2.7.1 SUMMARY OF BIOPHARMACEUTIC STUDIES AND ASSOCIATED ANALYTICAL METHODS

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AUC_{inf}	Area under the plasma concentration-time profile from time 0 to time infinity by extrapolation
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of last quantifiable plasma concentration
AUC_{tau}	Area under the plasma concentration-time profile over the dosing interval
BID	Twice a day dosing
CCR5	CC chemokine receptor 5
CDER	Centre for Drug Evaluation and Research
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CSR	Clinical study report
CV	Coefficient of variation
EMEA	European Medicines Evaluation Agency
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
HCl	Hydrochloric Acid
HIV	Human Immunodeficiency Virus
HDPE	High density polyethylene
HPLC	High-performance liquid chromatography
HPMC	Hydroxypropyl methylcellulose
IV	Intravenous
mg	Milligram
mL	Millilitre
n/c	Not calculated
NF	National Formulary
ng	Nanogram
OBT	Optimised background therapy
Q	Quantity of active released into the dissolution medium at a specific time
QC	Quality control
QD	Once a day dosing
Ph.Eur	European Pharmacopoeia
PVA	Polyvinyl alcohol
PVC	Polyvinyl chloride
t½	Half-life
rpm	Revolutions per minute
T_{max}	Time to reach C_{max}
USP	United States Pharmacopeia

2.7.1. SUMMARY OF BIOPHARMACEUTIC STUDIES AND ASSOCIATED ANALYTICAL METHODS

Maraviroc is a selective and reversible CC chemokine receptor 5 (CCR5) co-receptor antagonist which has been shown to be active *in vitro* against a wide range of clinical HIV-1 isolates, including those resistant to existing drug classes. The results of long-term phase 3 studies, A4001027 and A4001028 have shown that maraviroc when dosed with optimised background therapy (OBT) leads to a clinically and statistically significant greater decline in viral load than OBT alone. In these studies, maraviroc was dosed as 150 mg research tablets either QD (once a day) or BID (twice a day), except in the absence of a protease inhibitor or delavirdine (or presence of tipranavir/ritonavir) when two 150 mg research tablets were dosed QD or BID. All doses were given without regard to food.

The proposed commercial formulation for maraviroc is a tablet available in two product strengths, 150 mg and 300 mg. The formulation is dry granulated as a common formulation blend that is compressed at two different tablet core weights (600 mg and 1200 mg). The tablets are composed of maraviroc, microcrystalline cellulose, dibasic calcium phosphate, sodium starch glycolate and magnesium stearate. Both tablet strengths are oval in shape and film-coated with a blue film-coat. This module summarises the results from in vitro and clinical biopharmaceutical studies conducted with maraviroc during its development to support the registration of the commercial tablet formulation. These results indicate that:

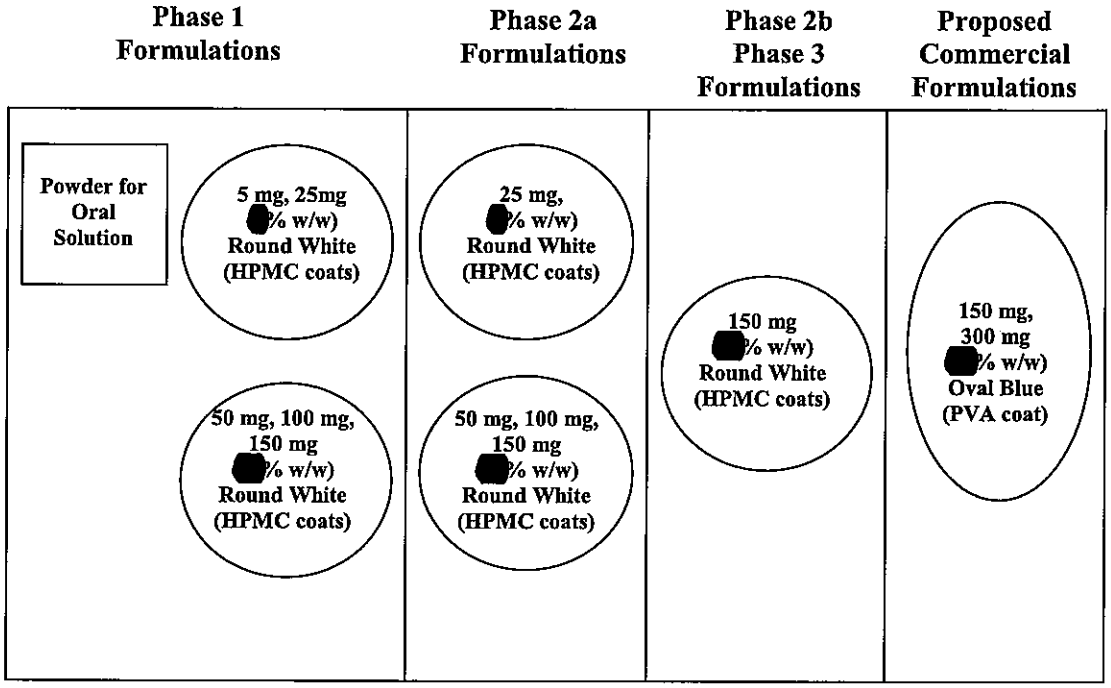
- The maraviroc commercial tablet (1 x 300 mg) and the research tablets used in Phase 2b/3 (2 x 150 mg) are bioequivalent.
- The oral bioavailability of maraviroc is dose dependent.
- The oral bioavailability of maraviroc is affected by food, and is dependent on the size of the maraviroc dose, but is independent of the tablet formulation studied.
- Maraviroc commercial and research tablets demonstrate rapid release characteristics in vitro.

2.7.1.1. Background and Overview

2.7.1.1.1. Overview of Formulation Development

Maraviroc is a white powder and is highly soluble in aqueous media across the physiological pH range 1-7.5. Solubility at 37°C ranges from values ≥ [redacted] mg/ml in acidic buffers to [redacted] mg/mL in pH 7.8, consistent with the basic nature of the molecule. Maraviroc has been formulated as a rapidly disintegrating tablet. Overall the composition of maraviroc tablets has remained largely unchanged throughout the clinical programme; development of the commercial tablet from the research tablet has required only minor changes to the level of lubricant, tablet shape and the film-coat. A schematic representation of maraviroc tablet formulation development is presented in Figure 1.

Figure 1. Schematic Representation of Maraviroc Formulation Development



In total, twenty-six Phase 1, two Phase 2a and three Phase 2b/3 clinical studies are presented in this dossier to support the use of maraviroc (in combination with other antiretroviral agents) for the treatment of treatment-experienced adult patients infected with CCR5-tropic HIV-1. Supportive pharmacokinetic and safety information only, from an interim analysis of Study A4001026 (additional ongoing Phase 3 study in treatment-naïve patients infected with CCR5 tropic HIV-1) is also included at this time.

Maraviroc tablets developed for use in clinical studies are round, convex tablets compressed as different strengths (5, 25, 50, 75, 100, and 150 mg) from a [redacted] formulation, blend, and film-coated white with a clear over-coat. The 75 mg tablet was not used in any of the clinical studies presented in this dossier. Identical round, convex, film-coated white with a clear overcoat placebo tablets were produced for all the strengths of maraviroc research tablets (up to 150 mg) for use in placebo controlled blinded studies.

A range of maraviroc research tablet strengths (from 5 mg to 150 mg) derived from [redacted] blend were used in Phase 1 studies as shown in Figure 1. The majority of Phase 1 clinical studies used the 50, 100 and 150 mg strength maraviroc research tablets, with the lower strengths (5 and 25 mg) being used in one of the drug interaction studies (A4001013) and the first Phase 2a study (A4001007) only. In the Phase 2b/3 studies, maraviroc was administered as 150 mg research tablets. In treatment-experienced Phase 2b/3 studies (A4001027, A4001028 and A4001029), patients received maraviroc or placebo in

combination with OBT. HIV-1 infected patients whose OBT contained a protease inhibitor (except tipranavir/ritonavir) or delavirdine received a regimen of 150 mg QD or BID (approximately equivalent to 300 mg QD or BID). All other patients, including those in the Phase 2b/3 study in treatment-naïve patients (A4001026), received a regimen of 300 mg (2 x 150 mg research tablets) QD or BID.

Full dosage form and product strength information for studies in the clinical programme can be found in Table 3.2.P.2.6-7, Section 3.2.P.2.6 Compatibility. An overview of the formulations used in studies within the maraviroc clinical programme presented within this dossier is shown in Table 1.

Table 1. Overview of Maraviroc Formulations Used in Clinical Studies

Formulation	Phase 1	Phase 2a	Phase 2b/3
Solution (Powder for Oral Solution)	A4001001, A4001002, A4001003, A4001010		
Intravenous (IV) Infusion	A4001009		
Research Tablet	A4001002, A4001003, A4001004, A4001005, A4001006, A4001008, A4001009, A4001011, A4001012, A4001013, A4001016, A4001017, A4001018, A4001019, A4001020, A4001021, A4001022, A4001025, A4001033, A4001038, A4001040, A4001042, A4001046	A4001007, A4001015	A4001026, A4001027, A4001028 A4001029
Commercial Tablet	A4001040, A4001043		

An overview of all Phase 1 and 2a studies is provided in Table 1, Module 2.7.2 Summary of Clinical Pharmacology Studies.

The maraviroc research tablets are round, white film-coated tablets. The proposed commercial tablets were developed from the same [redacted] formulation, blend, as the research tablets. Throughout the development of the tablet formulation, the excipients used in the tablet core remained qualitatively and quantitatively the same, with the exception of an increase in the level of lubricant [redacted]% w/w in the research tablet to [redacted]% w/w in the commercial tablet) and an equivalent minor decrease in diluent. The requirement for a higher commercial strength (300 mg) tablet resulted in the change from round to oval tablets to facilitate swallowing. A blue film-coat has been applied to the commercial tablet, replacing the white coating used for research tablets in the investigational clinical studies. The film-coat system, along with tablet shape and debossing, was changed to provide the coloured commercial image.

The proposed commercial formulation for maraviroc is a tablet in two strengths, 150 mg and 300 mg. A full description of the development of the proposed commercial products is described in Section 3.2.P.2.2 Drug Product.

2.7.1.1.2. Drug Product

2.7.1.1.2.1. Description of Drug Product

Maraviroc research tablets 5, 25, 50, 75, 100, and 150 mg are composed of maraviroc drug substance formulated with the following appropriate grade excipients; microcrystalline cellulose, dibasic calcium phosphate (calcium hydrogen phosphate, anhydrous), sodium starch glycolate, and magnesium stearate. The tablet cores are film-coated with [redacted] white followed by an over-coat with [redacted] Both coating systems use purified water (removed during processing) as a vehicle. The research tablets were round, convex and white with no engraving. The 5 mg tablets are 6 mm in diameter, 25 mg tablets are 11 mm in diameter, 50 mg tablets are 8 mm in diameter, the 100 mg tablets are 10 mm in diameter, and the 150 mg tablets are 12 mm in diameter.

Identical round, convex, white film-coated with a clear overcoat placebo tablets with no engraving were produced for all the strengths of maraviroc clinical tablets (up to 150 mg) for use in placebo-controlled trials. The tablet weight, size and ingredients of the placebo tablets were identical to the research tablets, with the exception of increases in microcrystalline cellulose and dibasic calcium phosphate to replace the maraviroc drug product.

The proposed commercial formulation comprised maraviroc, microcrystalline cellulose, dibasic calcium phosphate (calcium hydrogen phosphate, anhydrous), sodium starch glycolate and magnesium stearate. The tablets are film-coated using a single coat [redacted] developed by [redacted] Table 2 summarises the grade and function of the components used to manufacture maraviroc tablets.

Table 2. Formulation Components of Maraviroc Commercial Tablets

Component[a]	Grade (USP/Ph.Eur)	Function	150 mg Tablet[b] (mg/tablet)	300 mg Tablet[c] (mg/tablet)
Maraviroc	Pfizer	Active Ingredient	150.00	300.00
Microcrystalline Cellulose	USP/Ph.Eur	[redacted]	[redacted]	[redacted]
Dibasic Calcium Phosphate/ Calcium hydrogen phosphate	USP/Ph.Eur		[redacted]	[redacted]
Sodium starch glycolate	USP/Ph.Eur		[redacted]	[redacted]
Magnesium Stearate	NF/Ph.Eur		[redacted]	[redacted]
[redacted] (85G20583)[d]	Pharm/Pharm	Light Blue Film-Coat Solid	[redacted]	[redacted]
Purified Water [e]	USP/Ph.Eur	Vehicle	(As required)	(As required)

[a] both component names when different in the United states and Europe are presented
[b] Oval shaped (nominal 8.56 mm x 15.5 mm) pale blue film-coated tablets with appropriate debossing;
[c] Oval shaped (nominal 10.5 mm x 19.0 mm) pale blue film-coated tablets with appropriate debossing;
[d] [redacted] products are custom blended film-coating systems supplied by [redacted]
[e] Vehicle for film-coats. Evaporated during processing and does not appear in the final product
USP= United States Pharmacopeia, Ph.Eur = European Pharmacopoeia, NF = National Formulary

The proposed commercial maraviroc drug product is an oval-shaped blue, film-coated tablet. This product will be available commercially in two tablet strengths (150 mg and 300 mg)

with both strengths being manufactured from the [redacted] blend to produce a qualitatively and quantitatively equivalent set of products. The formulation is compressed at two different tablet core weights to produce the two tablet strengths which are discriminated by size and debossing.

The research tablets used to support the clinical investigational studies (including Phase 2b/3) were manufactured within the [redacted] UK. The formal registration stability batches were manufactured at the proposed commercial manufacturing site at [redacted] Germany.

2.7.1.1.2.2. Dissolution Testing of Drug Product Characteristics

Greater than [redacted]% dissolution of the maraviroc research tablet was obtained within [redacted] minutes in acidic dissolution media (up to pH [redacted]. Due to this high solubility of the tablet, a suitably sensitive dissolution methodology was established to discern formulation, drug product and stability changes that could impact tablet performance. The development of the dissolution methodology is described below.

Dissolution Methodology.

Conditions for dissolution studies (medium, apparatus, and agitation rate) were selected based on the recommendations in the FDA Guidance for Industry (Dissolution Testing of Immediate Release Solid Oral Dosage Forms, CDER, August 1997). Standard USP media were evaluated; i.e., 0.1M hydrochloric acid (HCl), 0.01M HCl, USP pH 4.5 buffer, and USP pH 6.8 buffer. Water was not investigated as a dissolution medium since its quality and pH can vary depending on the source; and the pH of the water may change during the course of the dissolution test.

Dissolution method development studies with maraviroc tablets were conducted using Dissolution Apparatus 1 (USP Baskets at 100 rpm) and 2 (USP Paddles at 50 and 75 rpm).

[redacted]

Therefore, the final conditions for dissolution testing of maraviroc tablets employed basket apparatus with the baskets rotating at [redacted] rpm in 900 mL of [redacted] held at 37 ± 0.5°C.

This method was used to generate dissolution data from the key research, stability and developmental batches manufactured (Section 3.2.P.2 Pharmaceutical Development).

Dissolution Testing of Drug Product Attributes

1) Developmental batches

Variations in the levels of [redacted] and [redacted] of 300 mg maraviroc tablets were evaluated for impact on dissolution performance. [redacted] (Section 3.2.P.1.2, Module 3.2.P.2 Pharmaceutical Development).

2) Particle size

The product attributes that the particle size of the drug substance could potentially affect are the tablet content uniformity and dissolution. [redacted] Section 3.2.S.2.6, Manufacturing Process Development.

[redacted]

3) Commercial Formulation

Development of the commercial tablet from the research tablet required only minor changes to the level of lubricant, the tablet shape and the film-coat.

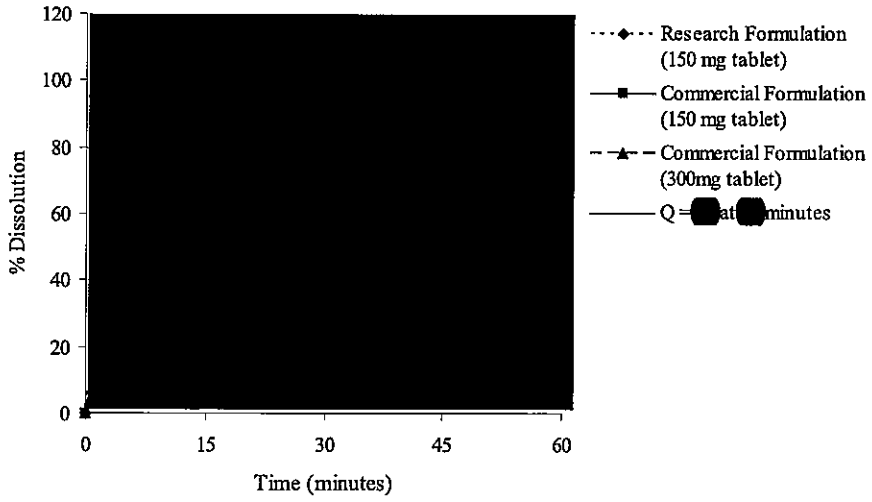
Dissolution testing of research and commercial 150 mg tablets resulted in similar dissolution profiles. The minor changes in lubricant, tablet shape and film coat had no effect upon dissolution of the commercial tablet formulation compared with the clinical tablet formulation.

An additional tablet strength (300 mg) was proposed for commercial use. This was achieved by using the [redacted] and increasing the tablet core compression weight. The requirement for the higher commercial tablet strength from the [redacted] necessitated a modification in tablet shape from round to oval to facilitate ease of swallowing, which was applied to both the proposed commercial strength tablets (150 mg

and 300 mg). The increase in tablet weight and change of tablet shape had no effect on tablet quality attributes such as dissolution.

The dissolution profile for the 150 mg research tablet, 150 mg commercial tablet and 300 mg commercial tablet are shown in Figure 2, illustrating the similarity in dissolution profiles across formulations and product strengths.

