/multiple organ failure.	190	18	No
Maraviroc BID	HIV disease progression	18	1	No
Maraviroc BID	Worsening chronic obstructive pulmonary disease (COPD)	35	On Treatment	No
Maraviroc BID	*Central nervous system lymphoma*	*62*	*48*	*No*
Study A4001029 – Treatment-Experienced Patients Infected with Non-CCR5 Tropic HIV-1[c]				
Maraviroc QD	Pneumonia, possible chest mass.	63	6	No
Maraviroc QD	Advanced HIV/AIDS Infection	195	19	No
Maraviroc BID	*Pneumocystis carinii* Pneumonia	31	23	No
Maraviroc BID	*Bacterial pneumonia*	*88*	*29*	*No*
Placebo	Worsening renal failure/ ascites/ hemothorax/ disease progression.	92	On Treatment	No
Placebo	Multiple cerebral lesions	Unknown[d]	Unknown	No
Placebo	*Multifocal leucoencephalopathy.*	*36*	*29*	*No*

Those deaths italicized in this table are those that occurred more than 28 days after discontinuation of treatment.
[a] Study A4001026 is an ongoing study and therefore treatments remain blinded except for deaths and patient management. The maraviroc QD treatment group was unblinded due to lack of efficacy, as described previously.
[b] Patient in-study-off-drug, previously randomised to receive maraviroc BID.
[c] Patients were infected with dual/mixed, CXCR4-tropic or non-phenotypable HIV-1.
[d] This patient died on day 85 but dosing data is not available.

Deaths Occurring in the Phase 2b/3 Treatment-Experienced Studies

There were a total of 25 (2.0% of treated patients [N=1235]) 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 on treatment or 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 (Table 58).

Table 58.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 59 presents these deaths according to the patients' original randomised treatment.

Table 59. 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 proportion of deaths in each treatment group were similar for the 'as-treated' and 'as-randomized' 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.

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 randomization for a variety of HIV-1 disease related causes, which are presented in Table 60.

Table 60. Causality of Deaths for Patients During the Pre-Randomisation Period[a] (Studies A4001027, A4001028 and A4001029)

Study	Cause of Death
A4001027	Pneumonia/respiratory failure
	Pulmonary tuberculosis
	Nocardia infection
	Death – unspecified
A4001028	Progressive multifocal leucoencephalopathy
	Respiratory failure
	Asthenia/anorexia/dehydration/left hemiplegia
	Pneumonia
	Renal insufficiency
	Hematemesis/respiratory arrest
	Disease progression
A4001029	Coma

[a] 5-6 week period in between screening and randomization 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 (Table 61). 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 61. 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)**

[a] 5-6 week period in between screening and randomization visit. The same population was screened for all treatment-experienced studies.
[b] Number of patients screened for randomization 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 Prezista™ [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.

The finding for the maraviroc Phase 2b/3 clinical program should be seen in the context of a 2:2:1 randomization 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 62 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 62. 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 63).

Table 63. 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 darunavir 1.2% (MR 2.6) versus 0% (MR 0).

Conclusion

Overall, the mortality data for the maraviroc Phase 2b/3 clinical program indicate that maraviroc is not associated with an increased 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.

9.7. Special Safety Considerations

The following sections discuss the safety considerations reviewed throughout the maraviroc clinical program 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.

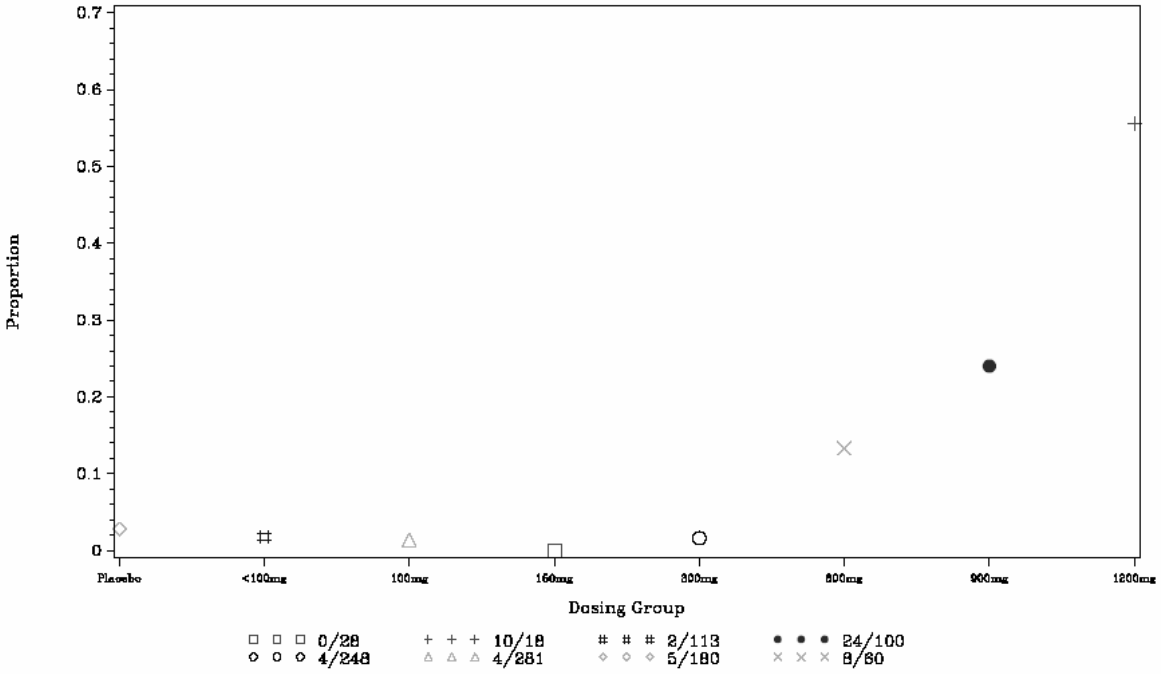
9.7.1. Cardiovascular Safety

Postural Hypotension:

Postural hypotension was identified as the dose limiting adverse event in the first Phase 1 single dose escalation study, which occurred at 1200 mg in 4 out of 9 subjects. Most of the postural events reported as adverse events in the Phase 1/2a studies occurred during protocol-defined postural blood pressure measurements. Events were coded as the Preferred Term 'postural hypotension' if the subject complained of symptoms of dizziness or

light-headedness on standing and had a recorded postural drop in blood pressure of greater than 20 mmHg systolic or 10 mmHg diastolic. If the subject was symptomatic without a recordable drop in blood pressure, this was recorded as 'dizziness on standing', which was coded as the Preferred Term 'dizziness'. If the subject was dizzy and could not stand for a BP reading, but the Investigator felt that postural hypotension was the most likely cause, the event was recorded as 'symptomatic postural hypotension', which was coded as the Preferred Term 'postural hypotension'. Events were rare at the therapeutic dose, with a similar rate to placebo; however, a dose response was demonstrated with the frequency increasing at unit doses ≥600 mg (Figure 17).

Figure 17. Observed Occurrence of Postural Hypotension by Unit Dose of Maraviroc in Phase 1/2a Studies



Subjects are counted at every exposure level that they had evaluable data. As such, a subject may appear more than once.

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 (Table 64).

Table 64. Number (%) of Patients with Postural Hypotension[a] in Phase 2b/3 Studies A4001027, A4001028 and A4001029

	Maraviroc QD (N= 477)	Maraviroc BID (N= 487)	Placebo (N= 271)
Baseline	15/399 (3.8)	14/423 (3.3)	6/235 (2.6)
Week 2	27/446 (6.1)	33/462 (7.1)	11/251 (4.4)
Week 24	16/311 (5.1)	19/323 (5.9)	5/117 (4.3)
Unplanned	0/11	1/17 (5.9)	1/11 (9.1)
Early Term	4/79 (5.1)	8/95 (8.4)	6/89 (6.7)

[a] Includes patients who experienced any of these criteria: decrease in supine to standing blood pressure of ≥ 10 mmHg (diastolic) or ≥ 20 mmHg (systolic), or a standing systolic blood pressure of < 90 mmHg.

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 (Table 65). In addition, there were no discontinuations due to postural hypotension in the Phase 2b/3 studies.

Table 65. Number (%) of Patients with AEs possibly related to Postural Hypotension in Studies A4001027 and A4001028, by Presence of Saquinavir/Ritonavir in OBT

	Maraviroc QD N=56	Maraviroc BID N=47	Placebo N=25
Hypotension	1 (1.8)	1 (2.1)	1 (4)
Orthostatic hypotension	0	2 (4.3)	0
Hypertension	0	1 (2.1)	0
Blood pressure diastolic increased	0	0	0
Blood pressure increased	0	0	0
Dizziness	7 (12.5)	3 (6.4)	0
Dizziness postural	0	1 (2.1)	0
Circulatory collapse	1 (1.8)	0	0
Loss of consciousness	0	1 (2.1)	0
Syncope	0	1 (2.1)	0

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.

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 repolarization 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 1541 ng/mL, which is approximately 10-fold the C_{max} at the therapeutic dose. 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.

Due to these pre-clinical findings there was detailed monitoring of ECG parameters during early clinical studies with maraviroc. Study A4001001 evaluated single doses of maraviroc, escalating to a maximum of 1200 mg. This maximum dose was associated with spontaneously observed postural hypotension in 4 of 9 subjects with associated changes in heart rate. ECG data collected in this study 2 hours after the 1200 mg dose showed a mean increase in QTcP (corrected for the specific population due to heart rate variability at this dose) of 7.8 msec; the corresponding QTcF value was 10.7 msec. The QTc observations from this study prompted the design of Study A4001016, a thorough QTc study. This was a single dose study in 30 male and 31 female healthy volunteers, at doses of 100, 300 and 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 1/2a studies. Due to the spontaneous cases of prolonged 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 upper limit of the 90% CI for the maximum difference between maraviroc 900 mg and placebo was less

than 7 msec, excluding a clinically meaningful effect at a supratherapeutic dose (Table 66). 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.

Table 66. Summary of Statistical Analysis of QTc Endpoints (Study A4001016)

Endpoint	Comparison	N	Adjusted Means (milliseconds)		Mean Difference[a] (90% CI)
			Active	Placebo	
QTcI at median Tmax[b]	Maraviroc 100 mg vs Placebo	59	399.67	400.39	-0.72 (-3.03, 1.59)
	Maraviroc 300 mg vs Placebo	58	400.84	400.59	0.24 (-1.85, 2.34)
	Maraviroc 900 mg vs Placebo	58	402.76	399.15	3.61 (1.01, 6.21)
	Moxifloxacin 400 mg vs Placebo	58	412.67	398.71	13.96 (11.49, 16.44)
Maximum Increase in QTcI from 1-4 hours after dosing	Maraviroc 100 mg vs Placebo	59	5.00	7.33	-2.33 (-4.44/-0.22)
	Maraviroc 300 mg vs Placebo	58	6.87	7.46	-0.59 (-2.55/1.37)
	Maraviroc 900 mg vs Placebo	58	8.68	7.70	0.98 (-0.85/2.80)
	Moxifloxacin 400 mg vs Placebo	58	21.11	8.18	12.93 (10.88/14.97)
Average QTcI from 1-4 hours post-dose	Maraviroc 100 mg vs Placebo	59	399.44	401.12	-1.68 (-3.29, -0.06)
	Maraviroc 300 mg vs Placebo	58	401.46	401.38	0.08 (-1.35, 1.50)
	Maraviroc 900 mg vs Placebo	58	401.95	400.76	1.19 (-0.30, 2.68)
	Moxifloxacin 400 mg vs Placebo	58	412.44	400.32	12.11 (10.68, 13.55)

[a] Difference between active and placebo
[b] Median Tmax for Maraviroc 100 mg = 3 hours, for Maraviroc 300 mg = 3 hours, for Maraviroc 900 mg = 2 hours, for Moxifloxacin 400 mg = 2 hours.