Figure 2. Dissolution Profiles of the Maraviroc Research Tablet (150 mg) and Commercial Tablet (150 mg and 300 mg)



Bioequivalence of the clinical and commercial formulations *in vivo* was investigated in Study A4001040 (Section 2.7.1.2.1).

2.7.1.1.2.3. Drug Product Stability

A stability programme consisting of one batch of 150 mg maraviroc commercial tablets, and three batches of 75 mg and 300 mg maraviroc commercial tablets was set up in accordance with ICH guidelines (Module 3.2.P.8.1, Stability Summary and Conclusions). All three strengths were manufactured from a common blend and manufactured and packaged at [redacted] Germany.

An overview of the schedule of stability tests for the thermal programme is presented in Table 3. At the time of submission, up to and including 12 months of stability testing has been performed.

Table 3. Summary of Stability Testing

Storage conditions	Interval							
	Initial	3M	6M	9M	12M	18M	24M	36M
Thermal Programme								
25°C/60% RH	A	B	A	B	A	B	A	A
30°C/65% RH		B	A	B	A	B	A	A
40°C/75% RH †		B	A					
5°C		Samples for appearance control at each test interval						

M = Months; RH= relative humidity
Sequence A: drug batches were tested for appearance, assay, degradation products, enantiomer content (chiral assay), dissolution, water content, hardness and microbiological quality
Sequence B: drug batches were tested for appearance, assay, degradation products, dissolution, water content and hardness

No trends were noted for any of the parameters analysed, therefore statistical analysis was not performed.

The 12-month stability data supports a 24-month shelf life for maraviroc tablets packaged in HDPE (high density polyethylene) bottles with heat induction seal and squeeze turn child resistant/ continuous turn closures and PVC (polyvinyl chloride) blisters.

2.7.1.1.3. Overview of Biopharmaceutic Studies

The maraviroc biopharmaceutic clinical development programme comprised five Phase 1 studies that examined the bioavailability and bioequivalence of maraviroc formulations. All studies were conducted in accordance with good clinical practice, and were consistent with US and European guidelines on bioequivalence, bioavailability and food effect studies (FDA. Guidance for Industry: Statistical Approaches to Establishing Bioequivalence. January 2001, FDA. Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations. March 2003, FDA. Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification. September 2002, CPMP Note for Guidance on the Investigation of Bioavailability and Bioequivalence, July 2001, FDA Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies, December 2002)

Summaries of all these studies and additional data from supportive clinical studies with investigative food restriction treatment groups are presented in Section 2.7.1.2 of this document. An overview of maraviroc biopharmaceutic studies are presented in Table 4.

Table 4. Overview of Maraviroc Biopharmaceutic Studies

Protocol	Design	Objective	Maraviroc Dose
Bioequivalence Study			
A4001040 (N=44)	Open, randomised 2-way crossover study	To compare the pharmacokinetics of maraviroc following a single dose of the proposed commercial tablet compared to the research tablet to determine bioequivalence between the formulations	Research Tablet 300 mg (2 x 150 mg tablets) Commercial Tablet 300 mg (1 x 300 mg tablet)
Bioavailability Studies			
A4001003 (N=15)	Open, randomised, 5-way crossover study in healthy male subjects	To investigate the pharmacokinetics of single oral tablet doses of maraviroc, the effect of food on a single dose (600 mg), the relative oral bioavailability of the tablet vs. oral solution (100 mg)	Research Tablet *Fasted*: 50 mg (1x50 mg tablet), 100 mg (1x100 mg tablet) and 600 mg (4x150 mg tablets) *Fed*[a]: 600 mg (4x150 mg tablets) Solution *Fasted*: 100 mg
A4001009 (N=20)	Cohort 1: double-blind (third party open), four-way crossover study, Cohort 2: open, two-way crossover study	To investigate the safety and toleration of intravenous (IV) maraviroc and to determine the absolute bioavailability of a 100 mg oral tablet dose.	Cohort 1: 3, 10 and 30 mg (IV) Cohort 2: 30 mg (IV), 100 mg (1x100 mg research tablet)
Food Effect Studies			
A4001004 (N=15)	Open, randomised, single dose, five way incomplete block design cross-over study	To investigate the effects of food administration at different times relative to oral dosing on the pharmacokinetics of a single 100 mg maraviroc dose (tablet).	Research Tablet *Fasted:* 100 mg (1x100 mg tablet) *Fed*[a]*:* 100 mg (1 hr before food, with food, 1 hr, 2 hr, 4 hr post food)
A4001043 (N=12)	Open, randomised 2-way crossover study	To determine the effect of food on the pharmacokinetics of the commercial formulation of maraviroc	Commercial Tablet *Fasted*: 300 mg (1x300 mg tablet) *Fed*[a]: 300 mg (1x300 mg tablet)
Supportive Food Effect Data from Clinical Studies			
A4001001 (N=24)	First in human, double-blind, dose escalating, single dose crossover study	To determine the safety, toleration and pharmacokinetics of single oral doses of maraviroc (1-1200 mg) in the fed and fasted states (100 mg comparison only)	Solution Cohort A: *Fasted:* 1, 10, 100, 900 mg *Fed*[a]*:* 100 mg Cohort B: *Fasted*: 3, 30, 300, 1200 mg
A4001015 (N=37)	Double-blind, randomised, placebo controlled five treatment, parallel group study	To assess the effect of food, and dose regimen on viral load response in HIV-1 infected patients on short-term maraviroc monotherapy.	Research Tablet *Fasted:* 100 mg QD (1x100 mg tablet), 150 mg BID (1x100 mg and 1x50 mg tablets) and 300 mg QD (3x100 mg tablets) *Fed*[b]*:* 150 mg BID (1x100 mg and 1x50 mg tablets)

[a]Fed refers to a high fat breakfast comprising approximately 1000 calories of which approximately half were derived from fat.
[b]In A4001015 in the fed group, maraviroc was administered in the morning with a high fat breakfast and in the evening with a standard meal supplemented with a high calorie drink.

The bioequivalence of the 300 mg proposed commercial tablet relative to 2x150 mg research tablets was evaluated in Study A4001040.

Two studies investigated the bioavailability of maraviroc research tablets. Study A4001003 evaluated the relative oral bioavailability of the 100 mg maraviroc research tablet compared with 100 mg of maraviroc solution. Study A4001009 determined the absolute bioavailability of maraviroc given as a 100 mg research tablet relative to a 30 mg intravenous (IV) infusion of maraviroc (approximately equivalent to 100 mg oral maraviroc). Study A4001003 also investigated the dose proportionality of oral maraviroc pharmacokinetics.

The effect of food on the pharmacokinetics of the proposed 300 mg maraviroc commercial formulation was investigated in Study A4001043. Information on the effect and timing of food on the pharmacokinetics of the maraviroc research tablet (100 mg) was investigated in Study A4001004. Additional information on the effect of food on the pharmacokinetics of a 600 mg maraviroc dose (4 x 150 mg research tablets) and 100 mg maraviroc solution were provided by studies A4001003 and A4001001 respectively. Study A4001015, a Phase 2a 10 day maraviroc monotherapy study provided some additional supportive information on the effect of food on maraviroc pharmacokinetics in HIV-1 infected patients (150 mg BID).

Pharmacokinetic and pharmacodynamic modelling of the Phase 1 and 2a studies was performed. A component of two of these analyses was to further characterise the effect of food on the bioavailability of maraviroc research tablets and solution, in order to predict the effect of food on maraviroc pharmacokinetics at doses not studied (Section 2.7.1.1.4.4). Full detail of the methodology and results can be found in the individual modelling reports located in Module 5.3.3.5.

The biopharmaceutic studies presented in this summary are a subset of the maraviroc clinical pharmacology programme; the remaining studies and pharmacokinetic/pharmacodynamic modelling are described in Module 2.7.2 Summary of Clinical Pharmacology Studies.

2.7.1.1.4. Overview of Methods and Analysis of Clinical Samples

2.7.1.1.4.1. Pharmacokinetic sampling

Blood samples (5 mL) were taken to provide at least 2 mL of plasma for measuring maraviroc concentrations. Samples were collected into heparinised tubes just prior to dosing and at protocol specified times after dosing as detailed in the individual clinical study reports. Within one hour of collection the samples were centrifuged at 1500 -1700g at 4°C for 10 minutes and the resulting plasma stored in screw capped polypropylene tubes at -20°C.

Where appropriate, urine samples were collected from each subject over protocol specified intervals. Following mixing, 10 mL aliquots of urine from each collection period were removed and transferred to tubes for storage at -20° C.

At a time determined by the sponsor plasma and urine samples were transported to the analytical laboratory to be assayed for maraviroc concentrations using previously validated

methods (further details provided Section 2.7.1.1.4.2 and Table 5). Final concentration data was transferred to the Pfizer Clinical Data System.

2.7.1.1.4.2. Pharmacokinetic Analytical Methods

In the first two completed Phase 1 studies (A4001001, A4001002), plasma and urine concentrations of maraviroc were determined by validated solid phase extraction and reverse phase chromatography methods developed in house by the 施設1*.
For all other clinical studies in healthy volunteers and HIV-1 infected patients, plasma and urine concentrations of maraviroc were determined using validated high-performance liquid chromatography (HPLC) coupled with tandem mass spectrometric detection (MS/MS) assays by the analytical laboratories 施設2* [redacted] Canada) and 施設3* [redacted] USA).

The bioanalytical methods used for the maraviroc programme are supported by validation reports provided in Module 5.3.14. The complete final analytical reports for each study are located within the individual study reports in Module 5.

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Table 5. Overview of Maraviroc Laboratory Analysis

Study	Company	Assay	Sample	Calibration curve
A4001001 and -1002	施設1*	Solid phase extraction of the analyte with separation by reverse phase chromatography followed by mass spectrometric detection using deuterated maraviroc (UK-462,015) as the internal standard	Plasma	0.25 -50 ng/mL (A4001001) 0.5 -200 ng/mL (A4001002)
		Solid phase extraction of the analyte with separation by HPLC followed by mass spectrometric detection using deuterated maraviroc (UK-462,015) as the internal standard	Urine	5-100 ng/mL
A4001003, -1004, -1005, -1006, -1007, -1008, -1009, -1010, -1011, -1012, -1013, -1015, -1016, -1018, -1019	施設2* Canada	Solid phase extraction of the analyte with separation by liquid chromatography followed by APCI and tandem mass spectrometric detection using deuterated maraviroc (UK-462,015) as the internal standard	Plasma	0.5, 1, 2, 5, 20, 40, 100 and 200 ng/mL
		Protein precipitation and analysis using a Sciex API III+ LC-MS-MS system using deuterated maraviroc (UK-462,015) as the internal standard	Urine	5, 10, 20, 50, 100, 200, 500, 750 and 1000 ng/mL
A4001021, -1022, 1025, -1026, 1027, -1028, 1029, -1033, 1038, -1040, 1042, -1043,-1046	施設3* USA	Protein precipitation for sample preparation and analysis using a Sciex API 4000 LC-MS-MS system using deuterated maraviroc (UK- 462,015) as the internal standard.	Plasma	0.5, 1, 2, 10, 40, 100, 200, 400 and 500 ng/ml.
			Urine	5, 10, 50, 100, 500, 1000, 2000, 4000 and 5000 ng/mL
Studies A1001004, -1040 and -1043 are described only this summary, the rest of the studies, with the exception of A4001026, -1027, -1028 and -1029, are described in Module 2.7.2, Summary of Clinical Pharmacology Studies. Phase 2b/3 studies (A4001026, -1027, -1028 and -1029) are described in Modules 2.7.3 and 2.7.4, Summary of Clinical Efficacy and Safety respectively.				

The assay linearity, accuracy, and precision were determined during method validation studies at both 施設2* and 施設3*, as described below. Further details regarding the validation of sample dilution integrity and sample stability can be found within the individual validation reports for each laboratory and assay which are located in Module 5.3.1.4.

The linearity of the assay over pharmacologically relevant concentrations was demonstrated by the fact that the correlation coefficients were near unity ($r^2 \geq 0.994$) for standard curves constructed at all analytical laboratories utilised.

Intra- and inter-assay precision and accuracy were determined in each laboratory using three quality control (QC) samples. As shown in Table 6, at every QC sample concentration intra- and inter-assay inaccuracy for plasma and urine measurements was $\leq 20\%$ and 17% for

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施設2* and ≤ 11% and 12% for 施設3*, respectively. Intra- and inter-assay imprecision was within 10% for all laboratories.

Table 6. Summary of Accuracy and Precision for Assays Measuring Maraviroc Concentration

Company/QC Sample Concentrations (ng/mL)	Inaccuracy (%)		Imprecision (% CV)	
	Range of Intra-assay Daily Mean	Inter-assay Mean	Range of Intra-assay Daily Mean	Inter-assay Mean
Plasma				
施設1*, *				
0.1	n/c	2.33	n/c	6.04
0.3	n/c	3.73	n/c	2.05
5.0	n/c	5.71	n/c	0.78
10.0	n/c	0.44.36	n/c	0.69
施設2*				
1.0	-9.8 to 8.0	-1.0	1.7 to 8.8	7.6
90.0	-10.8 to -5.7	-6.2	1.1 to 4.1	5.1
180.0	-19.4 to -1.7	-7.8	1.2 to 8.1	6.7
施設3*				
1.5	-6.0 to 0.7	-2.7	1.3 to 5.0	4.1
150.0	-10.7 to 4.7	-1.3	1.3 to 3.7	6.1
400.0	-2.5 to 4.3	-0.3	1.3 to 3.8	3.8
Urine				
施設1*, *				
5.0	n/c	-6.55	n/c	5.63
10.0	n/c	3.84	n/c	7.38
500.0	n/c	0.30	n/c	0.45
1000.0	n/c	2.60	n/c	3.46
施設2*				
15.0	-8.0 to 16.7	7.3	2.7 to 5.7	9.6
300.0	-1.7 to 3.3	1.0	0.8 to 4.6	3.4
900.0	-0.4 to 7.9	2.2	1.8 to 3.5	3.5
施設3*				
15.0	6.7 to 11.3	8.7	1.3 to 4.4	3.1
1500.0	8.0 to 10.0	8.7	1.2 to 2.8	2.0
3750.0	0.5 to 3.7	2.1	1.2 to 2.1	1.9

Source: Individual Assay Validation Reports in Module 5.3.1.4
*Results presented from replicates in validation run 3 for plasma and batch 2 for urine.
n/c=non calculated
A4009000: Validation report UK-427,857 in Human Plasma (施設1*)
A4009003: Validation report UK-427,857 in Human Urine (施設1*)
A4009001: Validation of an LC/MS/MS Method for the Quantitation of UK-427,857 in Human Plasma (施設2*)
A4009005: Validation of an LC/MS/MS Method for the Quantitation of UK-427,857 in Human Urine (施設2*)
A4009008: Quantitative Determination of UK-427, 857 and UK-408,027 in Human Plasma by LC/MS/MS (施設3*)
A4009009: Quantitative Determination of UK-427, 857 in Human Urine by LC/MS/MS (施設3*)

2.7.1.1.4.3. Pharmacokinetic Parameters and Statistical Methods

Methods for determination of pharmacokinetic parameters and methods for statistical comparisons, as well as data listings, summary statistics, and graphical presentations of pharmacokinetic data for all studies can be found in the individual clinical study reports

* ：新薬承認情報提供時に置き換えた

within Module 5 of this submission. Bioequivalence between treatment groups was deemed to be established if the 90% confidence intervals (CIs) for maraviroc AUC_{inf} were within established bioequivalence limits of 80% to 125% and pre-defined protocol limits for C_{max} of 70% to 143%.

2.7.1.1.4.4. Pharmacokinetic modelling of Phase 1/2a clinical data

The pharmacokinetics of maraviroc after single and multiple dosing were not dose proportional which is thought to be due to non linear absorption of maraviroc. In order to understand the absorption components of maraviroc pharmacokinetics further, pharmacokinetic modelling of clinical data was performed to investigate the non-proportional pharmacokinetics and the effect of dose, food and formulation on absorption and bioavailability. As these factors were a subset of the covariates examined in the modelling analyses, the full results are presented in the individual reports of the pharmacokinetic modelling analyses located in Module 5.3.3.5. Only the pertinent results relating to absorption and bioavailability from these reports will be discussed in this module. An overview of the objectives and data included in these reports are presented in Table 7.

Table 7. Overview of Pharmacokinetic Modelling (Pertinent to the Effects of Food and Formulation)

Analysis	Objectives	Data Included.
Population analysis of Maraviroc Phase 1 Non-compartmental Pharmacokinetic data	- to determine the effect of dose, food and formulation on single dose and multiple dose AUC and C_{max} - to predict AUC and C_{max} for food and formulation combinations at doses not included in studies - to provide a semi-quantative model for subsequent analyses.	Five Phase 1 studies (3 single dose: A4001001, A4001003, A4001004 and 2 multiple dose: A4001002, A4001019) Food Data Included Data from fasted occasions and when food (high fat meal) was administered simultaneously with the dose (A4001001, A4001003, A4001004).
Population Pharmacokinetics of Maraviroc After Oral Tablet Administration – A Pooled Analysis of Phase 1/2a Data	- to develop a compartmental structural pharmacokinetic model to describe rich maraviroc pharmacokinetic data after single and multiple oral dosing (tablet). - to quantify the variability of the pharmacokinetics of maraviroc. - to quantify the influence of covariates such as age, sex, race, HIV status and weight on the variability of the pharmacokinetics of maraviroc	15 studies in healthy volunteers (A4001003-1006, A4001011, A4001013, A4001016, A4001018, A4001019, A4001021, A4001022, A4001025, A4001038, A4001040, A4001043). 2 studies in HIV-1 infected patients (A4001007 A4001015). Food data included From study list above, only food data following oral administration of tablet doses under fasted (overnight fast and meals at least 4 hours post-dose) or fed (taken with high fat meal) conditions were included
Clearance and Mass Balance Model for Maraviroc	-to produce a model for the clearance and mass balance of maraviroc after single dose oral administration of 300 mg solution in healthy male volunteers	One single dose study (A4001010, 300 mg dose of [^{14}C] maraviroc solution in 3 healthy subjects)

2.7.1.2. Summary of Results of Individual Studies

A tabular summary of study design and estimated pharmacokinetic parameters for the 5 biopharmaceutic studies discussed below is provided in Table A1 in the appendix of this document. There were no safety issues raised during any of these studies; safety data are presented in Module 2.7.4 Summary of Clinical Safety.

2.7.1.2.1. Bioequivalence Study

The selected therapeutic doses for Phase 2b/3 studies were 300 mg QD or 300 BID in the absence of metabolic inducers or inhibitors. The unit dose of 300 mg was selected for the bioequivalence study and this was administered as one 300 mg commercial tablet or 2 x 150 mg research tablets, as 150 mg was the highest product strength of research tablet manufactured. The proposed commercial tablet will be available in two product strengths (150 mg and 300 mg) which are formulated from a common blend (i.e. identical proportions of active and inactive ingredients) and have similar in vitro dissolution performance.

Study A4001040

Study A4001040 was an open, randomised, 2 way crossover study to investigate the pharmacokinetics of maraviroc following a single dose of the commercial tablet compared to the research tablet in order to determine bioequivalence. The commercial tablet was manufactured at the proposed commercial manufacturing site of [redacted] Germany whilst the research tablet was manufactured in the development facility in [redacted] U.K.

Forty-four subjects participated in the study. Subjects received either the maraviroc research formulation (administered as 2 x 150 mg tablets) or the maraviroc 300 mg commercial formulation (administered as 1 x 300 mg tablet), on Day 1 in each treatment period, according to the randomisation schedule. There was a minimum 5 day washout period between each dose of study drug.

Administration of study drug occurred following an 8 hour fast from food and drink (except water). Water was restricted one hour pre-dose to two hours post-dose.

Results: For AUC_{inf} and C_{max} the 90% confidence interval of the ratios for the adjusted means fell within the acceptance range for bioequivalence of 80-125%. Although the protocol had allowed for wider CI for C_{max} the actual CI fell within the stricter 80-125% limits noted in regulatory guidances (FDA. Guidance for Industry: Statistical Approaches to Establishing Bioequivalence. January 2001, CPMP Note for Guidance on the Investigation of Bioavailability and Bioequivalence, July 2001). Mean T_{max} and $t_{½}$ were similar for both formulations.

The mean pharmacokinetic parameters and statistical comparisons are presented in Table 8

Table 8. Comparison of the Bioequivalence of the Commercial and Research Maraviroc Formulations at 300 mg

Parameter (units)	Mean Pharmacokinetic Values (range)		Ratio or Difference (90% CI)[a]
	Maraviroc 300 mg (1 x 300 mg Commercial Tablet) N=43[b]	Maraviroc 300 mg (2 x 150 mg Research Tablet) N=42	
AUC_{inf} (ng.h/ml)[c]	2720 (1470-4740)	2762 (1480-4510)	98.0% (93.9%, 102%)
AUC_{last} (ng.h/ml)[c]	2699 (1460-4650)	2729 (1470-4470)	98.4% (94.3%, 103%)
C_{max} (ng/ml)[c]	638 (343-1330)	654 (246-1220)	96.1% (88.1%, 105%)
T_{max} (h)[d]	2.47 (0.50-4.00)	2.45 (0.50-4.00)	0.04 (-0.33, 0.40)
$t_{½}$ (h)[d]	10.4 (8.51-14.7)	10.5 (8.51-13.7)	n/c

Source: A4001040 CSR Table 13.5.1, 13.5.3.2 and 13.5.3.3
[a] The ratios are expressed as percentages for AUC_{inf}, AUC_{last} and C_{max} and difference for T_{max}
[b] N=42 for AUC_{inf} and $t_{½}$
[c] Geometric means
[d] arithmetic means
CI=confidence interval, n/c=not calculated.

Since bioequivalence has been demonstrated between 2 x 150 mg research tablets and 1 x 300 mg commercial tablet, the Sponsor considered it unnecessary to investigate bioequivalence of 1 x 150 mg commercial tablet to 1 x 150 mg research tablet on the basis that 150 and 300 mg commercial tablets are manufactured from the same blend, and have identical compositions. Furthermore, the 150 mg research tablet and 150 mg commercial tablets are identical in terms of their in vitro dissolution performance

The results from Study A4001040 demonstrate that the commercial tablet is bioequivalent to research tablet at the therapeutic dose. The statistical comparisons of the research and commercial formulations were within the accepted levels used to assess bioequivalence in clinical studies for both AUC_{inf} and C_{max}. This study also underwrites the minor changes around lubricant level, film coat and image, in addition to the move of manufacturing from the development facility in [redacted] UK to the proposed commercial manufacturing site at [redacted] Germany.

2.7.1.2.2. Bioavailability Studies

Study A4001003

Study A4001003 was an open, randomised, five-way crossover study that investigated the pharmacokinetics of single oral doses of maraviroc (50, 100 and 600 mg), the effect of food on a single 600 mg dose and the relative oral bioavailability of the 100 mg research tablet versus the 100 mg oral solution. The 50 and 100 mg tablet doses were given as single research tablets and the 600 mg dose comprised 4x150 mg research tablets. Fifteen subjects entered the study. Subjects took single maraviroc doses of 50, 100 and 600 mg (4 x 150 mg research tablets) when fasted, 100 mg maraviroc as a solution fasted and 600 mg (4x150 mg research tablets) when fed. Successive treatments were separated by at least 5 days.

For the fasted periods, subjects fasted (except for water) from 22.00 hours the evening before each dose until at least four hours post-dose. For the fed period, subjects ate a high fat

breakfast within 20 minutes and received maraviroc within the subsequent five minutes. Subjects took maraviroc with 250 mL water and fluids were restricted one hour pre and post-dose. Dose proportionality was calculated using power law and dose divide methods as described in the statistical section of the clinical study report.

Results: Maraviroc pharmacokinetics were not dose proportional over the dose range 50 to 600 mg. Dose proportionality could not be concluded for C_{max} as the power law analysis indicated a deviation from linearity. The dose proportionality constant for AUC_{inf} was estimated as 1.18 (95% CI; 1.10, 1.26). Table 9 provides a summary of the pharmacokinetic data for the 50 mg, 100 mg and 600 mg doses of maraviroc.

Table 9. Summary of Mean Maraviroc Pharmacokinetic Parameters (A4001003)

Parameter (units)	Mean Parameter Values (range)		
	Maraviroc 50 mg Research Tablet N=15	Maraviroc 100 mg Research Tablet N=15	Maraviroc 600 mg (4 x 150 mg Research Tablets) N=15
AUC_{last}(ng.h/ml)[a]	209 (72.0 to 376)	555 (133 to 1070)	5636 (4150 to 9630)
AUC_{inf} (ng.h/ml)[a]	227 (80.2 to 396)	576 (150 to 1090)	5703 (4200 to 9750)
C_{max} (ng/ml)[a]	55.0 (25.9 to 124)	154 (28.3 to 470)	1221 (762 to 1910)
T_{max} (h)[b]	3.0 (1.00 to 6.00)	2.33 (0.50 to 4.00)	3.30 (1.00 to 6.00)
t½ (h)[b]	14.4 (10.1 to 20.5)	13.3 (7.48 to 17.7)	11.5 (9.32 to 14.2)

Source: A4001003 CSR Table 5.1.
[a] Geometric means
[b] arithmetic means

The relative bioavailability of the tablet compared to the solution in the fasted state (as assessed by ratio of AUC_{inf}) was 88% (90% CI; 74,105%). There was no clinically relevant difference in mean T_{max} and t½. Table 10 shows the relative bioavailability comparison between the 100 mg research tablet fasted and the 100 mg solution fasted and 90% CIs for each parameter.

Table 10. Comparison of the Relative Bioavailability of 100 mg Maraviroc Research Tablet and 100 mg Solution

Parameter (units)	Mean Parameter Values (range)		Ratio or Difference (90% CI)[a]
	Maraviroc 100 mg Research tablet (fasted) N=15	Maraviroc 100 mg solution (fasted) N=15	
AUC_{inf} (ng.h/ml)[b]	576 (383-1090)	654 (293-1160)	88 (74, 105)
C_{max} (ng/ml)[b]	154 (28.3-470)	170 (60.7-333)	90 (69, 118)
T_{max} (h)[c]	2.30 (0.50-4.00)	2.80 (1.00-4.00)	-0.43 (-1.24, 0.37)
t½ (h)[c]	13.3 (7.48-17.7)	12.6 (7.30-16.0)	0.65 (-0.57, 1.88)

Source: A4001003 CSR Tables 5.1 and 5.5.1;
[a] ratios (%) (tablet/solution) are presented for AUC_{inf} and C_{max} and differences are presented for T_{max} and t½;
[b] geometric means,
[c] arithmetic means,
CI = confidence interval

The effects of food on a single 600 mg dose of maraviroc are presented in section 2.7.1.2.3 of this document.

Study A4001009

Study A4001009 investigated the pharmacokinetics of escalating intravenous (IV) doses of maraviroc and determined the absolute bioavailability of 100 mg oral dose of maraviroc.

This study comprised two cohorts of subjects.

Cohort 1 involved a double-blind (third party open), four-way crossover study, where eight subjects received escalating IV doses (given as one hour infusions) of maraviroc (3, 10 and 30 mg) with placebo insertion. The safety, toleration and pharmacokinetics of each IV dose in Cohort 1 were assessed prior to the next dose, to allow adjustment of the subsequent doses (up or down as appropriate). The aim was for the maximum IV dose to have an exposure similar to that previously seen following a single oral dose of 100 mg tablet; this IV dose was to be used in Cohort 2.

Cohort 2 involved an open, two-way crossover study where 12 subjects received 30 mg maraviroc by IV infusion and 100 mg oral maraviroc research tablet in random order.

Subjects were fasted from food and drink (except water) from 22:00 hours on the evening prior to each dose until at least four hours post-dose the following morning. Water was restricted one hour pre-dose to one hour post-dose.

Results: Maraviroc IV pharmacokinetics appear linear (dose proportionality constant for AUC_{last} was 1.07 [95% CI: 1.01 1.12], and for C_{max} it was 1.03 [95%: 0.96, 1.11]), suggesting systemic clearance is independent of dose over this range of doses. The results from Cohort 1 are presented in Table 11.

Table 11. Mean Maraviroc IV Pharmacokinetic Parameters (Cohort 1, A4001009)

Parameter (units)	Mean Parameter Values (range)			Dose Proportionality Estimate[a] (95% CI)
	Maraviroc 3 mg IV infusion N=8	Maraviroc 10 mg IV infusion N=8	Maraviroc 30 mg IV infusion N=8	
AUC_{last} (ng.h/ml)[b]	57.6 (50.5 to 64.6)	201 (180 to 252)	670 (534 to 795)	1.07 (1.01, 1.12)
C_{max} (ng/ml)[b]	36.9 (23.4 to 44.6)	122 (104 to 156)	397 (308 to 464)	1.03 (0.96, 1.11)
T_{max} (h)[c]	0.94 (0.75 to 1.00)	0.94 (0.50 to 1.00)	0.91 (0.50 to 1.00)	n/c
$t½$ (h)[c]	n/c	n/c	13.2 (10. 3 to 18.3)	n/c

Source: A4001009 CSR Tables 5.1.1.1 and 5.4.
[a]dose normalized to 1mg; a dose proportionality constant has only been presented if there is evidence to assume both linearity and a common slope; CIs (confidence intervals),
[b]Geometric means;
[c]arithmetic means
CI= confidence interval, n/c not calculated

The mean oral bioavailability of 100 mg maraviroc was estimated as 23.1% (90% CI: 19.2%, 27.8%) and mean plasma pharmacokinetic parameters for the 30 mg IV and 100 mg oral doses in Cohort 2 are summarised in Table 12:

Table 12. Comparison of the Relative Bioavailability of Maraviroc Tablet (100 mg) versus Intravenous Solution (30 mg)-Cohort 2 (A4001009)

Parameter (units)	Mean Parameter Values (range)		Ratio Test/reference (90% CI)[a,b]
	Maraviroc 30 mg IV infusion (fasted)	Maraviroc 100 mg Research tablet (fasted)	
AUC_{inf} (ng.h/ml)[c]	656 (506-842)	506 (311-1030)	23.1 (19.2, 27.8)
C_{max} (ng/ml)[c]	374 (299-439)	122 (64.1-314)	n/c
T_{max} (h)[d]	0.98 (0.75-1.00)	3.08 (1.00-4.00)	n/c
$t_{½}$ (h)[d]	12.0 (9.64-14.9)	12.5 (9.66-15.0)	n/c

Source: A4001009 CSR Tables 5.1.2 and 5.5.2.
[a] Test = 100 mg oral maraviroc, Reference = 30mg IV maraviroc,
[b] Test and reference have been normalised to 1mg.
[c] Geometric means;
[d] arithmetic means
CI = confidence interval, n/c = not calculated

2.7.1.2.3. Food Interaction Studies

The effect of food on different maraviroc doses given as tablets was investigated in three studies in healthy volunteers. Studies A4001003, A4001004 and A4001043 investigated the effect of food on the pharmacokinetics of maraviroc at 600 mg (4 x 150 mg research tablets), 100 mg (1 x 100 mg research tablet) and 300 mg (1 x 300 mg commercial tablet) respectively. Study A4001004 also investigated the effect of timing of food relative to maraviroc dosing.

In addition, Study A4001001 (first in human study) also investigated the effect of food on the pharmacokinetics of maraviroc following 100 mg solution. Study A4001015 was not a formal fed/fasted comparison, but the results are included here to provide data on the effect of food on maraviroc pharmacokinetics in HIV-1 infected patients.

In all of these studies, subjects were given a high fat breakfast consistent with that recommended by the Food and Drug Administration for food- effect bioavailability studies (FDA Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies, December 2002).

Study A4001043

Study A4001043 was an open, randomised, 2 way crossover study to confirm the effect of food on the pharmacokinetics of the proposed maraviroc commercial tablet (1 x 300 mg commercial tablet).

Twelve subjects participated in the study and all subjects received a single 300 mg dose of maraviroc (1 x 300 mg commercial tablet) in each treatment period, either after an overnight fast, or following a high fat breakfast, according to the randomisation schedule. Subjects

were not permitted to eat or drink (except water) for four hours post-dose. There was a minimum 5 day washout period between each dose of study drug.

Results: Administration of the 300 mg commercial tablet with a high fat breakfast reduced maraviroc AUC_{inf} and C_{max} by approximately 33% compared to the fasted state. There were no clinically relevant changes in mean T_{max} or t½ following administration with of maraviroc with food (Table 13).

Table 13. Summary of the Effect of Food on the Maraviroc Commercial Formulation (300 mg tablet)

Parameter (units)	Mean Parameter Values (range) Maraviroc Commercial Tablet 300 mg		Treatment Comparison Ratio or Difference (90% CI)[a]
	Fasted N=12	Fed N=12	
AUC_{inf} (ng.h/ml)[b]	3117 (2280-4710)	2084 (944-4060)	67% (57%, 78%)
AUC_{last} (ng.h/ml)[b]	3079 (2250-4690)	2047 (892-3970)	67% (57%, 78%)
C_{max} (ng/ml)[b]	674 (345-1350)	454 (85-1180)	67% (49%, 93%)
T_{max} (h)[c]	3.00 (1.50-6.00)	4.00 (1.50-8.00)	0.90 (-0.60, 2.40)
t½ (h)[c]	11.0 (8.00-15.2)	10.3 (7.90-12.4)	n/c

Source: A4001043 CSR Table 13.5.1, 13.5.3.2 and 13.5.3.3
[a] The ratios are expressed as percentages for AUC_{inf}, AUC_{last} and C_{max} and the difference for T_{max}
[b] geometric mean
[c] arithmetic mean
CI=confidence interval, n/c=not calculated

Study A4001003

The study design and results of the relative bioavailability and dose proportionality components of Study A4001003 have already been described in this document (see section 2.7.1.2.2).

Following food, the mean C_{max} and AUC_{inf} of maraviroc 600 mg (4 x 150 mg research tablets) was reduced by 36% and 33 % respectively, compared to the fasted state. There were no clinically relevant changes in mean T_{max} or t½ (Table 14).

Table 14. Comparison of the Fed/Fasted Bioavailability of Maraviroc (600 mg, A4001003)

Parameter (units)	Mean Values (range)		Ratio or Difference (90% CI)[a]
	Maraviroc 600 mg (4x150 mg research tablets) Fasted N=15	Maraviroc 600 mg (4x150 mg research tablets) Fed N=15	
AUC_{inf} (ng.h/ml)[b]	5703 (4200-9750)	3805 (1960-6960)	66 (55, 79)
C_{max} (ng/ml)[b]	1221 (762-1910)	783 (450-1740)	64 (49, 84)
T_{max} (h)[c]	3.30 (1.00-6.00)	3.10 (1.00-6.00)	-0.23 (-1.04, 0.57)
t½ (h)[c]	11.5 (9.32-14.2)	13.6 (9.30-19.3)	2.15 (0.92, 3.37)

Source: A4001003 CSR Tables 5.1, 5.5.1 and 5.5.2
[a]ratios (%) (fed/fasted) are presented for AUC_{inf} and C_{max} and differences are presented for T_{max} and t½;
[b]geometric means,
[c]arithmetic means,
CI = confidence interval

Study A4001004

Study A4001004 was an open, randomised, single dose, five way incomplete block design crossover study in fifteen healthy volunteers to investigate the effects of food and timing of food intake on the pharmacokinetics of a 100 mg dose of maraviroc (1 x 100 mg research tablet). Each subject was randomised to receive the fasted treatment, and four of the five fed treatments.

For the fasted treatment, subjects were fasted overnight (at least 10 hours) until at least 4 hours post-dose. Subjects were administered the 100 mg dose with 250 ml of water. Water was allowed as desired, except for one hour pre- and post-dosing.