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 program] 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 program. 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.

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 program no clinically relevant effect was observed. Furthermore, on inspection of adverse event terms there was no evidence of an excess of adverse events suggestive of a potential for maraviroc to cause ventricular arrhythmias.

Cardiovascular Events Associated with Ischemia:

In Studies A4001027 and A4001028 the number of patients experiencing all causality cardiac-related adverse events were distributed between treatment groups; 12/414 (2.9%), 8/426 (1.9%) and 3/209 (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 5/414 (1.2%) patients in maraviroc QD treatment group and 5/426 (1.2%) patients in the maraviroc BID treatment group versus 0/209 (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, 2006) and the D.A.D. study (Friis-Møller N, 2003). Adjusted rates of myocardial infarction 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.

As would be expected for the patient population studied in the maraviroc Phase 2b/3 clinical program (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 factors, including diabetes mellitus, hypertension, previous myocardial infarction, known coronary artery disease, hyperlipidaemia and smoking. Dyslipidemia, insulin resistance and altered fat distribution are common in HIV infected adults who are receiving HAART), which appears to increase their risk of cardiovascular disease. Of note, there was an imbalance between the maraviroc-treated groups and the placebo group in Studies A4001027 and A4001028 with respect to past history of myocardial ischemia. Fourteen patients in the maraviroc QD group and 15 in the maraviroc BID group reported a previous myocardial infarction, compared to 1 in the placebo group. Other risk factors are typical for this advanced HIV population and balanced across treatment groups.

The only cardiovascular or cerebrovascular ischemic event reported in Study A4001029 was a myocardial infarction in the maraviroc BID treatment group. Study drug was continued and the event was described as unrelated to treatment.

No adverse events relating to myocardial ischemia have been reported from the patients who began open label maraviroc after initial failure on blinded therapy in Studies A4001027 and A4001028. One cerebral infarction and 1 cerebrovascular accident have been reported from that population.

No notable cardiac events were reported in Study A4001026.

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 patient-years exposure and follow-up for placebo.

9.7.2. Hepatic Safety

Hepatic safety was monitored throughout the maraviroc clinical program with regular liver function test (LFT) evaluations and a review of hepatic-related adverse events. For the Phase 2b/3 studies ACTG Grade 3 and 4 laboratory abnormalities are presented.

Phase 1/2a Studies:

There were LFT abnormalities observed during 4 of the Phase 1 maraviroc studies. These abnormalities were sporadic in nature, did not appear to be treatment- or dose-related and the transaminase elevations were not associated with hyperbilirubinemia. In addition no hepatic-related adverse events were reported during these studies. Two subjects discontinued treatment due to LFT abnormalities: a subject with abnormal LFTs in the placebo run-in phase (A4001008), and a subject who had an ALT 3.7x ULN at discontinuation on Day 10 of maraviroc 300 mg BID (A4001021).

A single HIV-1-infected subject in the Phase 2a Study A4001007 had an elevated ALT at baseline, which was further elevated on Day 5 of receiving maraviroc 300 mg BID and recorded as an adverse event. This event did not lead to discontinuation from the study and LFT values reduced whilst on therapy.

Phase 2b/3 Studies:

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). Given the high background rates of elevated liver enzymes in this population and in view of the unmet medical need, exclusion criteria of >5× ULN for transaminases and >2.5× ULN for bilirubin were used. However, for the treatment-naïve study, patients with transaminase values >3× ULN and bilirubin >1.5× ULN were excluded.

Hepatic-Related Adverse Events

For Studies A4001027 and A4001028, Grade 3/4 hepatic-related adverse events were reported at an incidence of 26 (6.3%), 37 (8.7%) and 12 (5.7%) in the maraviroc QD, BID and placebo treatment groups respectively (Table 67). 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, 11 (2.7%), 19 (4.5%) and 2 (1.0%) 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.

Table 67. Grade 3 and 4 Hepatic Adverse Events in Phase 3 A4001027 and A4001028

Event	Maraviroc QD		Maraviroc BID		Placebo	
	All causality	Treatment-related	All causality	Treatment-related	All causality	Treatment-related
Number of subjects	**414**		**426**		**209**	
Alanine aminotransferase increased	6 (1.4%)	3 (0.7%)	6 (1.4%)	4 (0.9%)	0	0
Aspartate aminotransferase increased	6 (1.4%)	4 (1.0%)	11 (2.6%)	7 (1.6%)	1 (0.5%)	0
Blood alkaline phosphatase increased	1 (0.2%)	1 (0.2%)	0	0	0	0
Blood bilirubin increased	3 (0.7%)	0	2 (0.5%)	0	1 (0.5%)	0
Cholecystitis	0	0	1 (0.2%)	0	0	0
Cholecystitis acute	0	0	1 (0.2%)	0	0	0
Cholelithiasis	0	0	0	0	1 (0.5%)	0
Cytolytic hepatitis	0	0	0	0	1 (0.5%)	1 (0.5%)
Gamma-glutamyltransferase increased	5 (1.2%)	2 (0.4%)	4 (0.9%)	4 (0.9%)	3 (1.4%)	0
Hepatic cirrhosis	0	0	2 (0.5%)	1 (0.2%)	0	0
Hepatic enzyme increased	0	0	1 (0.2%)	1 (0.2%)	0	0
Hepatic failure	1 (0.2%)	0	0	0	0	0
Hepatomegaly	0	0	0	0	1 (0.5%)	0
Hyperbilirubinemia	2 (0.5%)	0	4 (0.9%)	0	1 (0.5%)	0
Jaundice cholestatic	0	0	1 (0.2%)	0	0	0
Liver function test abnormal	1 (0.2%)	1 (0.2%)	2 (0.5%)	1 (0.2%)	2 (1.0%)	1 (0.5%)
Portal vein thrombosis	0	0	1 (0.2%)	0	0	0
Hepatitis toxic	0	0	0	0	1 (0.5%)	0
Transaminases increased	1 (0.2%)	0	1 (0.2%)	1 (0.2%)	0	0
Total number of Events	**26**	**11**	**37**	**19**	**12**	**2**

Five cases of ocular icterus were reported (3 Grade 1 and 2 Grade 2); 2 in the maraviroc QD group and 3 in the maraviroc BID group. Three of these cases were attributed to atazanavir, 1 to study drug and 1 to disease under study. Nine events of jaundice were reported by 8 patients (5 in maraviroc QD, 3 in maraviroc BID and 1 in placebo). All the patients on maraviroc QD received concomitant atazanavir, as was the patient receiving placebo and 1 of the 3 patients receiving maraviroc BID. The only case of treatment-related jaundice occurred on maraviroc BID; jaundice was reported on Day 2; no abnormal bilirubin was recorded and the patient withdrew consent on Day 15. The third patient, receiving maraviroc BID, had an event of cholestatic jaundice on Day 19, which was attributed to an opportunistic infection.

One adverse event each of 'liver tenderness', 'hepatitis C' and 'hepatic enzyme increased' and 4 adverse events of 'GGT increased' have been reported from the 109 patients who began open label maraviroc after initial failure on blinded therapy in Studies A4001027 and A4001028.

A review of the serious adverse event database, from Studies A4001027, A4001028 and A4001029, also revealed that more 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). This led to permanent discontinuation in 2 patients and temporary discontinuation in the third patient. No serious adverse events of a hepatobiliary nature have been reported from the 109 patients who began open label maraviroc after initial failure on blinded therapy in Studies A4001027 and A4001028. Table 68 presents hepatobiliary serious adverse events related to study drug during the maraviroc Phase 2b/3 clinical program.

Table 68. Hepatobiliary System Serious Adverse Events Related to Study Drug in Studies A4001027, A4001028 and A4001029

Drug Dose or Placebo	Study	Event	Start date Stop date	Outcome Action ***Investigator Causality***
Maraviroc QD	A4001028	Blood bilirubin increased	82 >112	**Still present** No action *Concomitant treatment-atazanavir*
Maraviroc QD	A4001029	Hepatitis (also pancreatitis)	20 days post therapy-	**Recovered** Not related *Disease under study*
Maraviroc QD	A4001027	Hepatic failure	35/42	**Resolved** Permanently discontinued *Other event – possibly related to recreational drug use or interaction with antiretrovirals, also Campylobacter septicemia.*
Maraviroc BID	A4001028	ALT	127 135	**Resolved** Permanently discontinued *Study Drug*
		AST	127 134	**Resolved** Permanently discontinued *Study Drug*
Maraviroc BID	A4001027	ALT increased	55 77	**Resolved** No action taken *related to Hepatitis B*
		AST increased	55 77	**Resolved** No action taken *related to Hepatitis B*
Maraviroc BID	A4001028	Hepatic enzyme increased	150 >150	**Still present** Study drug stopped temporarily *Study drug*
Maraviroc BID	A4001027	Hyperbilirubinemia	42 >42	**Still present** Permanently discontinued *Other illness – HCV/alcohol*
Maraviroc BID	A4001027	Transaminase increased	187 193	**Resolved** Permanently discontinued *Study drug*
Maraviroc BID	A4001028	Jaundice Cholestatic	11 19	**Resolved** No action taken *Other event – opportunistic infection.*

Table 68. Hepatobiliary System Serious Adverse Events Related to Study Drug in Studies A4001027, A4001028 and A4001029

Drug Dose or Placebo	Study	Event	Start date Stop date	Outcome Action *Investigator Causality*
Maraviroc BID	A4001027	Hepatic cirrhosis	18 >18	**Still present** No action taken *Other event – portal vein thrombosis*
Maraviroc BID	A4001027	Cholecyctitis	134 206	**Resolved** No action taken *Other event – other illness*
Placebo	A4001027	Hepatomegaly	96 101	**Resolved** No action taken *Other event – rule out malignancy*
Placebo	A4001027	Gamma-Glutamyltransferase	1 14	**Resolved** No action taken *Other event - hepatitis*

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; QD = Once daily dosing; BID = Twice daily

For the 3 treatment-related serious adverse event cases initially attributed to study treatment, an alternative non-study-drug cause has been identified following thorough review of the details by the company internal medical review committee and two independent external experts. The events occurred at Day 127, 150 and 187 of therapy; two of these subjects permanently discontinued study drug and the other temporarily discontinued study drug.

- A 49 year old male patient, experienced Grade 4 transaminase elevations on Day 127 of treatment with maraviroc BID. This patient was also receiving OBT, which included enfuvirtide, lamivudine, abacavir, tipranavir, ritonavir. He was clinically stable and well. Study drug and OBT were discontinued as the consulting hepatologist indicated that the abnormalities were compatible with drug hepatotoxicity. These events were considered related to study drug, tipranavir and ritonavir by the Investigator. The transaminases subsequently normalized, but the subject permanently discontinued from the study because of treatment (virologic) failure.

- A 63 year old male patient received maraviroc BID for a total of 177 days. He had elevated transaminases on 2 separate occasions. On Day 3 he had a Grade 3 elevation in transaminase which occurred at the time of a nevirapine hypersensitivity reaction. On Day 184 he experienced heat exhaustion with rhabdomyolysis, which was still ongoing when on Day 187 he had another serious adverse event of elevated Transaminases and was discontinued from the study. Although the transaminase elevation was reported separately and ascribed to study drug by Investigator, it seems likely that it was related to the previously reported event. He was diagnosed with hepatic cirrhosis on Day 190.