The five fed treatments were:

- Dosing one hour prior to commencement of high fat breakfast
- Dosing within five minutes following completion of high fat breakfast
- Dosing one hour after completion of high fat breakfast
- Dosing two hours after completion of high fat breakfast
- Dosing four hours after completion of high fat breakfast

For the fed treatments, subjects were fasted overnight (at least 10 hours). The high fat breakfast had to be consumed within 20 minutes and maraviroc was administered with 250 mL of water. No additional food was allowed for at least four hours post-dose. Water was allowed as desired, except for one hour pre- and post-dosing.

Results: When maraviroc was dosed with food and up to 2 hours after food, mean C_{max} and AUC_{inf} were reduced by approximately 70% and 50% respectively compared to the fasted state. Dosing 1 hour prior to food, or 4 hours after food, led to smaller reductions in C_{max} and AUC_{inf} (≥ 20%) compared to the fasted state. There were no clinically relevant effects of food on mean T_{max} or t½ (Table 15, Table 16).

Table 15. Summary of Mean Maraviroc Pharmacokinetics Parameters (A4001004)

Parameter (units)	Mean Values (range) Maraviroc 100 mg Research Tablet					
	Fasted N=14	Dosing 1h prior to food N=11	Dosing with food N=11	Dosing 1h post food N=12	Dosing 2h post food N=11	Dosing 4h post food N=11
AUC_{inf} (ng.h/ml)[a]	505 (345-951)	387 (223-869)	249 (149-510)	274 (187-370)	295 (195-462)	397 (198-727)
C_{max} (ng/ml)[a]	113 (55-322)	107 (56-391)	38.7 (12.1- 88.0)	38.4 (14.6-76.2)	39.5 (17.1-84.1)	88.4 (55.4-176)
T_{max} (h)[b]	3.2 (1.50-4.0)	2.1 (0.5-4.0)	3.1 (0.5-6.0)	3.8 (1.5-6.0)	3.6 (1.0-6.0)	2.7 (0.5-6.0)
t½ (h)[b]	12.5 (8.1-16.1)	13.4 (8.9-18.9)	13.8 (8.3-24.2)	12.5 (9.0-16.5)	14.1 (7.4-19.9)	13.2 (9.1-17.0)

Source: A4001004 CSR Tables 5.1.1, 5.1.2, 5.1.3, 5.1.4, 5.1.5 and 5.16
[a] geometric mean
[b] arithmetic mean

The statistical results of the fed/fasted comparison for each treatment group are presented in Table 16.

Table 16. Summary of Statistical Comparisons for Study A4001004

Comparison	Ratios % (90% CI)[a]	
	AUC_{inf}	C_{max}
Dosing 1h prior to food v fasted	79.5% (67.0, 94.3)	98.6% (71.8, 135.5)
Dosing with food v fasted	48.0 % (40.7, 56.7)	31.8% (23.1, 43.7)
Dosing 1h post food v fasted	50.0 % (42.4, 59.0)	32.6% (24.0, 44.4)
Dosing 2h post food v fasted	55.2% (46.5, 65.5)	34.6% (25.2, 47.6)
Dosing 4h post food v fasted	80.3% (68.1, 94.7)	83.4% (60.7, 114.6)

Source: A4001004 CSR Tables 5.3 and 5.4
CI=Confidence Interval

Study A4001001

Study A4001001 was a double blind (3rd party open), placebo controlled, dose escalating, crossover study to investigate the safety, toleration and pharmacokinetics of single oral doses (solution) of maraviroc in healthy male subjects in the fed and fasted states. Study A4001001 is described fully in section 2.7.2.2.2, Module 2.7.2 Summary of Clinical Pharmacology

Subjects fasted from 22:00 hours the day before each dose until at least four hours post-dose (except for subjects during their fed study period). Water was only restricted one hour pre and post-dose. In the fed period, after an overnight fast, subjects had to eat their high fat breakfast within 20 minutes and receive study drug within the subsequent five minutes.

Food reduced maraviroc mean AUC_{inf} and C_{max} by approximately 63% and 88% respectively (Table 17).

Table 17. Summary of Mean Maraviroc Pharmacokinetic Parameters (A4001001)

Parameter (units)	Mean Values (range) 100 mg Maraviroc Solution		Ratio or Difference (90% CI)a
	Fasted N=9	Fed N=12	
AUC_{inf} (ng.h/ml)[b]	619 (557-730)	222 (148-412)	37.4 (30.5,45.9)
C_{max} (ng/ml)[b]	172 (132-229)	19.3 (13.1-83.7)	12.2 (8.3,17.9)
T_{max} (h)[c]	3.10 (2.00-4.00)	2.90 (1.50-6.00)	0.17 (-0.79,0.45)
t½ (h)[c]	9.90 (7.40-14.0)	14.0 (9.00-18.4)	2.66 (0.62,4.70)

Source: A4001001 CSR Table 5.1.1
[a] ratios (%) (fed/fasted) are presented for AUC_{inf} and C_{max} and differences are presented for T_{max} and t½;
[b] geometric mean,
[c] arithmetic mean
CI=confidence interval

Study A4001015

Study A4001015 was a randomised, double blind, placebo controlled study, to assess the effect of food and the effect of QD compared to BID dosing on the anti-viral effects of maraviroc and the pharmacokinetic-pharmacodynamic relationships in HIV-1 infected subjects on short-term maraviroc monotherapy. Pharmacokinetic data only are presented here, with efficacy data being presented in Module 2.7.3, Summary of Clinical Efficacy.

Thirty-seven subjects participated in the study. Subjects took the morning dose of the study drug to which they were randomised, under supervision with 250 mL water. Subjects took the evening dose 12 hours after the morning dose.

Fasted subjects received study drug in the morning at least one hour before breakfast and in the evening they fasted for four hours pre-dose and one hour post-dose. They had lunch but were not permitted water for one hour pre and post-dose.

Fed subjects ate a high fat breakfast within a 20 minute period and within 30 minutes of starting breakfast they received study drug. Subjects took the evening dose not more than 30 minutes after starting their evening meal and were provided with a high calorie drink to consume with this meal.

Results: A formal statistical comparison of the pharmacokinetic data from the two groups of subjects was not conducted, however the mean C_{max} and AUC_{tau} of 150 mg BID appeared to be approximately 60% and 50% lower respectively, when fed compared to fasted (Table 18).

Table 18. Summary of the Effect of Food on Maraviroc Pharmacokinetics in HIV-1 Infected Subjects (150 mg)

Parameter (units)	Mean Parameter Values (range) Maraviroc 150 mg BID (1 x 100 mg and 1 x 50 mg research tablets)	
	Fasted N=8	Fed N=8
AUC_{tau} (ng.h/ml)[a]	933 (374-1700)	474 (163-1030)
C_{max} (ng/ml)[a]	273 (90.1-658)	110 (39.6-248)
T_{max} (h)[b]	3.00 (1.00-6.00)	2.30 (1.00-4.00)

Source: A4001015 CSR Table 5.1.
[a] geometric mean
[b] arithmetic mean

2.7.1.3. Comparison and Analyses of Results Across Studies

2.7.1.3.1. Bioequivalence of Maraviroc Tablet Formulations

In Study A4001040, the ratios for the adjusted means and the 90% CI for the comparison between research and commercial tablets lay within the acceptable range for bioequivalence of 80-125% for AUC_{inf} and C_{max}, confirming bioequivalence of the formulations (section 2.7.1.2.1).

2.7.1.3.2. Bioavailability of Maraviroc

After oral administration, C_{max} is generally achieved between 0.5 and 4 hours after dosing for both maraviroc solution and tablet formulations. Formal assessment of dose proportionality following single doses of 50, 100, and 600 mg confirmed that the pharmacokinetics of the maraviroc research tablet were not dose proportional over this dose range. It is estimated that a doubling in dose will lead to a 2.3-fold increase (95% CI; 2.2, 2.4) in mean AUC_{inf} over this dose range.

As the IV kinetics of maraviroc are linear (over the 3-30 mg IV dose range, Study A4001009), this suggests that the non-proportionality of maraviroc oral pharmacokinetics derives from factors influencing rate and extent of absorption of maraviroc, rather than clearance. A comparison of oral research tablet and IV data from Study A4001009 calculated the absolute mean bioavailability of a 100 mg oral maraviroc research tablet to be 23.1%.

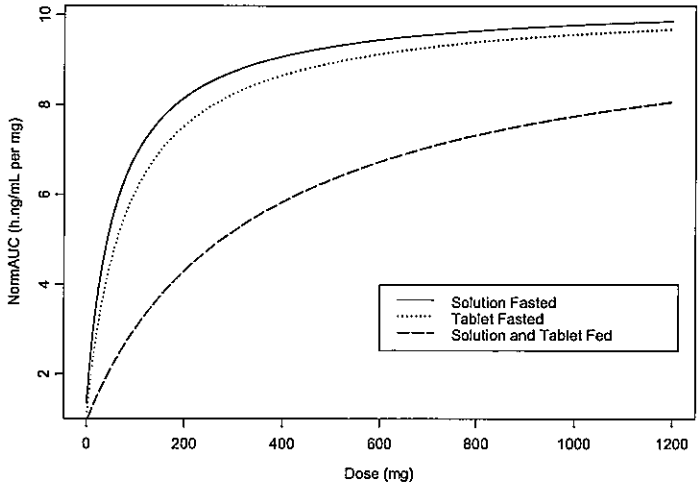
Pharmacokinetic Modelling

An overview of the objectives and methodology of the modelling analyses are presented in section 2.7.1.1.4.4 and Table 7.

Pharmacokinetic modelling of dose normalised AUC_{inf} and C_{max} from five Phase 1 studies, expressed the dose nonlinearity in quantitative terms to allow predictions for doses not studied (Module 5.3.3.5, Population Analysis of Phase 1 Non-compartmental Pharmacokinetic Data). Calculations of dose normalised AUC_{inf} indicated that the non-

proportional behaviour of maraviroc oral pharmacokinetics was most apparent at maraviroc doses below 300 mg. Above 300 mg, there is a trend towards dose proportionality which is illustrated by the plateauing of the dose-normalised AUC_{inf} curve in Figure 3.

Figure 3. Maraviroc Dose-Normalised Steady State



From Figure 3, it can be seen that the bioavailability of the tablet and solution are predicted to be similar across the dose range up to 1200 mg (Module 5.3.3.5, Population Analysis of Maraviroc Phase 1 Non-compartmental Pharmacokinetic Data). Limited clinical data is available with maraviroc solution, but when included in pharmacokinetic modelling it was predicted that the maximum bioavailability of maraviroc solution would be 22.9% and 33.3% for a 100 mg and 300 mg unit dose of maraviroc solution respectively (Module 5.3.3.5, Clearance and Mass Balance Model for Maraviroc).

Pharmacokinetic modelling of concentration data from all Phase 1/2a studies with tablet doses of 100 mg and above, estimated that the rate of maraviroc absorption was dose-dependent, with a small increase in the rate with increasing maraviroc dose. The extent of maraviroc absorption was also dose-dependent with bioavailability increasing with increasing maraviroc dose. For the tablet formulation, pharmacokinetic modelling estimated that the oral bioavailability of unit doses of maraviroc would be 24% at 100 mg, 31% at 300 mg and approximately 33% for unit doses of 600 mg and above (Module 5.3.3.5; Population Pharmacokinetics of Maraviroc after Oral Tablet Administration – A Pooled Analysis of Phase 1/2a Data). Predictions for bioavailability of maraviroc at a 100 mg unit dose are very similar across the modelling analyses and are consistent with the estimated oral absolute bioavailability (23.1%) from Study A4001009. However at very high doses of maraviroc, the value for the typical individual from the pooled phase 1/2a analysis of tablet data is slightly lower than that predicted from the earlier work using solution (33 versus 40%) (Module 5.3.3.5, Population Analysis of Maraviroc Phase 1 Non-compartmental Pharmacokinetic Data and Module 5.3.3.5 Clearance and Mass Balance Model for Maraviroc). Overall the predictions of the oral bioavailability of maraviroc were consistent across the studies used and the range of dose data.

The oral bioavailability of maraviroc is thought to be limited overall by high first pass extraction by the liver and metabolism by CYP3A4 enzymes in the gut wall. Additionally, *in vitro* studies have shown that maraviroc is a substrate for P-glycoprotein and it is likely that maraviroc may interact with other transporters as well. Therefore a postulated hypothesis for the non-proportionality of maraviroc pharmacokinetics is by means of saturation of gut transporters with increasing maraviroc dose, thereby leading to changes in bioavailability with dose.

2.7.1.3.3. Effect of Food on the Bioavailability of Maraviroc

Dosing of maraviroc with food (high-fat meal) caused a reduction in mean maraviroc exposure for the solution and tablet (C_{max} and AUC_{inf}). The extent of the effect of food on maraviroc bioavailability was dose-dependent and dependent on the timing of food as shown in Table 19.

Table 19. Summary of the Effect of Food on Maraviroc Pharmacokinetics

Study	Maraviroc Dose	Formulation	Timing of Food	C_{max}	AUC_{inf}
A4001001	100 mg	Solution	With Food	12%	37%
A4001004	100 mg	Research Tablet	1h before Food	103%	80%
A4001004	100 mg	Research Tablet	With Food	32%	48%
A4001004	100 mg	Research Tablet	1h after Food	30%	51%
A4001004	100 mg	Research Tablet	2h after Food	33%	58%
A4001004	100 mg	Research Tablet	4h after Food	87%	79%
A4001043	300 mg	Commercial Tablet	With Food	67%	67%
A4001003	600 mg	Research Tablet (4x150 tablets)	With Food	64%	67%

Results from the food effect studies in healthy volunteers and HIV-1 infected subjects indicate that:

- Maraviroc exposure was reduced by 33% for 300 mg commercial tablet and 600 mg dose (4 x 150 mg research tablet) of maraviroc. The effect of food was greater at lower doses.
- The greatest extent of the food effect on maraviroc exposure was seen with administration of maraviroc (100 mg research tablet) either at the same time as the high fat meal or up to 2 hours afterwards. A high fat breakfast taken 1 hour before or 4 hours after maraviroc administration had relatively small effects on mean C_{max} and AUC_{inf}.
- HIV-1 infected patients who received maraviroc 150 mg BID research tablet in the fed and fasted states for 10 days appeared to have a reduction in maraviroc exposure (C_{max} and AUC_{tau}) in the presence of food in line with that seen in healthy volunteers.

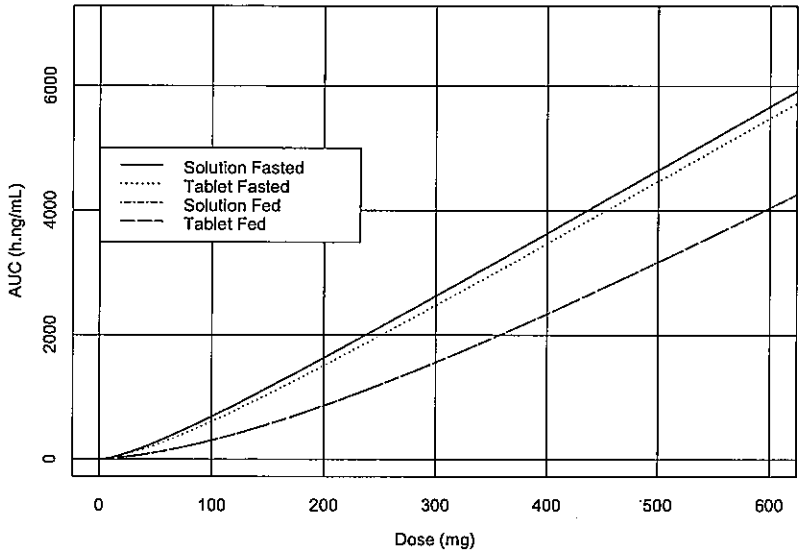
Pharmacokinetic Modelling

Pharmacokinetic modelling of clinical data was performed to investigate the effect of food on components of maraviroc pharmacokinetics, and specifically the effect of food and formulation and unit dose on absorption and bioavailability of maraviroc. An overview of

the objectives and methodology of the modelling analyses are presented in section 2.7.1.1.4.4 and Table 7.

Predicted population AUC_{inf} values were plotted against maraviroc dose for fasted and fed states for the solution and tablet formulation as shown in Figure 4.

Figure 4. Predicted Steady State AUC_{inf} for Maraviroc Solution and Research Tablet in the Fasted and Fed State.



Note the solution fed and the tablet fed prediction curves overlap (lower graph line) and are indistinguishable on the graph.

Predicted population AUC_{inf} values illustrate the dose-dependent extent of the food effect (Figure 4). For both predicted population AUC_{inf} and C_{max} values, the magnitude of the food effect was similar for both the maraviroc solution and research tablet. Furthermore, population AUC_{inf} and C_{max} values for the maraviroc solution and research tablet were predicted to be indistinguishable in the fed state at doses up to 600 mg (Figure 4 and Module 5.3.3.5, Population Analysis of maraviroc Phase 1 non-compartmental pharmacokinetic data).

Population predictions of AUC_{inf} and C_{max} values and resulting fed/fasted ratios were consistent with those observed in the single dose food studies included in the analysis (Module 5.3.3.5, Population Analysis of Maraviroc Phase 1 non-compartmental Pharmacokinetic Data). Predictions for the relative bioavailability of fed to fasted states of possible dosing regimens (up to 600 mg) were made and these predicted fed/fasted ratios were consistent with those observed in the single dose food studies included in the analysis (Table 20). .

Table 20. Predicted Population AUC_{inf} Fed/Fasted Ratios after Multiple Tablet Dosing

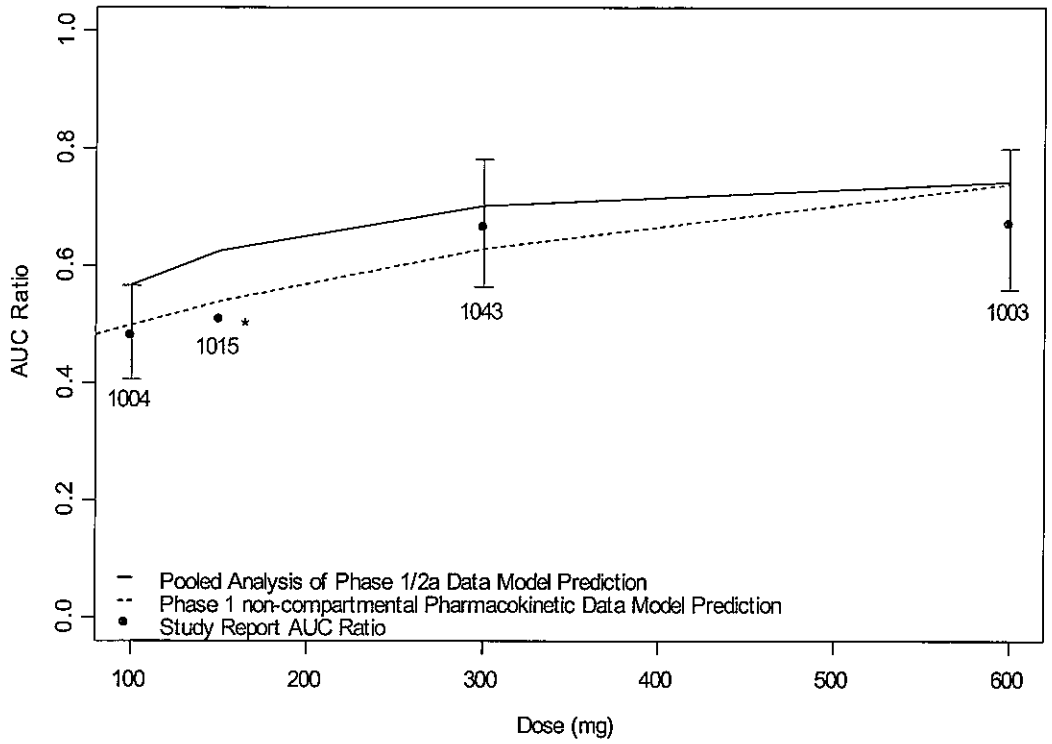
Tablet Dosing	Fed/Fasted Relative Bioavailability (%)
100 mg BID or QD	50
150 mg BID or QD	54
300 mg BID or QD	63
600 mg BID or QD	74

Studies A4001015 and A4001043 were not initially included in the population analysis of the Phase 1 non-compartmental pharmacokinetic parameters. But subsequent data from these studies were in line with the predictions of this modelling analysis. The predictions of the fed/fasted ratio for multiple dosing at 150 mg (54%) agree closely with the observed fed/fasted ratio from A4001015 data (approximately 50%). The most recent food effect study (A4001043) investigated the effect of food on the commercial tablet of maraviroc at 300 mg. C_{max} and AUC_{inf} were reduced by approximately 33%, consistent with the model predictions of the food effect on AUC_{inf} at 300 mg doses (37% reduction, Table 20). These data helped to support the application of the pharmacokinetic model.

Population Analysis of pooled Phase 1/2a studies was subsequently derived from all studies including those that investigated the effect of food on maraviroc tablet pharmacokinetics. This analysis predicted that administration of maraviroc with a high fat meal would reduce exposure (AUC_{inf}) by 43% for a 100 mg dose through effects on bioavailability. The extent of the food effect reduces to a constant of a 25% reduction at doses of 600 mg and above (Module 5.3.3.5, Population Pharmacokinetics of Maraviroc after Oral Tablet Administration – A Pooled Analysis of Phase 1/2a Data).

The results of the fed/fasted ratio predictions from the two modelling analyses and actual data from clinical studies are illustrated in Figure 5

Figure 5. Fed/fasted AUC Ratios from Clinical Studies and Pharmacokinetic Modelling



*Data from A4001015 is not from a formal statistical analysis

Conclusions

- Development of the commercial tablet from the research tablet required only minor changes in the level of lubricant, tablet shape and tablet film coat. The research and commercial 150 mg tablets had rapid and comparable in vitro dissolution profiles.
- The 12-month stability data supports a 24-month shelf life for the proposed commercial formulation. No trends were noted for appearance, assay, impurities, water content, enantiomer content (chiral), powder X-Ray diffraction and microbiological quality testing
- Statistical comparisons of the ratios of pharmacokinetic parameters of research and commercial tablets in Study A4001040 were within the accepted bioequivalence limits. Therefore the research tablet used in Phase 2b/3 studies is bioequivalent to the commercial tablet.
- The absolute oral bioavailability of maraviroc is dose dependent (23.1% at 100 mg).

- There is a dose dependent effect of food on maraviroc pharmacokinetics but it is independent of dosage form. The extent of the food effect is reduced with higher maraviroc doses. At 300 mg, food reduced exposure of the 300 mg maraviroc commercial tablet by 33%.

- Conclusions from the clinical trial programme conducted with the research tablet are therefore valid for consideration for the use of the commercial tablet.

2.7.1.4. Appendix

Section 2.7.1 Table A1 Summary of Bioavailability and Bioequivalence Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	AUC(0-t) (ng·h/mL)	AUC(0-∞) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001009 (Belgium)	To investigate the safety and toleration of intravenous (IV) maraviroc and to determine the absolute bioavailability of a 100 mg oral dose.	Cohort 1: double-blind (third party open), four-way crossover study Cohort 2: open, two-way crossover study COHORT 1 Subjects: 8 Sex: 8 M/0 F Mean Age (min/max): 34.5 (27/40) years						
		Evaluated for: PK: 8; Safety: 8	3 mg maraviroc IV (fasted)	57.6	n/c	36.9	0.94	n/c
		Evaluated for: PK: 8, Safety: 8	10 mg maraviroc IV (fasted)	201	n/c	122	0.94	n/c
		Evaluated for: PK: 8; Safety: 8	30 mg maraviroc IV (fasted)	670	687	397	0.91	13.2
		COHORT 2 Subjects: 12 Sex: 12 M/0 F Mean Age (min/max): 32 (22/42) years						
		Evaluated for: PK: 12; Safety: 12	30 mg maraviroc IV (fasted)	645	656	374	0.98	12.0
		Evaluated for: PK: 12: Safety: 12	1x100 mg maraviroc tablet (fasted)	492	506	122	3.08	12.5

Source: Clinical Study Report A4001009 and Tables 1.1, 2.1, 5.1.1.1 and 5.1.2.
AUC(0-t), AUC(0-∞) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated, t=tlast, the last time with a quantifiable concentration.

Section 2.7.1 Table A1 Summary of Bioavailability and Bioequivalence Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	AUC(0-t) (ng·h/mL)	AUC(0-∞) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001040 (Singapore)	To compare the pharmacokinetics of maraviroc following a single dose of the proposed commercial tablet compared to the research tablet to determine bioequivalence between the formulations.	Open-label, randomised, single-dose, 2 way crossover study Subjects: 44 Sex: 33 M/11 F Commercial tablet Mean Age (min/max): 26 (21/39) years Research tablet Mean Age (min/max): 29 (21/54) years						
		Evaluated for: PK: 44; Safety: 44	300 mg (2 x 150 mg) commercial tablet	2699	2720	638	2.47	10.4
		Evaluated for: PK: 42; Safety: 42	1 x 300 mg maraviroc research tablet	2729	2760	654	2.45	10.5

Source: Clinical Study Report A4001040 Tables 13.1.1, 13.2.1 and 13.5.1.
AUC(0-t), AUC(0-∞) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated.
t=tlast, the last time with a quantifiable concentration.

Section 2.7.1 Table A1 Summary of Bioavailability and Bioequivalence Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters				
				AUC(0-t) (ng·h/mL)	AUC(0-∞) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001001 (Belgium)	To determine the safety and toleration of single oral doses of maraviroc.	Double-blind (3rd party open), placebo-controlled, dose escalating, crossover study COHORT A Subjects: 12 Sex: 12 M/0 F Mean Age (min/max): 28.1 (21/45) years						
		Evaluated for: PK: 9; Safety: 9	1 mg maraviroc solution (fasted)	n/c	n/c	n/c	n/c	n/c
		Evaluated for: PK: 9; Safety: 9	10 mg maraviroc solution (fasted)	17.2	n/c	2.92	2.50	n/c
		Evaluated for: PK: 9; Safety: 9	100 mg maraviroc solution (fasted)	583	619	172	3.11	9.86
		Evaluated for: PK: 9; Safety: 9	100 mg maraviroc solution (fed)	205	222	19.3	2.88	14.0
		Evaluated for: PK: 9; Safety: 9	900 mg maraviroc solution (fasted)	7279	7358	1632	1.94	11.3
		COHORT B Subjects: 12 Sex: 12 M/0 F Mean Age (min/max): 29.1 (22/41) years						
		Evaluated for: PK: 9; Safety: 9	3 mg maraviroc solution (fasted)	2.25	-	0.58	2.06	-

Section 2.7.1 Table A1 Summary of Bioavailability and Bioequivalence Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	AUC(0-t) (ng·h/mL)	AUC(0-∞) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001001 continued		Evaluated for: PK: 9; Safety: 9	30 mg maraviroc solution (fasted)	80.9	117	15.3	2.89	8.91
		Evaluated for: PK: 9; Safety: 9	300 mg maraviroc solution (fasted)	2187	2313	621	1.64	10.6
		Evaluated for: PK: 9; Safety: 9	1200 mg maraviroc solution (fasted))	11321	11432	2807	1.78	12.5

Source: Clinical Study Report A4001001; Tables 1.1, 2.1, 5.1.1 and 5.1.2.
AUC(0-t), AUC(0-∞) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated.
t=tlast, the last time with a quantifiable concentration.

Section 2.7.1 Table A1 Summary of Bioavailability and Bioequivalence Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	AUC(0-t) (ng·h/mL)	AUC(0-∞) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001003 (Belgium)	To investigate the pharmacokinetics of single oral tablet doses of maraviroc 50, 100 and 600 mg, the effect of food on a single 600 mg tablet dose, the relative oral bioavailability of the 100 mg tablet versus 100 mg oral solution doses and the safety and tolerability of single oral 50, 100 and 600 mg doses.	Open, randomised, five-way crossover study. Subjects: 15 Sex: 15 M/0 F Mean Age (min/max): 31.3 (20/44) years						
		Evaluated for: PK: 13; Safety: 15	1 x 50 mg maraviroc tablet (fasted)	209	227	55	3.00	14.4
		Evaluated for: PK: 15; Safety: 15	1 x 100 mg maraviroc tablet (fasted)	555	576	154	2.33	13.3
		Evaluated for: PK: 15; Safety: 15	100 mg maraviroc solution (fasted)	638	654	170	2.77	12.6
		Evaluated for: PK: 15; Safety: 15	600 mg (4 x 150 mg tablets) maraviroc (fasted)	5636	5703	1221	3.30	11.5
		Evaluated for: PK: 15; Safety: 15	600 mg (4 x 150 mg tablets) maraviroc (fed)	3715	3805	783	3.07	13.6

Source: Clinical Study Report A4001003; Tables 1.1, 2.1 and 5.1.
AUC(0-t), AUC(0-∞) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated.
t=tlast, the last time with a quantifiable concentration.

Section 2.7.1 Table A1 Summary of Bioavailability and Bioequivalence Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters				
				AUC(0-t) (ng·h/mL)	AUC(0-∞) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001004 (Belgium)	To investigate the effects of food administration at different times relative to oral dosing on the pharmacokinetics of a single 100 mg dose of maraviroc in tablet form.	Open, randomised, incomplete block, five-way cross-over study Subjects: 15 Sex: 15 M/0 F Mean Age (min/max): 34.5 (20/45) years						
		Evaluated for: PK: 14; Safety: 15	1 x 100 mg maraviroc tablet (fasted)	491	505	113	3.21	12.5
		Evaluated for: PK: 11; Safety: 11	1 x 100 mg maraviroc tablet (1 hour prior to food)	361	387	107	2.14	13.4
		Evaluated for: PK: 11; Safety: 11	1 x 100 mg maraviroc tablet (with food)	230	249	38.7	3.14	13.8
		Evaluated for: PK: 12; Safety: 12	1 x 100 mg maraviroc tablet (1 hour after food)	244	274	38.4	3.83	12.5
		Evaluated for: PK: 11; Safety: 11	1 x 100 mg maraviroc tablet (2 hours after food)	270	295	39.5	3.64	14.1
		Evaluated for: PK: 11; Safety: 11	1 x 100 mg maraviroc tablet (4 hours after food)	378	397	88.4	2.73	13.2

Source: Clinical Study Report A4001004; Tables 1.1, 2.1 and 5.1.1 to 5.1.6.
AUC(0-t), AUC(0-∞) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated, t=tlast, the last time with a quantifiable concentration.

Section 2.7.1 Table A1 Summary of Bioavailability and Bioequivalence Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters				
				AUC(0-t) (ng·h/mL)	AUC(0-∞) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001043 (Singapore)	To determine the effect of food on the pharmacokinetics of maraviroc (300 mg commercial formulation).	Open-label, randomised, single dose, 2 way crossover study Subjects: 12 Sex: 8 M/4 F Mean Age (min/max): 28.4 (21/40) years						
		Evaluated for: PK: 12; Safety: 12	1 x 300 mg maraviroc commercial tablet (fasted)	3079	3117	673	3.04	11.0
		Evaluated for: PK: 12: Safety: 12	1 x 300 mg maraviroc commercial tablet (fed)	2047	2084	454	3.96	10.3

Source: Clinical Study Report A4001043; Tables 13.1.1, 13.2.1 and 13.5.1.
AUC(0-t), AUC(0-∞) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated.
t=tlast, the last time with a quantifiable concentration.

Section 2.7.1 Table A1 Summary of Bioavailability and Bioequivalence Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	AUC(0-t) (ng·h/mL)	AUC(0-∞) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001015 (Germany, U.K, U.S.A)	To assess the effect of food and the effect of once daily (QD) compared to twice daily (BID) dosing on the anti-viral effect and the pharmacokinetic-pharmacodynamic relationships in HIV-1 infected subjects on short-term maraviroc monotherapy, and to assess the safety and tolerability of maraviroc.	Randomised, double-blind, placebo-controlled, multicentre, five treatment, parallel group study.						
		Subjects: 9 Sex: 9 M/0 F Mean Age (min/max): 36 (31/45) years Evaluated for: PK: 9; Safety: 9	100 mg QD (1x 100 mg tablet);	571	n/c	161	3.25	n/c
		Subjects: 8 Sex: 8 M/0 F Mean Age (min/max): 40 (32/53) years Evaluated for: PK: 8; Safety: 8	150 mg BID (1x 100 mg tablet and 1 x 50 mg tablet), fasted	933	n/c	273	3.00	n/c
		Subjects: 8 Sex: 8 M/0 F Mean Age (min/max): 39 (27/48) years Evaluated for: PK: 8: Safety: 8	150 mg BID (1x 100 mg tablet and 1 x 50 mg tablet) (fed)	474	n/c	110	2.25	n/c
		Subjects: 8 Sex: 6 M/2 F Mean Age (min/max): 38.6 (30/53) years Evaluated for: PK: 8; Safety: 8	300 mg QD (3 x 100 mg tablets); fasted	2264	n/c	484	3.25	n/c

Source: Clinical Study Report A4001015; Tables 1.1, 2.1 and 5.1.

AUC(0-t), AUC(0-∞) and Cmax are expressed as geometric means ; Tmax and t½ are expressed as arithmetic means.

M=Male F=Female PK=Pharmacokinetics n/c=not calculated.

For A4001015, AUC(0-t) is actually AUC_{tau} which is 0-12 for BID regimens and 0-24 for QD regimens.

2.7.2 SUMMARY OF CLINICAL PHARMACOLOGY STUDIES

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACTG	Aids Clinical Trial Group
AIDS	Acquired Immuno-Deficiency Syndrome
AUCinf	Area under the plasma concentration-time profile from time 0 to time infinity by extrapolation
AUClast	Area under the plasma concentration-time profile from time 0 to the time of last quantifiable plasma concentration
AUCtau	Area under the plasma concentration-time profile over the dosing interval
BID	Twice a day dosing
C_{ave}	Average plasma concentration
CCR5	CC chemokine receptor 5
CI	Confidence Interval
CL	Total clearance
CL_r	Renal Clearance
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
CSR	Clinical study report
CV	Coefficient of Variation
CYP	Cytochrome
ECC	Equivalent Constant Concentration
ECG	Electrocardiogram
EMEA	European Medicines Evaluation Agency
F	Bioavailability
F_{ABS}	Extent of absorption
FDA	Food and Drug Administration
GAM	Generalized Additive Models
GTN	Glyceryl Trinitrate
HAART	Highly active anti-retroviral therapy
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
IC_{50}	Inhibitory Concentration 50%
ICG	Impedence Cardiography
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IV	Intravenous
Ka	Absorption rate constant
KD	Dissociation rate constant
kg	Kilogram
Ki	Inhibition constant
Km	Michaelis-menton constant
MIP-1⇓	Macrophage Inhibitory Protein 1⇓
MDR	Multi-Drug Resistant
MR	Metabolic Ratio
MRP	Mulit-drug Resistance Protein
MVC	Maraviroc
mg	Milligram
µM	Micromolar
n/c	Not calculated
NK	Natural killer

NNRTI	Non-Nuclcotide Reverse Transcriptase Inhibitor
NRTI	Nucleotide Reverse Transcriptase Inhibitor
OBT	Optimised Background Therapy
P-gp	P-glycoprotein
PI	Protease Inhibitor
QD	Once a day dosing
SAP	Statistical Analysis Plan
QT	Time from the beginning of the QRS complex to the end of the T wave in the electrocardiogram
QTc	QT interval, corrected for heart rate.
QTcB	QTc interval with Bazett's correction
QTcF	QTc interval with Fredericia's correction
QTcI	QTc interval, calculate using an individual correction factor
-/r	Ritonavir boost
t½	Half-life
T_{max}	Time to reach C_{max}
Vss	Volume of Steady State distribution

2.7.2. SUMMARY OF CLINICAL PHARMACOLOGY STUDIES

2.7.2.1. Background and Overview

Maraviroc is a selective and slowly reversible CC chemokine receptor 5 (CCR5) co-receptor antagonist which has been shown to be active in vitro against a wide range of clinical HIV-1 isolates, including those resistant to existing drug classes.