- A 61 year old white male patient experienced increased hepatic enzymes from Day 150 of treatment with maraviroc BID. This was considered related to study drug by the Investigator. Study drug and OBT were temporarily discontinued. ALT and AST

subsequently normalized and remained within normal limits after study drug was restarted. The subject later developed aortic valve endocarditis with *Streptococcus pneumoniae* and died.

The case of hepatic failure was unrelated to study drug and is described below.

- A patient receiving maraviroc QD experienced hepatic failure on Day 35 of treatment. This event was Grade 4 and it was considered related to another factor (possible interaction between a recreational drug and antiretrovirals) by the Investigator. The subject was also septic from *Campylobacter jejuni* with disseminated intravascular coagulation and subsequently admitted to crystal methamphetamine use. Study drug was permanently discontinued and the event resolved.

Overall, 11 patients discontinued from study drug due to hepatic-related adverse events in the Phase 3 registrational studies; 4 (1.0%) in the maraviroc QD treatment group, 5 (1.2%) in the maraviroc BID treatment group and 2 (1.0%) in the placebo treatment group. When corrected for exposure the discontinuation rate was evenly distributed between treatment groups.

Of the patients who temporarily discontinued study drug due to hepatic events 6 were rechallenged, as described below; the LFT abnormalities resolved for 3 patients; for a further 3, LFT abnormalities persisted but patients were able to continue study drug to time of data cut or discontinuation due to other causes.

- A patient in Study A4001027 receiving maraviroc BID temporarily discontinued study drug due to increased AST. Increased AST started on Day 15 of treatment and resolved on Day 27. Study drug was restarted and no further increases in AST were reported. The patient had taken study drug up to Day 334 at the date of cut-off.

- A 61 year old white male patient in Study A4001028 receiving maraviroc BID, experienced increased hepatic enzymes from Day 150, which was considered related to study drug by the Investigator. Study drug and OBT were temporarily discontinued. ALT and AST normalized and remained within normal levels after study drug was restarted. The patient subsequently developed aortic valve endocarditis with *Streptococcus pneumoniae* and died.

- A patient in Study A4001028 receiving maraviroc BID temporarily discontinued study drug due to increased AST and blood creatine phosphokinase. Study drug was temporarily stopped due to increased AST from Day 15 to 22 and increased creatine phosphokinase from Day 15 to 22 and Day 29 to 37. These resolved and the patient had taken study drug up to Day 182 at the time of cut-off.

- A patient in Study A4001028 receiving maraviroc QD temporarily discontinued study drug due to increased ALT and AST. This patient had elevated ALT and AST at baseline and had increased ALT from Day 59 to 65. The abnormalities resulting in temporary discontinuation started on Day 85 and were lower on Day 93. Study drug was restarted. Although ALT and AST had decreased on Day 93 these parameters

remained above ULN for the remainder of the study. The patient had taken study drug up to Day 164 at time of loss to follow up.

- A patient in Study A4001027 receiving maraviroc BID temporarily discontinued study drug due to increased ALT, AST and GGT. These elevations were first reported on Day 147 and did not resolve. Study drug was restarted and there were no further elevations in LFTs. The patient had taken study drug up to Day 173 at the date of cut-off.

- A patient in Study A4001028 receiving maraviroc BID temporarily discontinued study drug due to increased ALT, AST and GGT. This adverse event started on Day 283 and did not resolve. The patient had taken study drug up to Day 323 at the date of cut-off.

The negative rechallenge in these patients illustrates the difficulty in definitively assessing the causality of hepatic enzyme abnormalities in a population that consists of patients being treated with multiple medications for complex and often serious conditions, many of which might cause hepatic abnormalities.

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 program has occurred in Study A4001026 in a treatment-naïve patient randomised to receive maraviroc QD and is described below. 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.

- A 24 year old Asian female patient, who had increased LFTs at baseline (normal at screening) after having initiated trimethoprim-sulphamethoxazole and isoniazid therapy 7 weeks prior to commencing maraviroc in Study A4001026, presented with pyrexia, rash and elevated liver function test on Day 5 of dosing with maraviroc (had erroneously been receiving 150 mg QD). Although maraviroc dosing was discontinued, she continued to receive drugs that have been implicated in hepatotoxicity for several more days (including intravenous acetaminophen for fever, lopinavir/ritonavir, zidovudine/lamivudine and trimethoprim-sulphamethoxazole). Her condition deteriorated and she received a liver transplant on Day 16. The abnormal liver function tests at baseline (increased from normal values at screening) indicate that trimethoprim-sulphamethoxazole and isoniazid (which were initiated at the screening visit) are most likely to have been the cause of her hepatic dysfunction. Rash and fever are typical of trimethoprim-sulphamethoxazole toxicity, although the hepatic abnormalities are less common. Of note is that the patient was rechallenged with trimethoprim-sulphamethoxazole post-transplant without ensuing derangements in transaminases or bilirubin, although the outcome of this rechallenge may be

confounded by the presence of immunosuppressive agents. This patient was found to possess the NAT2 alleles that are associated with slow acetylation phenotype and an increased risk of isoniazid induced hepatitis, and CYP21E genotype that is also associated with increased susceptibility to hepatoxicity in slow acetylators. Although it is not possible to exclude a causative role for maraviroc in this case of hepatotoxicity, isoniazid and trimethoprim-sulphamethoxazole are thought the more likely causal factors. The DSMB subsequently recommended that isoniazid use be excluded from the maraviroc Phase 2b/3 program and Bactrim™ to be introduced at least 60 days before maraviroc therapy.

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

Liver Function Tests

LFTs were performed at screening, baseline and at the 2-week and 1-month visits, and then monthly until 24 weeks. Thereafter they were assessed every 8 weeks.

The numbers of patients with grade 3 or 4 LFT abnormalities were low and fairly evenly distributed across the treatment groups (Table 69). Although there were slightly higher numbers of Grade 3 and 4 AST abnormalities in the maraviroc BID treatment group, for ALT the numbers of patients with such abnormalities were higher in the placebo and maraviroc QD groups. Most bilirubin abnormalities were associated with concomitant atazanavir use.

Table 69. Frequency of Grade 3/4 LFTs in Studies A4001027 and A4001028

	Maraviroc QD (N= 408)			**Maraviroc BID (N= 421)**			**Placebo (N= 207)**		
	Gr 3	Gr 4	**Gr 3+4**	Gr 3	Gr 4	**Gr 3+4**	Gr 3	Gr 4	**Gr 3+4**
AST	11	2	**13 (3.2%)**	13	6	**19 (4.5%)**	6	0	**6 (2.9%)**
ALT	14	1	**15 (3.7%)**	6	4	**10 (2.4%)**	6	1	**7 (3.4%)**
Bilirubin	28	4	**32 (7.8.%)**	21	3	**24/420 (5.7%)**	8	3	**11/206 (5.3%)**

The patient with hepatic failure (maraviroc QD – Grade 4 ALT and AST and Grade 3 bilirubin) does not appear in this table.

Shifts in ALT levels, generally considered the most sensitive biomarker for hepatotoxicity (since AST is also present in muscle), are presented in Table 70. Three patients with normal or Grade 1 abnormal baseline ALT experienced an increase to a Grade 4 level, 1 in each treatment group.

Table 70. Shift Table for Liver Function Test Maximum ALT Value on Treatment versus Baseline, Studies A4001027 and A4001028

	Maximum Alanine Aminotransferase ALT (IU/L)														
	Ungraded			Grade 1			Grade 2			Grade 3			Grade 4		
	N			N			N			N			N		
Baseline	**QD**	**BID**	**Pbo**	**QD**	**BID**	**Pbo**	**QD**	**BID**	**Pbo**	**QD**	**BID**	**Pbo**	**QD**	**BID**	**Pbo**
Ungraded	232	241	110	71	57	35	8	21	8	6	1	2	0	1	1
Grade 1	25	23	14	37	39	21	9	14	5	2	0	1	1	0	0
Grade 2	2	2	0	5	7	5	4	4	2	4	4	2	0	2	0
Grade 3	0	0	0	0	0	0	0	3	0	2	1	1	0	1	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL	259	266	124	113	103	61	21	42	15	14	6	6	1	4	1

Pbo – placebo
Ungraded - <1.25 ULN; Grade 1 - ≥1.25 ULN to ≤2.5 ULN; Grade 2 - >2.5 ULN to ≤5.0 ULN; Grade 3 - >5.0 to ≤10.0 ULN; Grade 4 - >10.0 ULN.
Shading represents no change in grade from baseline to last on treatment value.
Only patients with both a valid baseline and an on-treatment value for the parameter were included in the table.
The patient with hepatic failure (maraviroc QD – Gr 4 ALT and AST and Gr 3 bilirubin) does not appear in this table.

In each maraviroc treatment group, 101 subjects increased their ALT by a Grade or more compared with 54 subjects on placebo. For normal baseline ALT the frequency of subjects with a Grade 3 or 4 ALT abnormality was equivalent to placebo for QD dosing but slightly lower than placebo for BID dosing. For an abnormal baseline ALT the frequency of subjects with a Grade 3 or 4 ALT abnormality was equivalent to placebo for BID maraviroc but slightly higher for QD maraviroc. In summary, there is no evidence of a greater shift from baseline in subjects receiving maraviroc and there does not appear to be a clinically significant difference between the BID and the QD doses.

No Grade 3 or 4 LFT abnormalities have been identified from among 99 patients evaluable for laboratory data who began open label maraviroc after initial failure on blinded therapy in Studies A4001027 and A4001028.

Eight patients were recorded to have Grade 3 or 4 ALT abnormalities during the double-blind treatment phase of maraviroc QD in Study A4001026; just 2 of 129 patients were observed to have Grade 3 or 4 elevations during the maraviroc BID open label phase.

Analysis of those cases that showed an increase in either ALT or AST >3x ULN combined with an increase in total bilirubin >3 mg/dL is presented in Table 71. Such elevations, without evidence of biliary obstruction and in the absence of any other evident possible explanation ('Hy's Law', first proposed in 1978 by Hyman Zimmerman), are an ominous marker for drug-induced liver injury. 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 noted in these studies with an increase of ≥3 ×ULN in ALT or AST and a simultaneous increase of ≥3 mg/dL in total bilirubin had an identifiable cause for these abnormalities apart from study drug. Therefore no subjects met the criteria for Hy's Law.

Table 71. Cases with Episode of >3x ULN Transaminases and >3 mg/dL Total Bilirubin in Studies A4001027 and A4001028

Dose	Time of event (Week)	Alternative pathology	Hy's Law
Maraviroc QD	16	Atazanavir	No
Maraviroc QD	2	Atazanavir	No
Maraviroc QD	5	Campylobacteremia, methamphetamine use	No
Maraviroc BID	48	Atazanavir	No
Maraviroc BID	8	Alcohol , active HCV	Possible
Maraviroc BID	2	Cholestatic jaundice	No
Maraviroc BID	8	Atazanavir	No
Placebo	4	Atazanavir	No

The numbers of patients enrolled in the Phase 3 trials co-infected with HCV (HCV RNA positive at baseline) and HBV (HBsAg positive at screening) were low. Co-infection rates with HCV were 4%, 7% and 9% and for HBV were 5%, 7% and 3% for maraviroc QD, maraviroc BID and placebo groups, respectively, making it difficult to interpret adverse event data in these subgroups.