Maraviroc is a moderately lipophilic and basic molecule with a log $D_{7.4}$ of 1.9, pKa of 7.7 and a molecular weight of 513.7. Polarised 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). Maraviroc is eliminated predominantly by metabolism, primarily by CYP3A4, and does not inhibit major drug metabolising cytochrome P450s in vitro, including CYP3A4 (IC_{50}'s > 30uM) (Sections 2.4.3.2 and 2.4.3.4, Module 2.4, Nonclinical Overview).

Maraviroc (up to 10 μM) had little interaction with physiologically important receptors, binding sites, enzymes or ion channels apart from weak functional activity at the human μ opiod 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 10 μM), to be inactive in viral protein mediated cell fusion assays and devoid of any relevant pharmacological activity against physiological receptors ions and enzymes tested (Sections 2.4.2.5 and 2.4.2.5.6, Module 2.4 Nonclinical Overview).

Maraviroc will be administered with multiple drugs, including other antiretroviral agents, nucleoside reverse transcriptase inhibitors (NRTI), non- nucleoside reverse transcriptase inhibitors (NNRTI), fusion inhibitors and protease inhibitors (PI), 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 module summarises the results from clinical pharmacology studies conducted with maraviroc during its development. Data from clinical pharmacology studies indicate that:

The clinical pharmacology profile of maraviroc supports therapeutic dosing at 300 mg given twice a day (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 protease inhibitors).

2.7.2.1.1. Overview of Clinical Studies

Twenty-six Phase 1 and two Phase 2a clinical studies were conducted to explore the pharmacology of maraviroc in both healthy volunteers and HIV-1 infected patients and are included in this Summary of Clinical Pharmacology. All studies were conducted in accordance with Good Clinical Practice, and are consistent with US, European and ICH guidelines on drug development (FDA. Guidance for Industry: In vivo Drug Metabolism/Drug Interaction Studies – Study Design, Data Analysis, and Recommendations for Dosing and Labelling. November 1999; ICH Notes on Guidance on the Investigation of Drug Interactions. December 1997; CPMP. Note for Guidance on the Investigation of Drug Interactions, June 1998).

Appendix Table A1 provides a listing of the study numbers, designs, objectives, and treatment regimens and key pharmacokinetic results for all studies included in this Summary of Clinical Pharmacology. Discussion of the bioequivalence study (A4001040) and food effect data from studies (A4001001, A4001003, A4001004, A4001015 and A4001043) on the bioavailability of maraviroc can be found in Section 2.7.1.3.2, Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods. Summaries of the Phase 2b/3 studies in which data relevant to discussions of clinical pharmacology were collected can be found in either Modules 2.7.3 or 2.7.4 (Summary of Clinical Efficacy and Summary of Clinical Safety respectively). Modules 2.4 (NonClinical Overview) and 2.6.4 (Pharmacokinetics Written Summary) contain information on in vitro and preclinical pharmacokinetics. Safety data from Phase 1 studies are discussed in Module 2.7.4 (Summary of Clinical Safety). Individual study reports for all studies included in this summary are located within Module 5.

An overview of the clinical pharmacology studies presented in this module is presented in Table 1.

Table 1. Overview of Maraviroc Clinical Pharmacology Studies

Study (n)	Design and Objective	MVC dose
Single Dose Studies		
A4001001[a] (N=24)	First in human, DB (3rd party open), dose escalating, XO study in two cohorts of healthy male subjects to determine the safety and toleration and pharmacokinetics of single oral doses of MVC in the fed and fasted states.	Cohort A: 1, 10, 100, 900 mg and 100 mg (fed) Cohort B: 3, 30, 300 and 1200 mg
A4001003[a] (N=15)	Open, R, 5-way XO study in healthy male subjects to investigate the pharmacokinetics of single oral tablet doses of MVC and a single oral solution dose and the effect of food on MVC pharmacokinetics (600 mg oral tablet only)	50 100 mg tablet (fasted), 600 mg tablet (fasted/fed), 100 mg solution (fasted)
A4001009 (N=20)	Cohort 1: DB (3rd party open), four-way XO study, Cohort 2: open, two-way CO study to investigate the safety and toleration of escalating intravenous (IV) doses of MVC and to determine the absolute bioavailability of MVC after oral administration.	Cohort 1: 3, 10 and 30 mg (iv) Cohort 2: 30 mg (iv), 100 mg (oral)
A4001040[b] (N=44)	Open, R, 2-way XO study to compare the pharmacokinetics of maraviroc following a single dose of the proposed commercial tablet compared to the research tablet to determine bioequivalence between the formulations	300 mg
Mass Balance study		
A4001010 (N=3)	An open study to investigate the absorption, metabolism and excretion of [^{14}C] MVC.	300 mg
Multiple Dose Studies		
A4001002 (N=72)	DB (3rd party open), parallel group, PC SD and MD escalating oral dose study to investigate the safety, toleration and pharmacokinetics of multiple oral doses of MVC in healthy male subjects.	3, 10, 25, 100 and 300 mg BID (solution) 600 mg QD (tablet)
A4001008 (N=54)	DB, R, PC study to investigate the safety of multiple oral doses of MVC for 28 days in healthy subjects	100 or 300 mg BID
A4001019 (N=36)	DB, 3rd party open, PC, parallel group study to investigate the safety, toleration and pharmacokinetics of multiple escalating oral doses of MVC in healthy subjects.	Days 1-7: 300 or 600 mg BID or 900 mg QD Days 8-14: 600 mg BID, 900 mg BID, 1200 mg QD
Food Effect Studies		
A4001004[a] (N=15)	Open, R, SD, five way incomplete block design XO study to investigate the effects of food administration at different times relative to oral dosing on the pharmacokinetics of a single 100 mg MVC dose (tablet).	100 mg (fasted), 1hr before food, with food, 1hr, 2hr, 4hr post food)
A4001043[a] (N=12)	Open, R, 2-way crossover study to determine the effect of food on the pharmacokinetics of the commercial formulation of maraviroc	300 mg
Drug Interaction Studies		
Effect of Maraviroc on 'Other' Drugs		
A4001005 (N=15)	DB, R, PC, two way crossover study to investigate the pharmacokinetics, safety and toleration of MVC in healthy young women and the effect of MVC on the pharmacokinetics of oral contraceptive steroids..	100 mg BID
A4001012 (N=12)	DB, R, PC, two-period crossover study to investigate the effect of steady state MVC on the pharmacokinetics of a single dose of midazolam	300 mg BID
A4001020 (N=12)	DB, 3rd party open, R, PC, two period XO study to investigate the effect of steady state MVC on the steady state pharmacokinetics of Zidovudine/Lamivudine*.	300 mg BID
Effect of 'Other' Drugs on Maraviroc		
A4001006 (N=24)	Open, R, PC, 2 way crossover study to investigate the effect of ketoconazole and saquinavir on the steady state pharmacokinetics, safety and toleration of MVC.	100 mg BID
A4001011 (N=36)	Open, R, PC, parallel group study to investigate the effects of rifampicin and efavirenz on the steady state pharmacokinetics of MVC and whether MVC dose adjustment can compensate for these effects.	Days 1-21: 100 mg BID Days 21-28: 200 mg BID

MVC=maraviroc, DB=double blind, R=Randomised, PC=placebo controlled, OL=open label, SD=single dose, XO=crossover

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Table 1. Overview of Maraviroc Clinical Pharmacology Studies

Study (n)	Design and Objective	MVC dose
A4001013 (N=32)	Open label, R, PC, four treatment, four group, parallel group study to investigate the effects of ritonavir, saquinavir + ritonavir and lopinavir + ritonavir on the steady state pharmacokinetics of MVC and whether MVC dose adjustment can compensate for these effects.	Days 1-7, 8-21:100 mg BID Days 22-28: 25 50 or 100 mg BID
A4001017 (N=29)	Open, parallel group study to investigate the effect of selected antiretroviral combinations on the pharmacokinetics of a single oral dose of MVC in HIV-1 infected patients.	300 mg QD
A4001018 (N=16)	Open label, R, PC, two-period XO study to investigate the effect of Trimethoprim/ Sulfamethoxazole* on the steady-state pharmacokinetics of MVC.	300 mg BID
A4001021 (N=36)	Open, R, PC, two-way XO study to investigate the effect of co-administration of efavirenz with Lopinavir/Ritonavir*, efavirenz with boosted saquinavir and efavirenz with both Lopinavir/Ritonavir* and boosted saquinavir on the pharmacokinetics of MVC	100 and 300 mg BID
A4001022 (N=12)	Open, R, PC, two-way XO study to investigate the effect of tenofovir on the pharmacokinetics of MVC	300 mg BID
A4001025 (N=12)	Open, R, PC, two-way XO study to investigate the effects of atazanavir (alone and boosted with ritonavir) on the pharmacokinetics of MVC	300 mg BID
A4001042 (N=12)	Open, R, PC, two-period XO study to investigate the effects of boosted tipranavir on the pharmacokinetics of MVC	150 mg BID
A4001046 (N=8)	Open, single period study to investigate the range of MVC exposures in HIV-1 infected patients receiving antiretroviral therapy containing boosted saquinavir	150 mg
Special Populations		
A4001038 (N=24)	Open, parallel group study to compare the pharmacokinetics of a single dose of maraviroc between Asian and Caucasian healthy male subjects.	300 mg
Pharmacodynamic Studies		
A4001016 (N=61)	R, SD, placebo and active controlled five way XO study to assess the effect of three oral doses of MVC on the QTc interval in healthy subjects.	100 , 300 and 900 mg
A4001033 (N=16)	Open, R, two-period, XO study to investigate the haemodynamic effects effect of oral doses of MVC in healthy male subjects.	900 mg
Phase 2a Studies		
A4001007 (N=45)	DB, R, PC, parallel group study to investigate the pharmacokinetics, pharmacodynamics, safety and toleration of MVC in asymptomatic HIV-1 infected patients	25 mg QD, 50 mg BID, 100 mg BID and 300 mg BID
A4001015[a] (N=37)	DB, R, PC, five treatment, parallel group study to assess the effect of food, and dose regimen on viral load response in HIV-1 infected patients on short-term MVC monotherapy,	150 mg BID(fasted and fed), 100 mg QD (fasted) and 300 mg QD (fasted)

[a] Food effect studies or food effect data from studies are discussed in Module 2.7.1, Summary of Biopharmaceutics and Analytical Methods.
[b] The bioequivalence of the research and commercial tablet formulations is discussed in Module 2.7.1, Summary of Biopharmaceutics and Analytical Methods.
MVC=maraviroc, DB=double blind, R=Randomised, PC=placebo controlled, OL=open label, SD=single dose, XO=crossover

Clinical Program Overview

Study A4001001 was the first in human Phase 1 study to explore the safety and pharmacokinetics of escalating single doses of maraviroc in healthy subjects. Additional single dose studies defined the absolute (A4001009) and relative bioavailability (A4001003) of maraviroc and the bioequivalence of the commercial and research formulations (A4001040).

The effect and timing of food on the pharmacokinetics of maraviroc given as solution or tablets at different doses has been investigated (Studies A4001001, A4001003, A4001004, A4001043) In addition, a Phase 2a study (A4001015) investigated the

food effect in HIV-1 infected patients. The effect of food on the pharmacokinetics of maraviroc is discussed in Section 2.7.1.3.2, Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods.

Multiple dose studies (A4001002, A4001008 and A4001019) characterised the longer-term safety and tolerability and steady state pharmacokinetics of maraviroc. Doses studied included the highest dosing regimen used in the Phase 2b/3 program (300 mg BID) and escalations from 3 mg to 900 mg BID and 600 mg to 1200 mg QD.

Definitive metabolism and mass balance after a single oral dose of [^{14}C] maraviroc (300 mg) in healthy subjects was determined in Study A4001010.

Effect of Maraviroc on 'Other Drugs'

Preclinical studies suggest that maraviroc does not inhibit any of the major P450 enzymes at clinically relevant concentrations. The effect of maraviroc on markers of CYP3A4 (6β-hydroxycortisol/cortisol ratio and midazolam pharmacokinetics) and CYP2D6 activity (debrisoquine metabolic ratio) were investigated in Studies A4001002 and A4001012.

The effect of maraviroc on the pharmacokinetics of oral contraceptive steroids (ethinylestradiol and levonorgestrel) was investigated in A4001005.

The effect of maraviroc on the steady state pharmacokinetics of Zidovudine/Lamivudine*, (lamivudine and zidovudine, Study A4001020) was investigated as these nucleoside reverse transcriptase inhibitors (NRTIs) were to be used in Study A4001026 as part of the highly active anti-retroviral therapy (HAART) and are cleared predominantly by renal and/or non-P450 metabolic routes.

Effect of 'Other Drugs' on Maraviroc

Preclinical studies suggest that maraviroc is a substrate for CYP3A4 and P-gp and hence its pharmacokinetics are likely to be affected by modulators of these enzymes/transporters (section 2.7.2.2.1). Therefore drug interaction studies investigated the effect of probe and clinically relevant CYP3A4/P-gp inhibitors and inducers to support dose recommendations in the Phase 2b/3 studies. Protease inhibitors co-administered with ritonavir (ritonavir boost) will be abbreviated with the suffix of /r after the protease inhibitor.

CYP3A4/P-gp inhibitors and inducers studied included ketoconazole, saquinavir (A4001006), ritonavir, Lopinavir/Ritonavir*(lopinavir/ritonavir), saquinavir/r (A4001013, A4001021, A4001046), atazanavir, atazanavir/r (A4001025), efavirenz, rifampicin (A4001011, A4001021), tipranavir/r(A4001042).

Effects of clinically relevant renal substrates and renal transport inhibitors on the pharmacokinetics of maraviroc were also investigated; tenofovir (A4001022) and Trimethoprim/Sulfamethoxazole* (A4001018).

A probe study to investigate the effect of 4 different HAART regimens on the pharmacokinetics of a single dose of maraviroc in HIV-1 infected patients was conducted, with data compared to historical controls (A4001017).

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Preclinical data indicated that maraviroc had the potential to increase the QT interval in man at high concentrations (Sections 2.4.5.5.2 and 2.4.5.3, Module 2.4, Nonclinical overview). Therefore a prospectively designed specific QT study to investigate the effect of maraviroc on QTc was performed (A4001016).

The dose limiting adverse event for maraviroc in clinical studies is postural hypotension, therefore the effect of maraviroc on haemodynamic parameters was investigated in healthy male subjects (A4001033).

Two Phase 2a studies (A4001007, A4001015) were performed to aid in selection of the therapeutic doses of maraviroc to be used in pivotal Phase 2b/3 studies.

2.7.2.1.2. Overview of Clinical Methods and Analysis

2.7.2.1.2.1. Pharmacokinetic/Pharmacodynamic and Safety Evaluations

Blood and urine samples for measurements of maraviroc concentration were collected at protocol specified pre-dose and post-dose times. Detailed methods and times of maraviroc sampling and safety assessments can be found in the individual Clinical Study Reports (CSR) in Module 5. Pharmacokinetic sampling procedures and analytical methods for determining the concentration of maraviroc are summarised in Section 2.7.1.1.4.2, Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods.

Pharmacodynamic assessments, including visual nearpoint, pupillometry, salivary flow, CCR5 receptor occupancy and effectors of immune function were carried out at specified times pre-dose and post-dose in selected studies as detailed in the individual CSR.

Visual nearpoint, pupillometry and salivary flow measurements were performed in early clinical pharmacology studies (A4001001 and A4001002) to evaluate whether there was clinical evidence of maraviroc activity at the muscarinic and μ-opioid receptors.

CCR5 receptor occupancy was measured in several Phase 1 studies (A4001002, A4001005) to evaluate the degree of CCR5 receptor occupancy obtained with different doses of maraviroc. In the Phase 2a studies (A4001007 and A4001015) CCR5 receptor occupancy was measured in addition to plasma drug concentrations in order to evaluate whether this would correlate with efficacy as measured by plasma viral load reduction. CCR5 receptor occupancy was determined by an experimental macrophage inhibitory protein-1⇓ (MIP-1⇓) internalisation assay and flow cytometric analysis of CCR5 expression (Fatkenheuer G et al, 2005). In brief, receptor occupancy was reported as the percentage of cell-surface-expressed CCR5 on peripheral blood lymphocytes remaining when peripheral blood lymphocytes - enriched plasma from patients was incubated ex vivo with recombinant MIP-1⇓ either in the presence or absence of maraviroc. Samples were processed at the study site and shipped to a centralised laboratory [redacted]USA) where flow cytometric analysis was performed. As this is a biological assay, it is likely to have an inherent variability of (± 10-20%) generally associated with most validated assays. Study site processing and the experimental nature of the assay could lead to even greater variability. The detailed report of this experimental methodology can be found in the relevant study reports in Module 5.

As maraviroc binds to a cellular receptor involved in immune signalling there is a theoretical risk that it can affect immune function. Blood samples were therefore collected in selected studies (A4001001, A4001002, A4001005, A4001006, A4001008, A4001007, A4001015) to evaluate the effects of maraviroc on effectors of immune function by assessment of immunophenotyping (T, B, macrophage/monocyte and natural killer (NK) cell subsets)and S-immunoglobulins (Igs) IgA, IgD, IgE and subclasses, and IgM.

Safety evaluations comprised of adverse event recording, laboratory testing, physical examinations, vital signs and 12-lead electrocardiograms were performed at time-points specified in the relevant CSR.

Blood samples were also analysed for CCR5. 32 mutation genotyping and additional consent was obtained to evaluate other potential polymorphisms that may affect CCR5 expression and to examine polymorphisms in genes for drug metabolising enzymes and drug transport proteins as specified in the individual study protocols.