Table 72. Percentage of Co-infected Patients with a Grade 3 or 4 abnormality regardless of baseline in Studies A4001027, A4001028 and A4001029

		Co-infection positive			Co-infection negative		
HCV or HBV co-infection		Maraviroc QD	Maraviroc BID	Placebo	Maraviroc QD	Maraviroc BID	Placebo
HCV RNA detectable	ALT	3/20	2/30	1/20	13/448	8/449	8/243
HBV Surface Ag positive	ALT	0/26	1/31	2/22	15/438	9/447	7/240

Patients may appear be co-infected with both HCV and HBV

Although the numbers are small, it appears that within both the HCV and HBV co-infected populations, Grade 3 and 4 hepatic abnormalities are evenly distributed among the treatment groups (Table 72). Generally, the frequency of Grade 3 and 4 hepatic events is higher in hepatitis co-infected patients, as might be expected.

No hepatobiliary AEs were reported for patients in the Phase 3 maraviroc QD and placebo groups who were co-infected with HCV. However, there were 4 (14%) events reported in patients who received maraviroc BID (cholecystitis, cholelithiasis, hepatosplenomegaly and hyperbilirubinemia). In the HBV co-infected subjects (Phase 3), there was only 1 adverse event, a case of cytolytic hepatitis on placebo.

In patients co-infected with HCV at baseline, HCV RNA was measured again at Week 12 and Week 24. By Week 24 the mean HCV RNA in subjects in both maraviroc arms was reduced relative to baseline, but in placebo patients it had increased. However the subject numbers are very small and data are highly variable (Table 73).

Table 73. Summary of Change from Baseline for Hepatitis C Viral Load (IU/mL) by Visit (Studies A4001027 and A4001028)

		Change in Hepatitis C Viral Load (IU/mL)		
		Maraviroc QD (N=414)[a]	**Maraviroc BID (N=426)[a]**	**Placebo (N=209)[a]**
Week 12	N[b]	12	23	15
	Mean (SD)	-1137333.3 (5025853)	1205752.2 (24216112)	2373733.3 (9707908)
	Median (min, max)	-1570000.0 (-10270000, 9980000)	3180000.0 (-94400000, 32680000)	2780000.0 (-21730000, 20703000)
Week 24	N[b]	7	23	7
	Mean (SD)	-3928571.4 (5882345)	-6346873.9 (28055243)	2597214.3 (9165602)
	Median (min, max)	-4790000.0 (-12400000, 4020000)	380000.0 (-127300000, 13420000)	40000 (-8033500, 21803000)
Early Termination	N[b]	2	1	N/A
	Mean (SD)	-1700 (2404)	8300000	N/A
	Median (min, max)	-1700 (-3400, 0)	N/A	N/A

[a] Number of patients in treatment group.
[b] Number of patients contributing to summary statistics.
Table contains patients with baseline hepatitis C only.
Baseline refers to the baseline visit.
QD = Once daily dosing; BID = Twice daily dosing; N/A = Not available.

Conclusion

Although there were a higher number of patients in the maraviroc BID treatment group (in Studies A4001027 and A4001028), 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. An additional patient in Study A4001026 experienced severe hepatotoxicity, which resulted in a liver transplant. Although this case was considered possibly related to study drug it is complicated by the co-administration of multiple other drugs, which are known to be associated with alterations in liver function. In Studies A4001027 and A4001028 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. However, from the population pharmacokinetic-pharmacodynamic analysis from the patients in Studies A4001027 and A4001028 there were no exposure related increases in the change from baseline for ALT and AST identified at Weeks 4 and 24.

Overall, the clinical and laboratory data for the maraviroc clinical development program indicates that any adverse effect on hepatic function in patients receiving maraviroc is unlikely.

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

In treatment-experienced patients infected with CCR5 tropic HIV-1 (Studies A4001027 and A4001028) adverse events relating to the MedDRA system organ class 'infections and infestations' were reported for 198 (48%), 214 (50%) and 80 (38%) patients in the maraviroc QD and BID and placebo groups, respectively. The infections with higher frequencies among maraviroc patients tended to be either those common in the general healthy population (such as respiratory tract infections) or opportunistic infections common in the treatment-experienced population (such as *Candida*, herpes and staphylococcal infections). Indeed, when the frequency of all infections was adjusted for exposure, no clear difference was observed between treatment groups: 121 per 100 patient-years for maraviroc QD, 126 per 100 patient-years for maraviroc BID and 118 per 100 patient-years for placebo. The difference between treatment groups in the non-adjusted analysis may therefore be explained by the longer treatment duration in the maraviroc treatment arms. No unusual infections occurred and there was no clear difference in the severity of the infections between treatment groups, with most being mild to moderate in severity. The overall incidence of adverse events related to infection or infestation was not affected by the baseline value of CD4 count in the maraviroc treatment groups.

Four deaths due to infection were reported (Table 74). One death occurred in the placebo arm, compared to 2 in the maraviroc QD and 1 in the maraviroc BID treatment arms.

Table 74. Death Resulting from Infections in Phase 3 Studies A4001027 and A4001028

Event	CD4 count (cells/μl)		Length of treatment (days)	Treatment	Time to death (days)
	At Baseline	At Time of death (or closest timepoint)			
Septic shock	63	92 (55)	79	Maraviroc QD	81
Pneumonia Bacterial	0	3 (30)	63	Maraviroc QD	88
Pneumonia, Endocarditis bacterial	111	101 (169)	190	Maraviroc BID	208
Pneumonia	231	256 (57)	88	Placebo	88

It is worth noting that 11 subjects died in the 5 to 6 weeks between screening and randomization, including 5 deaths due to infections, which reflect the advanced stage of disease of this study population.

Category C Events:

In Studies A4001027 and A4001028, there were 48 subjects reporting Category C infections, with a similar incidence in the 3 treatment groups 23 (5.6%), 16 (3.8%) and 9 (4.3%) in maraviroc QD, BID and placebo groups (Table 75). Herpes simplex and esophageal candidiasis were the most commonly reported, with slightly higher proportion 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.

Table 75. Incidence of Category C AIDS-defining Infections in Studies A4001027 and A4001028

	Maraviroc QD N (%)	**Maraviroc BID N (%)**	**Placebo N (%)**
N	**414**	**426**	**209**
Candidiasis	2 (0.5)	1 (0.2)	0
Cytomegalovirus choriortinitis	2 (0.5)	0	0
Cytomegalovirus gastrointestinal infection	0	1 (0.2)	0
Cytomegalovirus infection	0	1 (0.2)	0
Gastroenteritis cryptosporidial	0	0	1 (0.5)
Herpes simplex	7 (1.7)	6 (1.4)	1 (0.5)
Herpes virus infection	3 (0.7)	0	1 (0.5)
Lobar pneumonia	0	0	1 (0.5)
Mycobacterial infection	0	1 (0.2)	0
Mycobacterial avium complex infection	0	1 (0.2)	3 (1.4)
Esophageal candidiasis	11 (2.7)	2 (0.5)	2 (1.0)
Pneumocystis jiroveci pneumonia	0	2 (0.5)	0
Pneumonia	1 (0.2)	0	1 (0.5)
Pneumonia bacterial	0	0	1 (0.5)
Progressive multifocal leukoencephalopathy	0	1 (0.2)	0
Total subjects	23 (5.6)	16 (3.8)	9 (4.3)
Total events	**26**	**16**	**11**

One patient experienced exacerbation of CMV retinitis, which occurred 21 days post-therapy and pre-open label maraviroc and therefore does not appear in the above table. A brief narrative for this patient is included below.

- A 37-year-old white male with a screening viral load of 4.91 $\log_{10}$ copies/mL and a screening CD4 cell count of 3 cells/μL, with a past history of CMV retinitis, HIV-associated wasting and herpes simplex virus infection. The patient received 28 days of blinded study drug (maraviroc 150 mg BID) until early termination due to lack of efficacy. On Day 21 post therapy, he was diagnosed with bilateral progression of CMV retinitis. The patient had been on valganciclovir which was continued. He was started on open label maraviroc BID 10 days after the diagnosis of CMV exacerbation was made. The event was considered moderate in severity, not related to study drug and resolved on Day 41 of open-label therapy.

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.

Two recurrent Category C AIDS defining infections were reported by 3 patients: Patient 12040014 (maraviroc QD; A4001028) and Patient 10200001 (maraviroc BID; A4001028) each had 2 episodes of esophageal candidiasis, and Patient 10500013 (maraviroc QD; A4001027) had 2 episodes of herpes simplex virus. 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.

There was no evidence of any adverse effect on immune function in Study A4001029 in treatment-experienced patients infected with non-CCR5 tropic HIV-1. Adverse events of infections or infestations have been reported for 27 of the 109 patients who began open label maraviroc after initial failure on blinded therapy in Studies A4001027 and A4001028, of which the most commonly reported were condyloma acuminatum and nasopharyngitis, each with 5 events.

The incidence of category C infections was low in Study A4001026 in treatment-naïve patients infected with CCR5 tropic HIV-1. Six treatment-emergent category C AIDS-defining illnesses were reported in the maraviroc 300 mg QD treatment group (2 cases of tuberculosis, 3 cases of *Pneumocystis* pneumonia and 1 case of Kaposi's sarcoma), 3 of which were categorized as serious adverse events. There were no category C infection events in the open label maraviroc 300 mg BID group.

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 was 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 such infections are common in this population and difference in duration of exposure and follow-up may explain the difference in frequency.

Malignancies:

Infection with HIV-1 increases the risk of Kaposi's sarcoma, non-Hodgkin's lymphoma and a number of malignancies, including cervical cancer, lip cancer, lung cancer, connective tissue cancer, anal and penile cancer, testicular seminoma, multiple myeloma and leukaemia.

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. Table 76 presents the incidence of malignancies from Studies A400107 and A4001028 by patient's baseline CD4 cell count.

Table 76. Incidence of Malignancies by Baseline CD4 Cell Count, Studies A4001027 and A4001028

	Maraviroc QD	Maraviroc BID	Placebo
Malignancies at CD4 ≥50 cells/μL	**N= 325 (%)**	**N= 340 (%)**	**N= 171 (%)**
Anal cancer	1 (0.3)	3 (0.9)	2 (1.2)
Basal cell carcinoma	1 (0.3)	1 (0.3)	0
Bowens disease	0	1 (0.3)	0
Diffuse large B cell lymphoma	0	0	1 (0.6)
Kaposi's sarcoma	0	0	1 (0.6)
Lymphoma	1 (0.3)	0	1 (0.6)
Metastases to liver	1 (0.3)	0	0
Esophageal carcinoma	1 (0.3)	0	0
Squamous cell carcinoma	1 (0.3)	0	1 (0.6)
Squamous cell carcinoma of the skin	1 (0.3)	0	0
Sweat gland tumor	0	1 (0.3)	0
Tongue neoplasm	0	1 (0.3)	0
Malignancies at CD4 <50 cells/μL	**N= 88 (%)**	**N=86 (%)**	**N=37 (%)**
Anal cancer	2 (2.3)	0	1 (2.7)
Kaposi's sarcoma	1 (1.1)[a]	2 (2.3)	2 (5.4)
Lymphoma	1 (1.1)	1 (1.2)	0

[a] One testicular neoplasm was actually a Kaposi's sarcoma so has been included here

One event of anal cancer occurring in the maraviroc BID treatment group was noted to be due to a relapse. One subject (A4001028) in the maraviroc QD treatment group had a past medical history of adenocarcinoma of the colon and was reported to have developed liver metastases during the study.

Treatment-emergent benign neoplasms not included are: 1 benign neoplasm of the orbit (maraviroc QD), 2 events of seborrheic keratosis (maraviroc BID), 2 hemangiomas (maraviroc QD), 22 events of skin papilloma (11 maraviroc QD, 8 maraviroc BID and 3 placebo) and 1 sweat gland tumor (maraviroc QD).

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 a patient in Study A4001028 receiving maraviroc BID, with the presumptive central nervous system lymphoma. When a patient 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 the patient on open label in A4001027) and 2 on placebo – ie 7 cases reported in 1049 patients with CCR5 tropic HIV-1 infection. When the randomization schedule of 2:2:1 is considered, even without the longer exposure duration in the two maraviroc treatment groups, this also demonstrates no difference in frequency of lymphoma between maraviroc and placebo. This is in contrast to the lymphoma rate reported in ACTG 5211 where 4 lymphomas, albeit 2 Hodgkin's, were reported following vicriviroc therapy in 90 CCR5-tropic HIV-1 infected patients. The cases of lymphoma reported during the maraviroc clinical program are presented in Table 77.

Table 77 Cases of Lymphoma Reported During the Maraviroc Clinical Program

Study No.	Treatment	Event Name: Preferred Term	Active/Post-treatment	Start Date of Event[a]	Scr[b] CD_4 (cells/μL)	Scr[b] HIV-1 RNA(log_{10})	Patient Disposition	Biopsy	Definite	Related	Death[c]
A4001007	Maraviroc BID (100 mg 10 days monotherapy)	Large cell B-cell non-Hodgkin lymphoma	Post	>2 years	698	3.99	Post-study	Yes	Yes	Yes	No
A4001026	Maraviroc QD	Non-Hodgkin's Lymphoma	Active	36	434	5.13	Discontinued on day 35	Yes	Yes	No	Yes
	Still blinded	Non-Hodgkin's Lymphoma	Active	108	232	5.42	Ongoing	Yes	Yes	No	No
	Still blinded	Hodgkin's lymphoma	Active	11	96	5.69	Discontinued on day 15	Yes	Yes	No	No
	Efavirenz	Hodgkin's lymphoma	Active	11	87	5.78	Discontinued on day 11	Yes	Yes	No	Yes
	Efavirenz	*Castleman's disease*	*Active*	*33*	*218*	*5.15*	*Discontinued on Day 30*	*Yes*	*No*	*No*	*Yes*
A4001027	Maraviroc QD	B cell lymphoma	Active	25	55	4.88	Discontinued day 176	Yes	Yes	No	No
	Placebo	Large cell lymphoma	Active	118	144	4.01	Discontinued day 298	Yes	Yes	No	Yes
	Placebo	Large B-cell lymphoma	Active	209	178	4.83	Ongoing	Yes	Yes	No	No
	Placebo to day 85 MVC BID OL from day 1-143	Large B-cell lymphoma	Post Blinded Active (OL)	146 (OL phase)	191	5.4	Discontinued OL MVC on day 143	N/K	Yes	Yes	Yes
A4001028	Maraviroc BID	B cell lymphoma	Active	7	26	5.82	Ongoing	Yes	Yes	No	No
	Pre-randomisation	Hodgkin's lymphoma	N/A	N/A	150	3.8	Pre-randomisation	N/K	Yes	No	No
	Maraviroc QD	Non-Hodgkin's Lymphoma	Active	75	107	5.16	Discontinued day 79	Yes	Yes	No	Yes
	Maraviroc BID	*CNS lymphoma*	*Active*	*40*	*4*	*5.53*	*Discontinued day 62*	*No*	*No*	*No*	*Yes*

[a] Relative days post **initiation** of blinded study drug
[b] If screening value was not available, baseline value is given
[c] last information known to sponsor
Cases in italics are possible lymphoma
** Histology possible plasmablastic, large cell lymphoma*
*** Presumptive CNS lymphoma not biopsy confirmed.*
N/K = not known

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 program 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 program. 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 consistent with what would be expected from this population.

9.8. 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 phosphokinase, where larger mean increases were observed in the maraviroc treatment arms compared with the placebo group.

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 effects on lipid parameters were also observed in Study A4001029.

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. Sporadic 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 and by the higher rate of abnormal baseline values. In addition, from the population pharmacokinetic-pharmacodynamic analysis from the patients in Studies A4001027 and A4001028 there were no exposure related increases in the change from baseline identified at Weeks 4 and 24.

Three patients in Studies A4001027 and A4001028 reported adverse events of rhabdomyolysis or myositis and discontinued study drug.

- A 63 year old male, received maraviroc BID for a total of 177 days in Study A4001027. He experienced heat exhaustion with rhabdomyolysis on Day 184. He had elevated creatine kinase on Day 1 (423 U/L) which increased to 3318 U/L by Day 3, but returned to normal by Day 8. All other creatine kinase values up to Day 193 (when a minor increase to 215 U/L was recorded) were within normal limits. He also had elevated transaminases on 2 separate occasions starting on Day 2 and then again on Day 177 and, at that time, he was discontinued from the study. The elevated transaminases were considered related to study drug by the Investigator.

- A patient in Study A4001027 presented on Day 7 with rhabdomyolysis, candidiasis and hyponatremia. Study drug (maraviroc BID) was temporarily discontinued. The rhabdomyolysis had resolved on Day 10 and was considered related to concomitant therapy. Creatine kinase was increased at baseline (345 U/L), and further increased to 501 U/L by Day 21. The Day 28 value was 466 U/L. Serum sodium was normal at all timepoints, apart from a Grade 1 abnormality on Day 28. The patient was permanently discontinued from the study on Day 56 as he was no longer willing to participate and no further follow-up is available.

- A 38 year old female participating in Study A4001028, was hospitalized on [redacted] due to weakness in both legs and was diagnosed with myositis. She had stopped study drug on 17 February 2006 when the weakness had started. Prior to this, she had received maraviroc QD (150 mg) for 79 days. She also received tenofovir, emtricitabine, zidovudine and lopinavir/ritonavir as OBT. Screening and baseline creatine kinase were abnormal with values of 363 and 247 U/L, respectively. By Day 62 values have increased to 829 U/L. The muscle biopsy revealed marked CD8+ T cell infiltration of the muscle tissues compatible with T cell mediated (possibly autoimmune) myositis in conjunction with some evidence of zidovudine

induced toxic muscle fibre damage. In the opinion of the Investigator, there was a reasonable possibility that the myositis was related to maraviroc.

Two further patients receiving maraviroc QD in study A4001028 discontinued due to myalgia. In 1 patient no abnormal creatine kinase was recorded. In the second patient, the highest recorded creatine kinase values were pre-dose (1020 U/L and 281 U/L on Day 6 and Day 1, respectively).

- A patient receiving maraviroc BID in Study A4001027 temporarily discontinued study drug due to blood creatine kinase and increased hepatic enzymes on Day 335. The patient was in study at Day 347 (the date of cut-off). Creatine kinase values were 6566 U/L on Day 335 and had reduced to 492 U/L on Day 340. Creatine kinase was within normal limits on Day 347.

- A patient receiving maraviroc BID in Study A4001028 temporarily discontinued study drug due to Grade 4 AST and blood creatine kinase abnormalities. Study drug was temporarily stopped due to increased AST from Day 15 to 22 and increased creatine phosphokinase from Day 15 to 22 and Day 29 to 37. These resolved and the patient had taken study drug up to Day 182 at the time of cut-off. The patient had increased creatine phosphokinase on a number of other occasions during treatment; these all resolved with study drug continued unchanged.

In Study A4001029, which lacked significant differences in duration of exposure among treatment arms, the incidence of creatine kinase abnormalities (>2x ULN) in subjects receiving maraviroc QD and BID was 16% and 26%, respectively, compared to 26% on placebo. There were no temporary or permanent discontinuations due to increased creatine kinase, myalgia, myositis or rhabdomyolysis.

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. 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 phosphokinase measurements. The changes observed in lymphocyte count were expected given the nature of the CD4 and CD8 cell count increases on maraviroc therapy.

9.9. 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 were made to control for C_{max} in patients receiving PI-containing regimens.

- 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.

9.10. Updated Safety Information from the 3-Month Safety Update

A further 12 weeks of follow up of these patients was assessed in the maraviroc 3 month safety update. Overall the conclusions with respect to the safety of maraviroc are unchanged.

Table 78 and Table 79 respectively present new cases of death and lymphoma that have occurred since the NDA submission.

Table 78. Deaths in the Maraviroc Clinical Program Occurring Since the NDA Submission

Unblinded Treatment	Cause of Death	Total Days on Therapy †	Days Post-Therapy	Related
Study A4001027 – Treatment-Experienced Patients Infected with CCR5 Tropic HIV-1				
Maraviroc BID	T-cell lymphoma	349	0	No
Maraviroc BID	Death	Unknown	Unknown	No
Maraviroc BID	Suicide attempt	436	2	No
Study A4001028 – Treatment-Experienced Patients Infected with CCR5 Tropic HIV-1.				
Maraviroc BID	*cholangiocarcinoma / liver metastases / bone metastases / peritoneal metastases*	*250*	*39*	*Yes*
Placebo	*PML (reason for discontinuation),Pulmonary oedema (ultimate cause of death)*	*117*	*136*	*no*
Study A4001029 – Treatment-Experienced Patients Infected with Non-CCR5 Tropic HIV-1				
ISOD [Randomised to Placebo]	*Myocardial infarction*	*85*	*156*	*No*

Italicized rows in this table represent deaths that occurred more than 28 days after discontinuation of treatment.

Table 79. Lymphomas Reported in the Maraviroc Clinical Program Since the NDA Submission

Treatment	Preferred Term	Active/Post-treatment	Event Start Date[a]	Screening CD4[b] Cell Count (cells/µL)	Screening HIV-1 RNA[b] (log_{10} copies/mL)	Patient Disposition	Biopsy	Definite	Related	Death [c]
Study A4001027 - Treatment-Experienced Patients Infected with CCR5 Tropic HIV-1										
Maraviroc BID	T-cell lymphoma	Active	303	87	4.75	Study drug continued	Yes	Yes	No	Yes
Maraviroc BID	Large B-cell lymphoma	Active	374	54	5.44	Ongoing	Yes	Yes	No	No

[a] Days from initiation of blinded study drug
[b] If screening value was not available, baseline value is given
[c] last information known to sponsor

10. CONCLUSIONS AND RECOMMENDATIONS

10.1. Dose Recommendations for Prescribing

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 a manageable risk of hepatotoxicity and no observed risk of 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 may have some advantages relative to once daily dosing:

1. In the combined analysis of Studies A4001027 and A4001028 there were numerical trends in favor 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 $\geq$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, as demonstrated in the following table. Exploratory analyses of the discontinued maraviroc 300 mg QD treatment arm in Study A4001026 demonstrated similar trends when compred with the blinded maraviroc 300 mg BID/efavirenz 600 mg QD treatment arm.

HIV-1 RNA (copies/mL)	Maraviroc QD		Maraviroc BID[b]		Placebo	
	N[a]	n (%)	N[a]	n (%)	N[a]	n (%)
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 favor 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.