2.7.2.1.2.2. Pharmacokinetic Parameters

For all studies where serial plasma concentrations were taken, standard pharmacokinetic parameters were determined by non-compartmental analysis. The following pharmacokinetic parameters are those primarily used for comparisons and were assessed and defined according to standard criteria:

C_{max}	Maximum observed plasma concentration; taken directly from the plasma concentration time data.
AUC_{inf}	Area under the plasma concentration time curve from zero to infinity calculated as $AUC_{inf} = AUC_{last} + C_t/k_{el}$ where C_t is the last measurable concentration.
AUC_{last}	Area under the plasma concentration time curve up to the final measurable concentration
AUC_{tau}	Area under the plasma concentration time curve over the dosing interval (tau)
T_{max}	Time to first occurrence of C_{max}; taken directly from the plasma concentration time data.
$t_{1/2}$	Terminal half-life of plasma concentration time curve; calculated as $t½ = \ln 2/k_{el}$.
k_{el}	Terminal phase rate constant
CL	Total clearance (calculated after IV dosing)
CL_r	Renal clearance
CL_{nr}	Non-renal clearance (calculated after IV dosing)
Vss	Volume of distribution at steady state (calculated after IV dosing)
Ae_t	Total urinary recovery of unchanged drug over time t.

2.7.2.1.2.3. Statistical Methods

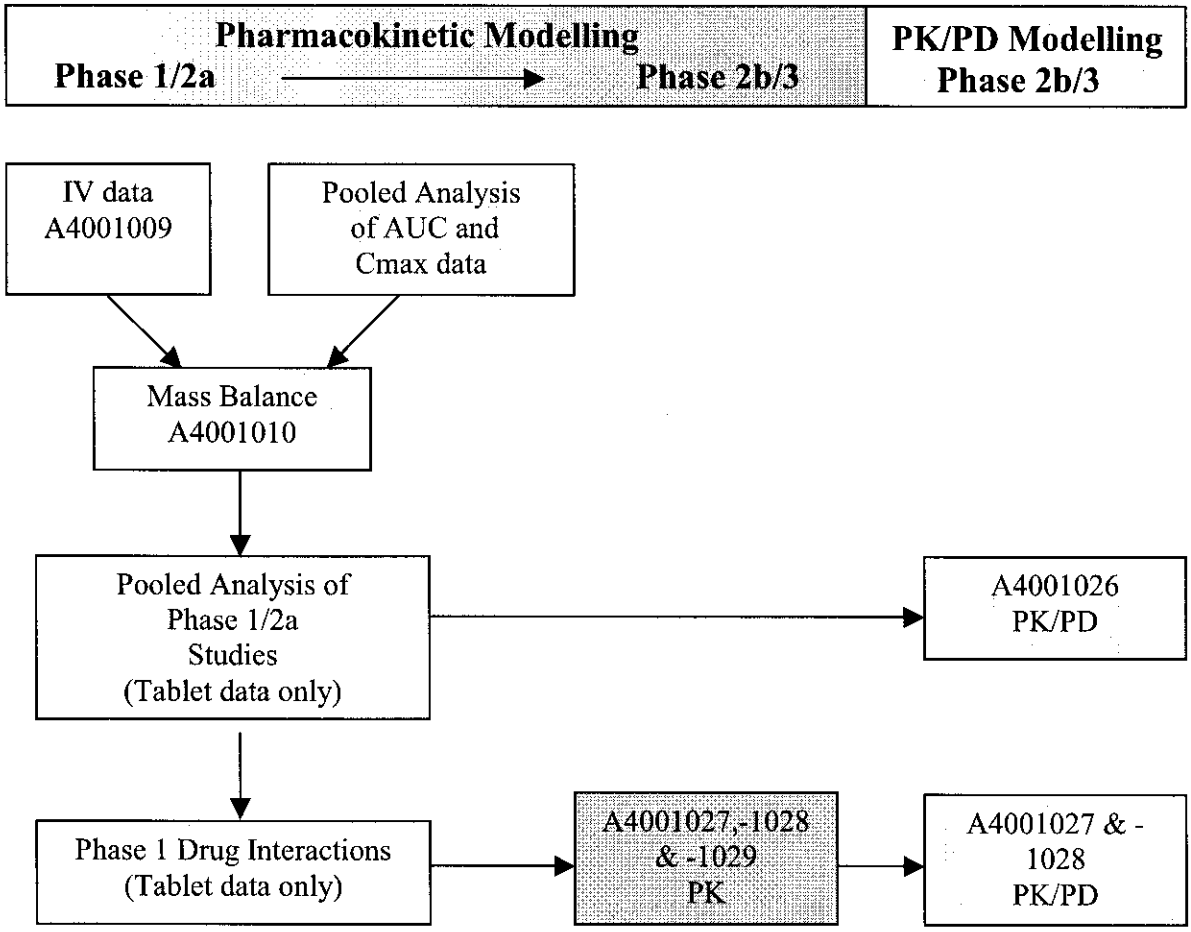
Full details of all statistical analyses are included in the study protocols and associated Statistical Analysis Plans (SAPs) of the individual studies which are located in the appendices of individual study reports in Module 5.

2.7.2.1.3. Pharmacokinetic Modelling

Full details regarding the methodology and results of pharmacokinetic modelling activities derived from analysis of Phase 1, 2a and 2b/3 studies can be found in the individual reports located in Module 5.3.3.5 for pharmacokinetic modelling reports; Module 5.3.4.1 for healthy subject pharmacodynamic and pharmacokinetic/pharmacodynamic reports and Module 5.3.4.2 for HIV-1 infected patient pharmacodynamic and pharmacokinetic/pharmacodynamic reports.

The modelling of Phase 1 and 2a pharmacokinetic data is covered by five reports which are interlinked as illustrated in Figure 1. Each of the boxes represents one modelling analysis, with Phase 1 analyses on the left and Phase 2b/3 analyses to the middle/right.

Figure 1. Schematic Representation of the Interdependencies of Modelling



The output from the population pharmacokinetic modelling of the data from the IV study (Module 5.3.3.5 Population Pharmacokinetics Analysis of Maraviroc IV Data from Phase 1 Study A4001009) together with that from the pooled analysis of noncompartmental parameters (Module 5.3.3.5, Population Analysis of Maraviroc Phase 1 Noncompartmental Pharmacokinetic Data) enabled the construction of a mass balance and clearance model for maraviroc when combined with information gained from the radiolabelled study (A4001010) (Module 5.3.3.5, Clearance and Mass Balance Model for Maraviroc).

Results from these 3 reports were used in developing a semi-physiological 2- compartment pharmacokinetic model (partition model) which was fitted to the pooled pharmacokinetic data from Phase 1 and 2a studies (using nonlinear mixed effects modelling) where maraviroc was administered alone or with placebo. Identification of extrinsic factors (covariates) which account for inter-individual variability was performed with this model (Module 5.3.3.5, Population Pharmacokinetics of Maraviroc after Oral Tablet Administration – A Pooled Analysis of Phase 1/2a Data partition and non-partition model). This partition model was further utilised to fit rich concentration data from a number of drug interaction studies where maraviroc was administered to HIV-1 infected patients and healthy volunteers together with various drugs including known P-gp and/or CYP3A4 inhibitors and inducers (Module 5.3.3.5, The Impact of Interacting Antiretroviral Drugs on Maraviroc Pharmacokinetics After Oral Tablet Administration – A Pooled Population Pharmacokinetic Analysis of Phase 1 Data). This analysis was performed to test the model assumptions and robustness of the methodology for generation of maraviroc individual exposure variables from post hoc Bayesian estimates of pharmacokinetic parameters, in the presence of interacting agents, prior to its application to data from treatment experienced patients in Phase 2b/3.

Additionally this final Phase 1/2a model was utilised for structure and parameter priors for the generation of post hoc Bayesian estimates of exposure variables for the Phase 2b/3 programme utilising sparsely sampled pharmacokinetics. The generation of the exposure variables is described in two reports, one for treatment naïve HIV-1 infected patients in A4001026 (Module 5.3.4.2, Preliminary PK/PD Analysis of the 300 mg QD Maraviroc Phase 2b Cohort in Study A4001026) and another covering the treatment experienced HIV-1 infected patients in studies A4001027, A4001028 and A4001029 (Module 5.3.4.2, Preliminary Population Pharmacokinetic Analysis of Maraviroc in Pooled Phase 2b/3 Studies of Treatment Experienced Patients on Optimized Background Therapy).

Study A4001026 is a 96 week multicentre, randomized (1:1:1) , double-blind, comparative non-inferiority Phase 2b/3 hybrid (run-in) study of maraviroc (300 mg QD and BID) versus efavirenz (600 mg once daily) in combination with Zidovudine/Lamivudine* for the treatment of antiretroviral-naïve CCR5 tropic HIV-1 infected subjects. A Data Safety Monitoring Board recommended discontinuation of the maraviroc 300 mg QD group because it failed to meet the pre-specified criteria for establishing non-inferiority to the efavirenz group. Therefore, exploratory analysis was performed using pharmacokinetic and efficacy data from the interim analysis subset of subjects (n=66 with concentration data, up to 24 weeks of data) who had been randomised to the discontinued 300 mg maraviroc QD arm.

Studies A4001027 and A4001028 are identical 48 week studies of maraviroc plus OBT in treatment experienced CCR5 tropic HIV-1 infected patients. A pre-planned interim analysis

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was performed when all subjects across the two studies reached 24 weeks on treatment and the studies were unblinded in [redacted] An early unblinding of the first 500 patients enrolled across both studies (approximately 350 in A4001027 and 150 in A4001028) was performed to enable completion of pharmacokinetic/pharmacodynamic analyses. The unblinding was conducted in accordance with Plan for Early Unblinding of Maraviroc Phase 3 Data (Protocols A4001027 and A4001028) for Population Pharmacokinetic and Exposure Response Analysis, ensuring that treatment codes were only accessible to a limited number of individuals (Module 5.3.4.2, Preliminary Population Pharmacokinetic Analysis of Maraviroc in Pooled Phase 2b/3 Studies of Treatment Experienced Patients on Optimized Background Therapy; Appendix 2).

Study A4001029 was a multicentre, randomised, double-blind, placebo-controlled trial of maraviroc, in combination with OBT versus OBT alone for the treatment of antiretroviral-experienced, non CCR5 tropic HIV-1 infected subjects. It provides additional data to support the treatment-experienced HIV-1 infected target population pharmacokinetic analysis. A full description of data included from Phase 2b/3 studies can be found in the modelling reports in Module 5.3.3.5 and 5.3.4.2.

The data included and objectives of each of the pharmacokinetic modelling analyses from Phase 1, -2a and -2b/3 studies are described in Table 2.

Table 2. Overview of Pharmacokinetic Modelling

Analysis	Data	Objectives
Pharmacokinetic Modelling in Phase 1/2a		
Population Analysis of Maraviroc Phase 1 Noncompartmental Pharmacokinetic Data	A4001001, A4001002, A4001003, A4001004 A4001019	To describe the effects of dose, food and formulation on single dose AUC_{inf} and multiple dose AUC_{tau} To describe the effects of dose, food and formulation on single and multiple dose Cmax To predict AUC and Cmax for food and formulation combinations over doses not included in the current studies. To provide a semi-mechanistic model for subsequent analysis and predictions of Cmax and AUC in interaction studies.
Population Pharmacokinetics Analysis of Maraviroc IV Data from Phase 1 Study A4001009	A4001009	To investigate the disposition pharmacokinetics of maraviroc after single dose administration of IV solution in healthy male volunteers. To quantify the variability of the pharmacokinetics of maraviroc after single dose administration of IV solution in healthy male volunteers. To predict the influence of clearance changes on the pharmacokinetic profile of maraviroc after IV dosing.
Clearance and Mass Balance Model for Maraviroc	A4001010	To produce a model for the clearance and mass balance of maraviroc after single dose oral administration of 300 mg solution in healthy male volunteers
Population Pharmacokinetics of Maraviroc after Oral Tablet Administration – A Pooled Analysis of Phase 1/2a Data	Data from 15 Phase 1 studies and 2 Phase 2a patient studies (A4001007 and A4001015)	To develop a compartmental structural pharmacokinetic model to describe rich maraviroc pharmacokinetic data after single and multiple oral dosing with tablet in healthy volunteers and HIV-1 infected subjects. To quantify the variability of the pharmacokinetics of maraviroc. To quantify the influence of key covariates such as age, sex, race, HIV status and weight on the variability of the pharmacokinetics of maraviroc. The results (models and parameter estimates) from this analysis are to be used to support the modelling of sparse data collected in the Phase 2b and 3 studies in both treatment naïve and treatment experienced patients infected with HIV-1 on combination therapies.

Table 2. Overview of Pharmacokinetic Modelling

Analysis	Data	Objectives
The Impact of Interacting Antiretroviral Drugs on Maraviroc Pharmacokinetics After Oral Tablet Administration – A Pooled Population Pharmacokinetic Analysis of Phase 1 Data	Data or selected data from A4001006, A4001011, A4001013, A4001021, A4001025, A4001017, A4001046	To apply a previously developed compartmental structural pharmacokinetics model for maraviroc to estimate the effects of concomitant interacting drugs across a group of Phase 1 studies (single and multiple oral tablet dosing in healthy volunteers and HIV-infected patients) with reference to the previously analyzed maraviroc alone data. To assess the impact of inhibitors/inducers of CYP3A4 on the terminal half-life of maraviroc. To qualify the methodology by comparing the model generated AUC ratios with those from the individual study report.
Pharmacokinetic Modelling in Phase 2b/3		
Preliminary Population Pharmacokinetic Analysis of Maraviroc in Pooled Phase 2b/3 Studies of Treatment-Experienced Patients on Optimised Background Therapy	A4001027 TE A4001028 TE A4001029 TE	To apply the previously developed 2 compartment maraviroc pharmacokinetic model to sparse concentration data to generate *post hoc* Bayesian estimates (PBEs) of individual pharmacokinetic parameters. To use individual pharmacokinetic parameters to generate subject specific exposure variables: average concentration (C_{ave}), minimum concentration (C_{min}) and equivalent constant concentration (ECC). To explore the influence of covariates (OBT and concomitant medication) on maraviroc concentration data and exposure variables.

TN=treatment naïve HIV-1 infected patients
TE=treatment experienced HIV-1 infected patients

2.7.2.1.3.1. Exposure Response Analyses of Phase 2b/3 Studies

Exploratory and descriptive exposure response analyses were performed for the Phase 2b/3 programme. The interdependency of these reports with pharmacokinetic modelling are illustrated in Figure 1 and an overview of the clinical data and objectives of these reports are described in Table 3.

Table 3. Overview of Phase 2b/3 Exposure-Response Modelling Analyses

Analysis	Data	Objectives
Preliminary Pharmacokinetic/ Pharmacodynamic Analysis of the 300 mg QD Maraviroc Phase 2b Cohort in Study A4001026	A4001026 TN (interim analysis data set QD arm on maraviroc treatment, 24 week cut)	To apply a pharmacokinetic model developed with Phase 1/2a data to data from Study A4001026 to generate individual *post hoc* Bayesian estimates (PBEs) of pharmacokinetic parameters and exposure variables; To compare maraviroc exposure variables in patients who were non-failures to those who failed treatment up to week 24; To explore the relationship between exposure to maraviroc and treatment response over the first 24 weeks.
Preliminary Modelling of Viral Load and CD4 count to explore the Relationship with Maraviroc Exposure and other Prognostic Factors for Trials A4001027 and A4001028.	A4001027 TE and A4001028 TE (500 patient cut)	To develop a regression model including exposure parameters and potential prognostic factors that can describe maraviroc's effect on viral load (as a binary outcome) in HIV-1 infected subjects in trials A4001027 and A4001028 To develop a regression model including exposure parameters and potential prognostic factors that can describe maraviroc's effect on CD4 count in HIV-1 infected subjects in trials A4001027 and A4001028

TN=treatment naïve HIV-1 infected patients
TE=treatment experienced HIV-1 infected patients

2.7.2.1.3.2. Semi-Mechanistic Drug Disease Modelling and Simulation

A semi-mechanistic pharmacokinetic/pharmacodynamic–viral dynamics model relating maraviroc exposure to viral load has been utilised for dose-response predictions throughout the clinical development programme of maraviroc. The assumptions and parameters of this model have been updated each time informative data has become available. The estimation of maraviroc in vivo potency has been described after incorporation of the short term maraviroc monotherapy from two Phase 2a studies in HIV-1 infected patients: (Module 5.3.4.2, Modelling and Simulation of Maraviroc to Support Phase III Trial Decisions. [redacted]. This report also covers the extension of the pharmacokinetic/pharmacodynamic-viral dynamic model to an integrated drug-disease model for clinical trial simulation by incorporating adherence, dropout and other antiviral agents with maraviroc effects for the prediction of Phase 2b/3 clinical trial outcome.

A descriptive analysis of maraviroc pharmacokinetics and CCR5 receptor occupancy relationship derived from early studies in patients and volunteers has been performed (Module 5.3.4.2, Pharmacokinetic/pharmacodynamic modelling of CCR5 receptor occupancy by maraviroc in healthy subjects and HIV-1 positive patients). A third report (Module 5.3.4.2, Semi-mechanistic pharmacodynamic model for CCR5 antagonist based on receptor theory) links receptor theory to the pharmacokinetic/pharmacodynamic-viral

dynamic model and offers a theoretical framework for explaining the apparent discrepancy between receptor occupancy and in vivo potency of maraviroc. An overview of the objectives and clinical study data in these viral dynamic modelling analyses are presented in Table 4.