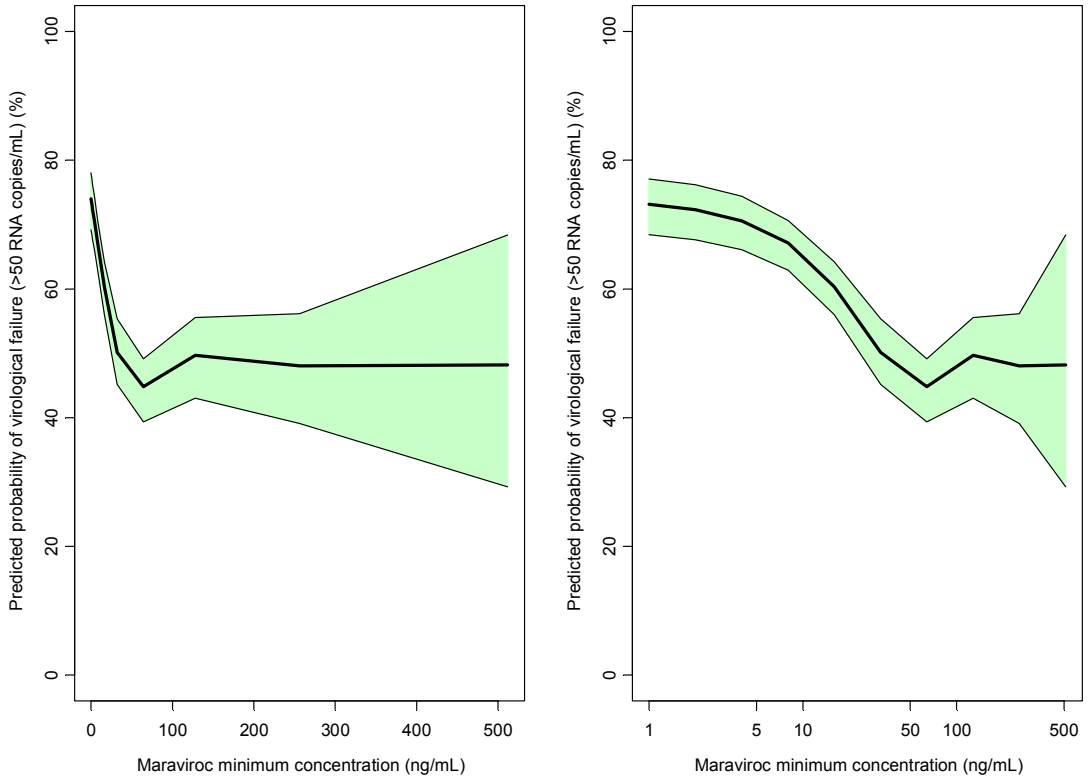
Although the effect is somewhat more subtle in this comparison of maraviroc QD versus BID, other clinical trials, such as with abacavir/lamivudine/zidovudine (Staszewski S, 2001) and with nelfinavir (King MS, 2004), have highlighted important treatment differences when the efficacy of two different treatment 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. 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 300 mg dose in the absence of a CYP3A4 inhibitor. The similarity of the maraviroc QD and BID arms of Studies A4001027 and A4001028 is probably the result of pharmacoenhancement with boosted and unboosted PIs, leading to adequate correction of maraviroc C_{max} and under-correction of maraviroc AUC (resulting in maraviroc AUCs that in many cases 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 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 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 modeled (Figure 18). There are many assumptions and confounders, and interactions between covariates have not been modeled. 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 18. 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.

Finally, and as will be described in more detail in the following 'Overall Benefit-Risk of Maraviroc' Section 10.2, 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 may provide some advantages, especially in patients with extremely low CD4 counts or high viral loads.

With respect to dosing recommendations, the maraviroc dose modification recommendations for the Phase 2b/3 clinical studies were successful in limiting C_{max} 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 80).

Table 80. 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	150 mg BID
CYP3A4 inducers (without a CYP3A4 inhibitor) including: • efavirenz and nevirapine • rifampin and rifabutin,	600 mg BID
Other concomitant medications, including all other antiretrovirals including tipranavir/ritonavir	300 mg BID

10.2. Overall Benefit-Risk of Maraviroc

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 program 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 2007 subject to satisfactory regulatory review.

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 C_{max} 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

CYP3A4 inhibitors) used to correct C_{max} 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 little indication of 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 the reported incidence of lymphoma appeared to be typical of this population and not different from placebo.

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 baseline viral load and CD4 cell counts for the maraviroc registrational studies were similar to those of currently marketed or recently approved antiretroviral agents. The increased efficacy of maraviroc, dosed either once-daily or twice-daily, versus patients receiving OBT alone, is comparable to other recently reported studies (Table 81).

Table 81. Baseline Viral Loads and CD4 Cell Counts for Studies of Antiretroviral Agents and Response to Treatment at 24 Weeks

		Median Baseline CD4 (cells/μL)	Median Baseline VL (log_{10} copies/mL)	Δ CD4 at Week 24 (cells/μL)	Δ VL at Week 24 (log_{10} copies/mL)
TORO 1[a]	Control	87	5.2	+32	-0.63
	Enfuvirtide	76	5.2	+76	-2.03
TORO 2[b]	Control	102	5.1	+38	-0.65
	Enfuvirtide	98	5.1	+66	-1.43
RESIST 1[c]	Control	123	4.84	+6	-0.28
	Tipranavir	123	4.81	+36	-0.88
RESIST 2[d]	Control	222 (mean)	4.77 (mean)	+18	-0.53
	Tipranavir	226 (mean)	4.76 (mean)	+51	-1.23
Combined POWER[e]	Control	163	4.56	+17	-0.48
	Darunavir 600 mg BID	153	4.52	+92	-1.89
Maraviroc A4001027	Placebo	163	4.92[f]	+52	-1.03
	Maraviroc QD	168	4.86[f]	+107	-1.82
	Maraviroc BID	150	4.87[f]	+111	-1.95
Maraviroc A400028	Placebo	174	4.80[g]	+64	-0.93
	Maraviroc QD	174	4.92[g]	+112	-1.95
	Maraviroc BID	182	4.84[g]	+102	-1.97

[a] Lalezari JP, 2003.
[b] Lazzarin A, 2003.
[c] Gathe J, 2006.
[d] Cahn P, 2006.
[e] Darunavir US Package Insert (USPI).
[f] Corresponding ***mean*** values in Study A4001027 were 4.84, 4.85 and 4.86 log_{10} copies/mL in the placebo, maraviroc QD and maraviroc BID treatment groups respectively.
[g] Corresponding ***mean*** values in Study A4001028 were 4.89, 4.87 and 4.84 log_{10} copies/mL in the placebo, maraviroc QD and maraviroc BID treatment groups respectively.

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.

A 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 or at a significantly different rate to placebo at doses equivalent to 300 mg QD and BID, 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) and c) the preclinical data indicating the potential for maraviroc to prolong the QTc interval has not been evident clinically at the therapeutic doses studied. 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 unlikely to cause harm 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.

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 Table 80).

11. PLANS FOR COMPLETING REQUIREMENTS FOR TRADITIONAL APPROVAL

11.1. Risk Management Plans

Reviews of potential safety risks, including theoretical concerns, have been conducted throughout the clinical development of maraviroc. In accordance with the US FDA Guidance for Industry Document, Development and Use of Risk Minimization Action Plans (March 2005), a risk management plan was developed for maraviroc and submitted as part of the NDA 22-218. A brief summary of the proposed actions is included in this section of the briefing document.

Safety of CCR5 blockade is in part supported by the presence of individuals in the general population who do not naturally express the CCR5 receptor (homozygous for the CCR5 Δ32 mutation). These individuals are strongly protected from HIV infection and are otherwise healthy although there are suggestions in the literature, often conflicting, that there may be subtle differences (both positive and negative) in susceptibility to some conditions. However, these individuals lack CCR5 receptors from birth, so extrapolation of findings from this population to a population treated with a CCR5 antagonist must be done with caution.

There is a complex association between HIV-1 co-receptor tropism, transmission and pathogenesis which is not yet fully understood. In the absence of a CCR5 antagonist, a change in viral tropism result from CCR5 tropic to CXCR4 or dual/mixed tropic is known to be associated with more rapid disease progression as measured by a faster decline in CD4 cell count. A cause and effect relationship has not been established and progression to AIDS may occur in the absence of measurable CXCR4 tropic virus. There was no evidence in the maraviroc clinical trial data that tropism change from CCR5 to dual/mixed or CXCR4 tropic virus, or dual/mixed tropic virus to CXCR4 has an adverse effect on immune function (as measured by CD4 cell count changes) when occurring in the presence of a CCR5 antagonist.

Altered immune function due to CCR5 inhibition is a potential safety risk that has been closely monitored during the development program. No increased susceptibility to infections or malignancies in patients receiving maraviroc versus placebo was observed in the Phase 3 safety database presented in the NDA.

The potential for hepatotoxicity has been raised through reports of hepatic toxicity from another experimental CCR5 antagonist, aplaviroc (GSK). The liver was a target organ in the rat with elevated transaminases, hepatocellular necrosis and bile duct vacuolation occurring at high exposures of maraviroc. Detailed assessment of hepatic safety in the development program has not identified maraviroc to have a significant adverse effect on the liver, there being no increased frequency of Grade 3 and 4 abnormalities or hepatic adverse events on maraviroc compared to placebo. There has been a single severe case of possibly maraviroc related hepatotoxicity. This case assessment was complicated by acetaminophen, co-administration of isoniazid and trimethoprim-sulphamethoxazole which are both associated with hepatotoxicity, and increasing liver enzymes which were present prior to maraviroc therapy.

The potential for QTc prolongation identified during preclinical testing required additional assessment during clinical development. Clinically meaningful QTc prolongation has not been demonstrated at or above the therapeutic dose.

Early Phase 1 studies identified postural hypotension as the dose limiting adverse-effect. At doses used in the phase 2b/3 clinical development program, postural hypotension and related adverse events were of similar incidence in patients receiving maraviroc compared with placebo and caused few patients to discontinue.

Maraviroc is a CYP3A4 substrate and co-administration of potent CYP3A4 inhibitors and inducers result in increased and decreased maraviroc plasma concentrations. Detailed prescribing guidance on potential drug-drug interactions is provided within the label.

There is no experience with maraviroc in children, adolescents (<16 years) or pregnant females, and limited experience in the elderly. The proportion of non-whites (16%) and women (11%) in the clinical trial population is small but no evidence of a difference in safety profile has emerged from the development program.

Below is a summary of important safety risks identified requiring further pharmacovigilance.

Important identified risks	None
Important potential risks	Potential to alter immune function Potential for hepatic effects
Important missing information	Pregnant women Paediatric and adolescent population

Table 82. Summary of the Maraviroc Risk Management Plan

Safety Concern	Proposed Pharmocovigilance Activities (routine and additional)	Proposed Risk Minimization Activities –all routine
Important		
Potential to alter immune function	Routine Pharmacovigilance 48 wk analysis in ongoing trials in TE subjects Longer term follow up data from ongoing TE studies EAP Maraviroc Patient Safety Registry[a] EuroSIDA data Data Capture Aid Expert panel if required 48 wk data in naïve subjects	Not applicable
Potential to alter hepatic function	Routine pharmacovigilance 48 wk analysis in ongoing trials in TE subjects Longer term follow up data from ongoing TE studies EAP to initiate 1Q2007 Maraviroc Patient Safety Registry[a] Hepatic impairment study DCA Expert panel if required 48 wk data in R5 naïve subjects	Caution advised in patients with abnormal hepatic function or known underlying hepatic disease
Exposure during Pregnancy	Routine pharmacovigilance The Antiretroviral pregnancy registry Exploring possibility of follow-up of maraviroc exposed infants in existing cohort studies	Use in pregnancy contraindicated in the USPI/SmPC unless benefit risk is such that it is deemed in the best interests of the patient
Pediatrics	Routine pharmacovigilance Paediatric Study A4001030 a Phase II, 48 week open label, non-randomized, non comparative, multi centre study to evaluate the safety, tolerability and pharmacokinetics of multiple doses of maraviroc added to OBT in R5 TE HIV-1 infected children.	Use in paediatric populations not supported in the USPI/SmPC
Other		
Possible imbalance in Cardiac Events	Routine pharmacovigilance 48 wk analysis in ongoing trials in TE subjects Longer term follow up data from ongoing TE studies EAP to initiate 1Q2007 Maraviroc Patient Safety Registry	Events are mentioned in the USPI/SmPC in the 'less common' AE section and 'undesirable effects'.
Postural Hypotension	Routine pharmacovigilance	A warning to use with caution is provided in SmPC/USPI for patients at high risk of postural hypotension
Drug drug interactions	Routine pharmacovigilance	Dosing advice SmPC/USPI

Table 82. Summary of the Maraviroc Risk Management Plan

Safety Concern	Proposed Pharmocovigilance Activities (routine and additional)	Proposed Risk Minimization Activities –all routine
Potential that Change in viral tropism result is linked to an adverse outcome	Routine Pharmacovigilance.	Not applicable
Potential for QTc prolongation	Routine pharmacovigilance	A warning is provided in the overdose section of USPI/SmPC.

[a] Brief details of the maraviroc patient safety registry are provided in Appendix 3.

11.2. Timelines for Completion of Studies for Traditional Approval

The Sponsor will provide 48-week data from the Phase 3 Studies A4001027 and A4001028, conducted in treatment-experienced patients infected with CCR5 tropic HIV-1, once the final analyses and clinical study reports are completed; these 48-week data are intended to support the application for Traditional Approval. It is anticipated that the 48-week clinical study reports will be available for submission in 3Q 2007.

The 48-week clinical study report for the Phase 2b Study A4001029 conducted in treatment-experienced patients infected with non-CCR5 tropic HIV-1 is complete.

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APPENDIX 1 METHODS OF ANALYSIS

Appendix 1.1 Viral Tropism Assessment

HIV-1 co-receptor tropism was carried out by Monogram Biosciences using an in vitro phenotypic assay (Trofile™ HIV Entry Tropism assay) (Limoli K, 2006, Whitcomb JM, 2003). The assay uses patient-derived virus envelope (gp160) sequences amplified from plasma to infect cell lines expressing CD4 and either CXCR4 or CCR5. Co-receptor usage is determined by the presence of viral replication in these cell lines, as indicated by the expression of a reporter gene. It is a reflection of the relative sizes of the CCR5- and CXCR4-using populations and is neither quantitative, nor absolute. In mixing experiments conducted in vitro, a 10% minority population of CXCR4-using clones could be detected with 100% sensitivity, while the presence of a 5% CXCR4-using population could be detected with 83% sensitivity. The assay has a lower limit of sensitivity for reliable amplification of 1000 copies of HIV-1 RNA/mL for amplification. In these studies, a lower limit of >500 copies/mL was used in order to increase the number of samples with low viral load for which tropism was determined. However, if viral load was ≤500 copies/mL, tropism was not determined at that timepoint or the result was censored. The principle of the test is shown schematically in Figure 19.

Figure 19. Schematic Diagram Showing the Principle of the Assay used to Determine Viral Tropism

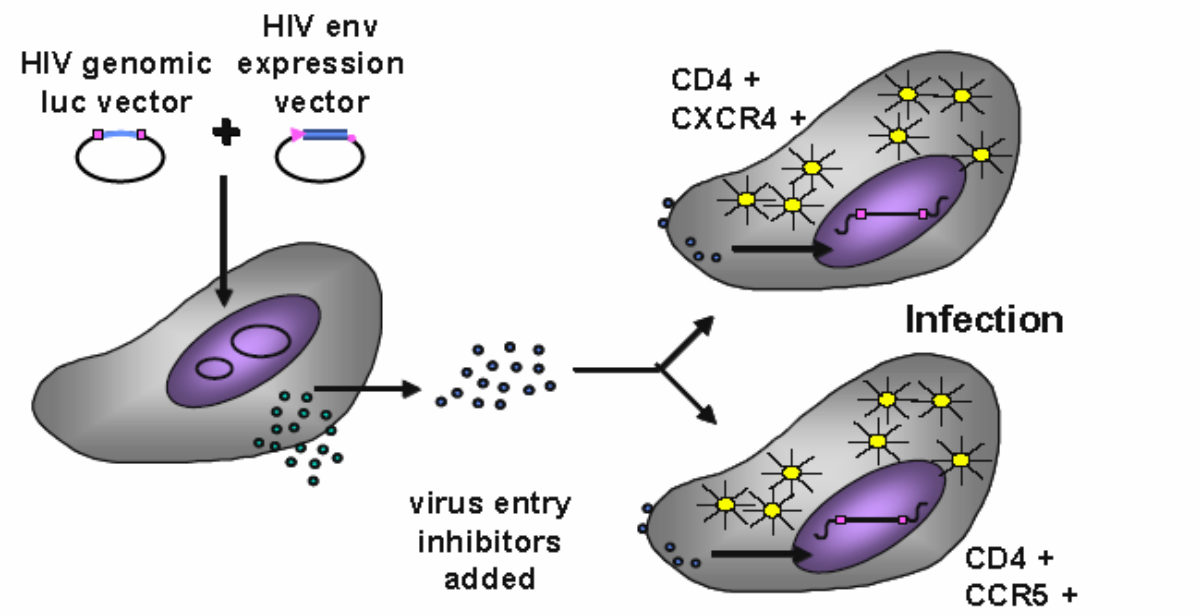

Figure Legend: The assay uses an ***HIV envelope expression vector*** that carries the entire HIV envelope encoding sequence amplified from the sample to be tested. When a plasma sample is analysed, an HIV expression vector library is created, which is composed of a large pool of sequences representing the plasma viral population at the time of sample collection (Limoli K, 2006, Whitcomb JM, 2003). Pseudovirus particles carrying envelope glycoproteins derived from the plasma virus are produced by transfecting producer cells with the purified envelope expression vector library and an HIV-1 genomic vector lacking the envelope-encoding region and containing a firefly luciferase gene (***HIV genomic luc vector***). Firefly luciferase protein catalyses luciferin oxidation to generate light, and is used to measure the ability of the pseudoviruses to infect target cells expressing CD4 and either CXCR4 or CCR5. To confirm the phenotype, CCR5-specific or CXCR4-specific entry inhibitors can be added prior to, or at the time of infection of target cells.

Individual HIV-1 strains are categorized in vitro as CCR5-tropic, CXCR4-tropic or dual-tropic. However, a single patient may harbor a heterogeneous population of viruses with different tropism. The Trofile™ HIV Entry Tropism assay cannot discern between true dual-tropic virus and a mixture of CCR5 and CXCR4 monotropic viruses. Patient samples that show any detectable replication in the CCR5-expressing and CXCR4-expressing cells are thus all collectively scored as 'dual/mixed tropic'.

The Trofile™ assay has been validated pre-clinically by Monogram Biosciences (Limoli K, 2006). The parameters investigated in this validation and key performance conclusions are listed in Table 83 below:

Table 83. Validation of the PhenoSense™ HIV Entry Tropism Assay (Monogram Biosciences)

Parameter	Overview	Key Performance Finding
Accuracy	Comparison to other methods using characterized and commercially available viruses	100% correlation for the viruses tested
Precision	Intra-assay variability	100% over ~1,000 pair-wise comparisons using 3 viruses
Reproducibility	Inter-assay variability	100% for 184 pair-wise comparisons using 36 patient samples
Sensitivity to amplify	Assay performance to report tropism using patient virus with low HIV RNA copies	Assay can be reliably performed on plasma samples with viral loads ≥1,000
Sensitivity to detect minor variants	CCR5-tropic and CXCR4-tropic envelope clones from the same patient mixed in defined ratios	100% of minor variants detected at the 10% mixture level. 83% of minor variants were detected at the 5% mixture level.
Linearity	Effect of virus load on tropism assignment (Tested in the range from ~3,000 to ~600,000 RNA c/mL).	Variations in virus concentration in plasma do not significantly affect assay results

A detailed exploratory analysis was conducted to identify the likely origin of CXCR4-using virus that emerged during treatment with blinded study drug.

Appendix 1.2 Resistance Mutations and Virus Susceptibility Scores

Susceptibility Testing for PIs, NRTIs and NNRTIs used in OBT

Phenotypic and genotypic resistance to PIs, NRTIs and NNRTIs were evaluated using the Monogram Biosciences PhenoSense™ GT (PSGT) assay (Petropoulos CJ, 2000) at the following timepoints: screening, Weeks 24 and 48, time of treatment failure and early termination visit. These results were used to calculate susceptibility scores for the OBT, as described below. A lower viral load limit of 500 copies/mL was used for these tests and therefore if the viral load was <500 copies/mL, no PSGT test was performed at that timepoint or the result was censored.

Susceptibility Testing for Enfuvirtide (T20) used in OBT

Genotypic resistance to enfuvirtide was determined by the British Columbia Centre for Excellence in HIV using gp41 sequencing and identification of specific mutations in the HR1 domain at the following timepoints: screening, Weeks 24 and 48, time of treatment failure or early termination visit. These results were used to calculate susceptibility scores for the OBT, as described below.

Calculation of Genotypic, Phenotypic and Overall Susceptibility Scores

In order to estimate the activity of OBT in each patient, the susceptibility testing as described above were used to calculate the GSS, PSS and OSS. Table 84 below presents an outline of these calculations. As a lower viral load limit of 500 copies/mL was used for PSGT testing, susceptibility scores were not calculated for timepoints where viral load was ≤500 copies/mL.

Table 84. Genotypic (GSS), Phenotypic (PSS) and Overall Susceptibility Score (OSS) Calculations

	Description	How it is Calculated
GSS	Sum of the number of active drugs in OBT based upon inspection of the derived amino acid sequences of RT, PR and gp41(HR1), following PCR amplification of (separately) the pol and Env genes from plasma.	For each drug in OBT: Score '1' if resistance mutations[a] are not detected ('Y' in PSGT report under column entitled 'Evidence of drug sensitivity GenSeq?'), or no relevant mutations are detected and 'Interpretation' is given as 'Resistance unlikely' for gp41) Score '0' if one or more resistance mutations[a] are detected ('N' in PSGT report under column entitled 'Evidence of drug sensitivity GenSeq?' or relevant mutations are detected and 'Interpretation' is given as 'Resistance likely' for gp41)
PSS	Sum of the number of active drugs in OBT based on testing the virus from the patient plasma in drug susceptibility assays in vitro. Drug susceptibility curves are used to determine the drug concentration that is required to inhibit replication of the patient virus by 50% (IC_{50})[b].	For each drug in OBT (except enfuvirtide): Score '1' if virus from patient is susceptible to drug ('Y' in PSGT report under column entitled 'Evidence of drug sensitivity PhenoSense?') Score '0' if virus from patient shows reduced susceptibility to drug[c] ('N' in PSGT report under column entitled 'Evidence of drug sensitivity PhenoSense?') For enfuvirtide: Use GSS method to score '1' or '0'
OSS	Sum of active drugs in OBT based on combined information from genotypic and phenotypic testing above (a 'net assessment'). Where the two tests above are in agreement then the net assessment will be the same. Where the tests are not in agreement then a proprietary algorithm[d] will determine whether sensitive or resistant.	For each drug in OBT (except enfuvirtide): Score '1' if virus from patient is sensitive to drug ('Sensitive' in PSGT report under column entitled 'Net Assessment') Score '0' if virus from patient shows reduced susceptibility to drug ('Reduced Susc.' in PSGT report under column entitled 'Net Assessment') For enfuvirtide: Use GSS method to score '1' or '0'

RT = reverse transcriptase; PR = protease; gp41(HR1) = the first heptad repeat domain of gp41, which is the region of the HIV-1 fusion glycoprotein to which enfuvirtide binds.
[a] Amino acid substitutions that are associated with reduced drug susceptibility in vitro and reduced efficacy in vivo, e.g. K103N is a resistance mutation associated with reduced susceptibility to efavirenz.
[b] Expressed as a fold change relative to the IC_{50} of a drug sensitive reference strain tested in the same assay.
[c] Monogram Biosciences have determined biological or clinical cut-offs of drug sensitivity for each drug.
[d] Proprietary to Monogram Biosciences and based on analysis of large panels of viruses with matched Phenotypic and Genotypic test results.

Virus Susceptibility to Maraviroc

Samples were collected for retrospective analysis of virus susceptibility to maraviroc in the Sponsor's laboratories. Techniques used include gp160 sequencing as well as the evaluation of CCR5-mediated phenotypic resistance to maraviroc in drug susceptibility assays.

APPENDIX 2 EFFICACY ENDPOINT ANALYSIS BY GENOTYPIC (GSS) AND PHENOTYPIC SUSCEPTIBILITY SCORE (PSS) AT BASELINE

Analysis by GSS at Baseline:

A treatment benefit for maraviroc for all endpoints was observed for each GSS group (Table 85).

Table 85. Summary of Change in HIV-1 RNA from Baseline to Week 24 Split by GSS at Baseline (Combined Studies A4001027 and A4001028)

GSS		Change from Baseline in HIV-1 RNA (log_{10} copies/mL)		
		Maraviroc QD (N= 414)[a]	Maraviroc BID (N= 426)[a]	Placebo (N= 209)[a]
0	N[b]	88	101	51
	Mean (SD)	-1.497 (1.143)	-1.682 (1.323)	-0.214 (0.705)
	Median (Range)	-1.481 (-3.525, 1.080)	-1.862 (-4.547, 1.317)	-0.045 (-2.915, 0.619)
1	N[b]	145	137	53
	Mean (SD)	-2.055 (1.257)	-2.040 (1.240)	-0.597 (0.864)
	Median (Range)	-2.337 (-4.492, 0.597)	-2.372 (-4.504, 0.780)	-0.351 (-3.198, 0.641)
2	N[b]	63	79	41
	Mean (SD)	-2.062 (1.421)	-2.434 (1.125)	-1.529 (1.167)
	Median (Range)	-2.384 (-4.295, 2.039)	-2.658 (-3.978, 0.532)	-1.772 (-3.344, 0.965)
≥3	N[b]	107	100	57
	Mean (SD)	-2.642 (1.065)	-2.587 (1.221)	-2.296 (1.188)
	Median (Range)	-2.967 (-4.428, 0.822)	-2.826 (-4.410, 1.200)	-2.676 (-4.148, 0.442)

[a] Number of patients in treatment group.
[b] Number of patients contributing to summary statistics, which were patients with valid values for baseline and on treatment. Last Observation Carried Forward (LOCF) has been used to impute missing values.
QD = Once daily dosing; BID = Twice daily dosing; SD = Standard deviation.

Table 86 and Table 87 present the results for the percentage of patients achieving <50 and <400 copies/mL at Week 24 by GSS.

Table 86. Percentage of Patients with an HIV-1 RNA <50 copies/mL at Week 24 by GSS (Combined Studies A4001027 and A4001028)

GSS	Percentage of Patients with HIV-1 RNA <50 copies/mL					
	Maraviroc QD (N= 414)[a]		Maraviroc BID (N= 426)[a]		Placebo (N= 209)[a]	
	N[b]	N (%)	N[b]	n (%)	N[b]	n (%)
0	88	25 (28.4)	101	33 (32.7)	51	1 (2.0)
1	145	68 (46.9)	137	64 (46.7)	53	6 (11.3)
2	63	34 (54.0)	79	44 (55.7)	41	15 (36.6)
≥3	107	66 (61.7)	100	59 (59.0)	57	29 (50.9)

[a] Number of patients in treatment group.
[b] Number of patients with a post-baseline observation used to calculate the percentage.
QD = Once daily dosing; BID = Twice daily dosing.

Table 87. Percentage of Patients with an HIV-1 RNA <400 copies/mL at Week 24 by GSS (Combined Studies A4001027 and A4001028)

GSS	Percentage of Patients with HIV-1 RNA <400 copies/mL					
	Maraviroc QD (N= 414)[a]		Maraviroc BID (N= 426)[a]		Placebo (N= 209)[a]	
	N[b]	N (%)	N[b]	n (%)	N[b]	n (%)
0	88	34 (38.6)	101	50 (49.5)	51	3 (5.9)
1	145	87 (60.0)	137	83 (60.6)	53	7 (13.2)
2	63	42 (66.7)	79	60 (76.0)	41	18 (43.9)
≥3	107	82 (76.6)	100	79 (79.0)	57	34 (59.7)

[a] Number of patients in treatment group.
[b] Number of patients with a post-baseline observation used to calculate the percentage.
QD = Once daily dosing; BID = Twice daily dosing.

Fewer patients with a GSS of 0 achieved viral loads of <50 and <400 copies/mL compared with patients with higher a GSS. For each treatment group the percentage of patients with a viral load of <50 and <400 copies/mL increased as GSS increased. For both secondary endpoints of viral load <50 and <400 copies/mL, both doses of maraviroc were superior to placebo at each category of GSS. Overall, more patients achieved a viral load <400 copies/mL compared with <50 copies/mL for all treatment groups, however, the pattern between treatment groups remained the same for each endpoint.

For both secondary endpoints, patients with a GSS of 0 appeared to respond better to treatment with maraviroc BID than QD, although both doses had a higher percentage of patients reaching <400 and <50 copies/mL than placebo (28.4% and 32.7% versus 2.0% patients receiving maraviroc QD, BID and placebo respectively achieved
<50 copies/mL and 38.6% and 49.5% versus 5.9% patients receiving maraviroc QD, BID and placebo respectively achieved <400 copies/mL). This pattern was not observed for the other categories of GSS.

Analysis by PSS at Baseline:

Patients with a PSS of 0 had less of a response to treatment irrespectiveof treatment group. Patients with a PSS of 1, 2 or 3 had a greater response to treatment that appeared to be graded; the higher the PSS the better the reduction in viral load from baseline (Table 88). For each PSS, however, both doses of maraviroc demonstrated statistically superior efficacy over placebo.

Table 88. Summary of Change in HIV-1 RNA from Baseline to Week 24 Split by PSS at Baseline (Combined Studies A4001027 and A4001028)

PSS		Change from Baseline in HIV-1 RNA (log_{10} copies/mL)		
		Maraviroc QD (N= 414)[a]	Maraviroc BID (N= 426)[a]	Placebo (N= 209)[a]
0	N[b]	44	49	29
	Mean (SD)	-1.277 (1.038)	-1.310 (1.296)	-0.134 (0.684)
	Median (Range)	-0.966 (-3.395, 0.080)	-1.029 (-3.511, 1.317)	-0.039 (-2.817, 0.641)
1	N[b]	113	114	38
	Mean (SD)	-1.835 (1.221)	-1.883 (1.332)	-0.402 (0.822)
	Median (Range)	-2.103 (-3.780, 1.080)	-2.256 (-3.956, 0.780)	-0.158 (-3.428, 0.571)
2	N[b]	93	107	58
	Mean (SD)	-2.062 (1.250)	-2.252 (1.073)	-0.899 (1.102)
	Median (Range)	-2.337 (-4.199, 2.039)	-2.582 (-4.547, -0.030)	-0.508 (-3.181, 0.965)
≥3	N[b]	152	145	77
	Mean (SD)	-2.529 (1.227)	-2.583 (1.189)	-2.141 (1.153)
	Median (Range)	-2.932 (-4.492, 0.822)	-2.852 (-4.504, 1.200)	-2.316 (-4.148, 0.442)

[a] Number of patients in treatment group.
[b] Number of patients contributing to summary statistics, which were patients with valid values for baseline and on treatment. Last Observation Carried Forward (LOCF) has been used to impute missing values.
QD = Once daily dosing; BID = Twice daily dosing; SD = Standard deviation.

Table 89 and Table 90 present the results for the percentage of patients achieving <50 and <400 copies/mL at Week 24 by PSS.

Table 89. Percentage of Patients with an HIV-1 RNA <50 copies/mL at Week 24 by PSS (Combined Studies A4001027 and A4001028)

PSS	Percentage of Patients with HIV-1 RNA <50 copies/mL					
	Maraviroc QD (N= 414)[a]		Maraviroc BID (N= 426)[a]		Placebo (N= 209)[a]	
	N	N (%)	N	n (%)	N	n (%)
0	44	8 (18.2)	49	12 (24.5)	29	1 (3.5)
1	113	49 (43.4)	114	50 (43.9)	38	3 (7.9)
2	93	45 (48.4)	107	57 (53.3)	58	10 (17.2)
≥3	152	90 (59.2)	145	80 (55.2)	77	37 (48.1)

[a] Number of patients in treatment group.
[b] Number of patients with a post-baseline observation used to calculate the percentage.
QD = Once daily dosing; BID = Twice daily dosing.

Table 90. Percentage of Patients with an HIV-1 RNA <400 copies/mL at Week 24 by PSS (Combined Studies A4001027 and A4001028)

PSS	Percentage of Patients with HIV-1 RNA <400 copies/mL					
	Maraviroc QD (N= 414)[a]		Maraviroc BID (N= 426)[a]		Placebo (N= 209)[a]	
	N	N (%)	N	n (%)	N	n (%)
0	44	10 (22.7)	49	19 (38.8)	29	2 (6.9)
1	113	66 (58.4)	114	66 (57.9)	38	3 (7.9)
2	93	56 (60.2)	107	75 (70.1)	58	14 (24.1)
≥3	152	112 (73.7)	145	110 (75.9)	77	43 (55.8)

a Number of patients in treatment group.
b Number of patients with a post-baseline observation used to calculate the percentage.
QD = Once daily dosing; BID = Twice daily dosing.

APPENDIX 3 MARAVIROC PATIENT SAFETY REGISTRY

Maraviroc Safety Registry: An International, Multicenter, Prospective Epidemiologic Cohort Study of the Safety of Maraviroc Used with Optimized Background Therapy Treatment-experienced HIV-1 infected Patients.

To characterize the safety of maraviroc as used in routine clinical practice settings, the sponsor plans to conduct an international, multicenter, prospective, open-label observational study of treatment-experienced patients infected with HIV-1 and treated with maraviroc in combination with optimized background therapy. Approximately 2,500 patients from the U.S., Europe, and other countries are anticipated to participate in the registry. Study endpoints were chosen based on theoretical risks identified with CCR5 antagonists as a class and will include the following: (1) liver failure and liver-related death, (2) non-AIDS-defining malignancies, (3) U.S. Centers for Disease Control and Prevention Category C AIDS-defining events (opportunistic infections and AIDS-defining malignancies), (4) myocardial infarction, and (5) all-cause mortality. Endpoints (1) through (4) will be ascertained for registry patients for up to six months following discontinuation of maraviroc; all-cause mortality will be ascertained for registry patients for up to five years following entry into the registry even is maraviroc has been discontinued. All endpoints will be screened and adjudicated by an independent Global Endpoint Committee according to algorithms commonly used in observational studies. In addition, an independent Scientific Steering Committee will be responsible for safeguarding the interests of registry patients and overseeing conduct of the study by establishing registry performance characteristics and developing recruitment and retention strategies.