Table 4. Overview of CCR5 Receptor and Viral Dynamics Modelling

Analysis	Data	Objectives
Modelling and Simulation of Maraviroc (UK-427,857) to Support Phase III Trial Decisions. [redacted]	A4001007, A4001015	Refinement of parameter estimates (including in vivo IC_{50}) for the semi-mechanistic PK/PD-viral dynamic model using all maraviroc monotherapy concentration and viral load data. Use of an integrated model (including adherence dropout and effects of concomitant antiretorvirals) to simulate Phase 2b/3 efficacy to assist with dose selection
Pharmacokinetic/pharmacodynamic Modelling of CCR5 Receptor Occupancy by Maraviroc in Healthy Subjects and HIV-1 Positive Patients	A4001002, A4001007	To develop a population pharmacokinetic/ pharmacodynamic model that describes the CCR5 occupancy by maraviroc after oral administration at different doses in healthy volunteers and HIV-1 infected patients. To provide guidance with respect to the value of measuring CCR5 receptor occupancy as an efficacy biomarker.
Semi-mechanistic Pharmacodynamic Model for CCR5 Antagonist based on Receptor Theory	Simulation	To develop a common theoretical framework based on receptor theory and operational model of (ant-agonism) to explain the apparent discrepancy between the estimated values of KD, in vitro IC_{50} and in vivo IC_{50} for maraviroc.

2.7.2.1.3.3. Pharmacokinetic/Pharmacodynamic Haemodynamic Modelling

The first in human study (A4001001) indicated that at doses of 1200 mg maraviroc haemodynamic changes occurred, including postural hypotension (4/9 subjects at 1200 mg). Doses up to 900 mg of maraviroc did not affect supine blood pressure or pulse rate and this was therefore regarded as the maximum tolerated dose. Although there were no clinically significant QT interval increases in A4001001 (*i.e.* no subjects with QTcB >450ms and no changes in baseline of >60ms), analysis of the ECG data showed evidence of a QTc interval increase after 1200 mg maraviroc. A number of later studies were either designed specifically to assess the effects of maraviroc on haemodynamics (A4001033) or QT (A4001016) or included additional monitoring of blood pressure and pulse rate (A4001002, A4001006). The dose related effects are discussed in the individual study reports. However, because of the potential for interacting drugs to substantially increase plasma concentrations of maraviroc in the clinical setting it was thought necessary to also define concentration effect relationships for QT and blood pressure changes.

Preclinical data indicated that maraviroc had the potential to increase the QT interval in man at high concentrations and in Study A4001001 there was a trend towards a treatment related effect on QTc following the highest non-therapeutic dose of maraviroc 1200 mg investigated in this study. Pharmacokinetic/pharmacodynamic modelling was therefore performed on data from Study A4001016 to characterise the relationship between plasma concentration ('exposure') and QT interval corrected for heart rate (QTc) (Module 5.3.4.1, Exposure-Response Modelling Report for Maraviroc Exposure on QT interval Corrected for Heart rate Phase 1 Data [Protocol A4001016]). The relationship between maraviroc plasma concentration and QT interval was also investigated. For this analysis RR interval was included in the exposure-response model to simultaneously estimate parameters describing the QT-RR relationship and the drug effect on QT and RR.

Pharmacokinetic/pharmacodynamic analysis of standing systolic/diastolic blood pressure data from two multiple dose Phase I studies (A4001002, A4001006) of maraviroc in healthy volunteers, at doses up to 600 mg twice daily, was performed to characterise the concentration response relationship of standing systolic and diastolic blood pressure of maraviroc in subjects who did not experience postural hypotension. These studies were chosen because patients received multiple doses of maraviroc and intensive blood pressure monitoring was performed at baseline and over the dose interval. As blood pressure shows diurnal variation, the model incorporated the cosine function methodology from a previous published pharmacokinetic/pharmacodynamic model of the antihypertensive drug moxonidine to account for baseline diurnal variation.

An overview of the objectives and clinical study data in these haemodynamic pharmacodynamic modelling analyses are presented in Table 5.

Table 5. Overview of Pharmacokinetic/Pharmacodynamic Haemodynamic Modelling

Analysis	Data	Objectives
Exposure-Response Modelling Report for Maraviroc Exposure on QT interval corrected for heart rate Phase 1 Data (Protocol A4001016)	A4001016	To explore and characterize the effect of maraviroc plasma concentration on the QT/QTc interval, following oral administration of maraviroc as a single dose to healthy male and female subjects.
Population Pharmacokinetic/ Pharmacodynamic Analysis of Blood Pressure for A4001002 and A4001006 Data from Phase I of Maraviroc	A4001002, A4001006	To describe the relationship between measured maraviroc plasma concentrations and the standing blood pressure (systolic and diastolic) using pharmacokinetic/pharmacodynamic modelling. To use the model to predict the change in standing systolic and diastolic blood pressure over the concentration range 0-2000 ng/mL maraviroc (concentrations achieved after 0-600 mg steady state dosing).

2.7.2.2. Summary of Results of Individual Studies

A tabular listing of the objectives, design and dosing schedules for all clinical pharmacology studies of maraviroc completed by [redacted] is provided in Appendix Table A1 (Summary of Human Pharmacokinetic Studies).

In this section, pharmacokinetic results are presented for all studies. Although safety and tolerability were primary endpoints in all studies, safety is mainly discussed in Module 2.7.4, Summary of Clinical Safety. In the sections below, safety/tolerability data are only presented for studies that provide essential important information which relate to key safety findings or maximum tolerated dose. Pharmacodynamic results from relevant studies are presented in section 2.7.2.3.2.

On the whole, food restrictions were in place across the studies. In general on pharmacokinetic sampling days, subjects were fasted overnight until 4 hours post-dose. For multiple dose studies, food intake was also controlled on the intervening study days, and generally subjects were required to abstain from food for two hours pre-dose until 1 hour post maraviroc dose. The exception to these restrictions was for fed treatment groups in studies (A4001001, A4001003, A4001004, A4001015, A4001043), where subjects generally took their maraviroc dose within 5 minutes of completing their meal. Full details of the study specific food restrictions can be found in the individual study reports.

2.7.2.2.1. Biomaterial Studies

Full details of in vitro and in vivo studies can be found in the nonclinical overview (Module 2.4) and associated written summaries (Modules 2.6.2, 2.6.4 and 2.6.6). In vitro studies have presented unbound concentrations in assays and where appropriate these have been compared with the mean unbound C_{max} at the maximum therapeutic dose in humans (300 mg BID: C_{max} 300 nM, 155 ng/mL, Study A4001007, Module 5 Section 5.3.4.2). Given the molecular weight of maraviroc (513.7), 1ng/mL equals 1.94nM.

Single Dose Pharmacokinetics in wild-type and multidrug resistance (Mdr) 1a/1b knockout Mice

Mdr 1a/1b double knockout mouse is a strain which is deficient in both Mdr 1a and Mdr 1b genes which encode murine P-glycoprotein. Following single oral (16 mg/kg) administration to Mdr 1a/1b knockout and wild type mice (N=2 per time point) plasma C_{max} values of 1119 and 536 ng/mL (respectively), were achieved at 0.5 hours post-dose, with AUC_{inf} values of 1247 and 440 ng.h/mL, respectively (Study No DM2, Section 2.6.4.3.1.1, Module 2.6.4 Pharmacokinetics Written Summary). The three-fold higher systemic maraviroc exposure of Mdr 1a/1b mice compared to wild type mice indicates that P-gp limits maraviroc absorption.

Affinity for P-glycoprotein

The affinity of maraviroc for the drug efflux transporter P-gp has been studied in vitro. The K_m value was 37 ± 6.4 μM, with a V_{max} of 55 ± 3.4 nmol/mg/min. The low K_m value indicates that maraviroc is a substrate for P-gp (Study No DM21, Section 2.6.4.4.5, Module 2.6.4 Pharmacokinetics Written Summary).

Plasma Protein Binding

Maraviroc showed moderate plasma binding in all species with an approximate two-fold range in unbound fraction from 0.25 (human) to 0.52 (monkey) (Study No. DM23, Section 2.6.4.4.3, Module 2.6.4 Pharmacokinetics Written Summary). Binding was independent of sex of the species studied (mouse, dog, monkey) and concentration range studied. Maraviroc (1, 30 and 1000 μg/ml) was shown to bind moderately to the physiological concentrations of human plasma proteins albumin (600 μM) and α1-acid glycoprotein (16 μM), with a mean maraviroc affinity of 56% for albumin and 69% for α1-acid glycoprotein 69% (Study No. DM18, Section 2.6.4.4.3, Module 2.6.4 Pharmacokinetics Written Summary).

Permeability in Caco-2 cells

In vitro permeability experiments with maraviroc (25 μM) in Caco-2 cell monolayers, indicated that maraviroc had limited permeability and showed polarised transport across the cell monolayer. The degree of polarised transport was inhibited by known inhibitors of P-gp transport (verapamil and CP-100,356) and the multidrug resistance protein inhibitor MK-571 (Study No. DM20, Section 2.6.4.4.6, Module 2.6.4 Pharmacokinetics Written Summary).

The efflux of [^{14}C]-maraviroc from Caco-2 cell monolayers has been studied in the presence of a number of known P-gp inhibitors. The rank order for efflux inhibition was ketoconazole > ritonavir > nelfinavir > saquinavir > indinavir, with IC_{50} values ranging from 2.25 μM to >100 μM (Study No. DM44, Section 2.6.4.4.6, Module 2.6.4 Pharmacokinetics Written Summary).

In vitro metabolism [enzymology]

The in vitro metabolism of maraviroc has been studied in hepatic microsomes from human livers with varying CYP3A4, 2C9 and 2D6 activities and in microsomes prepared from cells expressing individual cytochrome P450 enzymes. In microsomes prepared from cells expressing individual CYPs, maraviroc metabolism was only detected in incubations with CYP3A4 (major) and CYP2D6 (minor) (Study No DM5, Section 2.6.4.5.2.1, Module 2.6.4 Pharmacokinetics Written Summary).

In more definitive studies in hepatic microsomes, the disappearance half-life of maraviroc was extended by ketoconazole (CYP3A4 inhibitor, mean $t_{1/2}$ = 79 minutes) but was unaffected by sulphaphenazole (CYP2C9 inhibitor, mean $t_{1/2}$ = 13.3 minutes) and quinidine (CYP2D6 inhibitor, mean $t_{1/2}$ = 13.3 minutes). In addition, the use of recombinant enzyme systems confirmed a role for CYP3A4 (and its orthologue, CYP3A5) in the metabolism of maraviroc, and that none of the polymorphic P450 enzymes CYP2C19 or CYP2D6 contribute significantly to its metabolism (Study No DM24, Section 2.6.4.5.2.1, Module 2.6.4 Pharmacokinetics Written Summary).

The formation of the circulating N-dealkylated metabolite UK-408,027 has been shown to be mediated by CYP3A4 in human liver microsomes. The metabolic pathway in vitro was characterised by single enzyme kinetics, with a K_m of 23 μM and V_{max} of 154 pmol/mg/min. In incubations with individual CYPs, only CYP3A4 gave substantial metabolite formation,

with a K_m value of 13 μM (Study No DM35, Section 2.6.4.5.2.1, Module 2.6.4 Pharmacokinetics Written Summary).

In conclusion, whilst initial screening identified a potential role for CYP2D6, more definitive hepatic liver microsome studies have shown no CYP2D6 involvement in the metabolism of maraviroc. CYP3A4 is responsible for a large proportion of the metabolism of maraviroc and as a consequence its pharmacokinetics could be altered by co-administration of drugs that inhibit this enzyme.

In vitro metabolism [inhibition]

In in vitro experiments using recombinant enzyme systems and human liver microsomes (with and without preincubation), maraviroc did not inhibit any of the cytochrome P450 enzymes studied (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) at clinically relevant concentrations (IC_{50}> 30 μM) (Study Nos. DM7, DM22, DM33, Section 2.6.4.5.2.2, Module 2.6.4 Pharmacokinetics Written Summary).

As the IC_{50} values were greater than 30 μM which is approximately 100 fold higher than the free C_{max} of 300 mg BID maraviroc (155 ng/mL), maraviroc is considered unlikely to inhibit the metabolism of other P450 substrates at clinical doses in vivo.

Affinity of Maraviroc for the CCR5 Receptor

The biological mechanism by which maraviroc inhibits viral entry is discussed in Section 2.4.2, Module 2.4 Nonclinical Overview. Maraviroc binds to human CCR5 with a K_D of 0.86 nM and has a dissociation half-life of approximately 16 hours at room temperature (Study codes DI/012/1 and CG/015/02, Section 2.6.2.2.1.1 Module 2.6.2 Pharmacology Written Summary). Site directed mutagenesis and computer modelling studies locate the likely binding site of maraviroc to a pocket within the transmembrane region of CCR5 (DI/102/05) and these binding interactions contribute to prolonged CCR5 physical and functional occupancy at the receptor by maraviroc.

Affinity of Maraviroc for Other Receptors, Enzymes and Ion Channels

Maraviroc was profiled for its affinity for various pharmacologically relevant receptors, enzymes and ion channels. 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, and the human α_{2A} adrenergic binding assays (Sections 2.4.2.5.1.1, 2.4.2.5.1.2 and 2.4.2.5.1.3, Module 2.4 Nonclinical Overview).

Further investigations showed that maraviroc had no significant affinity for the human recombinant muscarinic receptor subtypes (CG/001/02) and was inactive at 1 μM in the guinea pig ileum (CG/006/00). Maraviroc gave a range of moderate-to-weak binding affinities for the human μ opioid receptor depending on the assay system used, K_i=106-209 nM (CG/013/00 & CG/009/01) and K_i = 589 nM (CG/001/03). Maraviroc (10 μM) had a weak agonist effect on agonist stimulated GTP-. -S binding to human μ

receptor (5137 ng/mL) (CG/011/01). Overall, these results indicate that maraviroc's weak affinity for the muscarinic and μ opioid receptors is unlikely to be of biological significance (Section 2.6.2.4.1, Module 2.6.2, Pharmacology Written Summary).

Maraviroc was shown to have a K_i of 5.47 μM at the human α_{2A} adrenergic receptor (CG/013/02). Extensive profiling of the interaction of maraviroc with adrenergic receptors in a variety of preparations, including rat vas deferens, recombinant human adrenergic receptor cell lines and isolated human saphenous vein. Maraviroc was also shown to be an antagonist at alpha adrenergic receptors in canine venous tissue (pK_B 5.72 nM versus phenylephrine and pK_B 5.21 nM versus noradrenaline, (CG/004/04 & CG/008/04) giving rise, in vitro, to relaxation of phenylephrine pre-constricted vessels (threshold effect level = 3 μM; CG/009/04). There was no relaxation in vessels preconstricted with potassium chloride (CG/006/04), indicating that the effect seen with phenylephrine was likely to have been mediated by an alpha adrenergic receptor mechanism. Overall, maraviroc showed no consistent adrenergic mediated activity (Section 2.6.2.4.1, Module 2.6.2, Pharmacology Written Summary).

Effect of Maraviroc on the Cardiovascular System

The potential for maraviroc to influence vascular tone and thereby produce symptoms of postural hypotension via a CCR5 mediated mechanism was investigated in human vasculature (DI/073/06). The CCR5 chemokine MIP-1β, at concentrations up to 0.1 μM, produced a concentration dependent vasoconstriction of isolated, endothelium denuded human saphenous vein tissues with an apparent pEC_{50} of 7.71±0.17 (n = 10 donors, 13 observations). Pre-incubation of the tissue with 300 nM maraviroc for 30 minutes had no effect on basal tension. However, in the presence of 300 nM maraviroc, MIP-1β failed to cause contraction of human isolated saphenous veins. Therefore MIP-1β can act as a potent, low efficacy vasoconstrictor of human venous tissue and this contractile response can be antagonised by 300 nM maraviroc; this is suggestive of a functional role for the CCR5 ligand-receptor system in vascular function in human saphenous veins (Section 2.6.2.4.1, Module 2.6.2, Pharmacology Written Summary).

In vitro testing of maraviroc (up to 10 μM) using [^{3}H] dofetilide binding (IC/001/02), hERG potassium channels (CG/001/00, IC/005/02) and Purkinje fibre action potential morphology (IC/006/01, IC/003/02) indicated that maraviroc is active at the human cardiac hERG channel and suggests that maraviroc has the potential to block the I_{Kr} current and affect cardiac repolarisation in vivo at unbound plasma concentrations greater than 3 μM (approximately 10-fold higher than the free C_{max} at 300 mg BID in HIV-1 infected patients [155 ng/mL]) (Section 2.6.2.4.3, Module 2.6.2, Pharmacology Written Summary).

In conscious freely moving dogs at oral maraviroc doses that achieved an unbound C_{max} of 168 nM (86 ng/mL), maraviroc caused no statistically significant changes to the QT interval (CG/003/00, CG/008/00). However, in a further study in the conscious dog a statistically significant 14.5 msec prolongation of the ECG QT interval was observed in the absence of an effect on heart rate at a mean unbound plasma concentration of approximately 1.2 μM (631 ng/mL), which is approximately 4-fold higher than the mean unbound C_{max} in HIV positive

patients at a dose of 300 mg BID (CG/007/02) (Section 2.6.2.4.3, Module 2.6.2, Pharmacology Written Summary).

2.7.2.2.2. Maraviroc Single Dose Pharmacokinetic Studies

Study A4001001

Study A4001001 was a double-blind (3rd party open), placebo-controlled, dose escalating, crossover study to investigate the safety, tolerability and pharmacokinetics of single oral doses (solution) of maraviroc in twenty-four healthy male subjects in the fed and fasted states. The study contained two parallel cohorts of 12 subjects each: Cohort A received 1, 10, 100, and 900 mg and Cohort B received 3, 30, 300 and 1200 mg. Cohort A subjects also received 100 mg after food in a non-randomised 5th period. In each cohort, nine subjects received maraviroc and three received placebo while fasted at each dosing period. Dosing periods were separated by at least seven days. Each subject had escalating maraviroc doses with one dose replaced by placebo (placebo substitution).

Pharmacokinetic Results: After oral dosing, maraviroc C_{max} is achieved generally within 0.5 to 4.0 hours. Maraviroc pharmacokinetics are non-proportional across the dose range studied (Figure 2 and Table 6). Urine pharmacokinetic results showed that the mean percentage of maraviroc dose excreted unchanged in the urine increased from 1.5% following 1 mg to 12% following 1200 mg. Renal clearance did not change notably with dose (Table 6).

Figure 2. Mean Maraviroc Plasma concentration versus time profiles (A4001001)

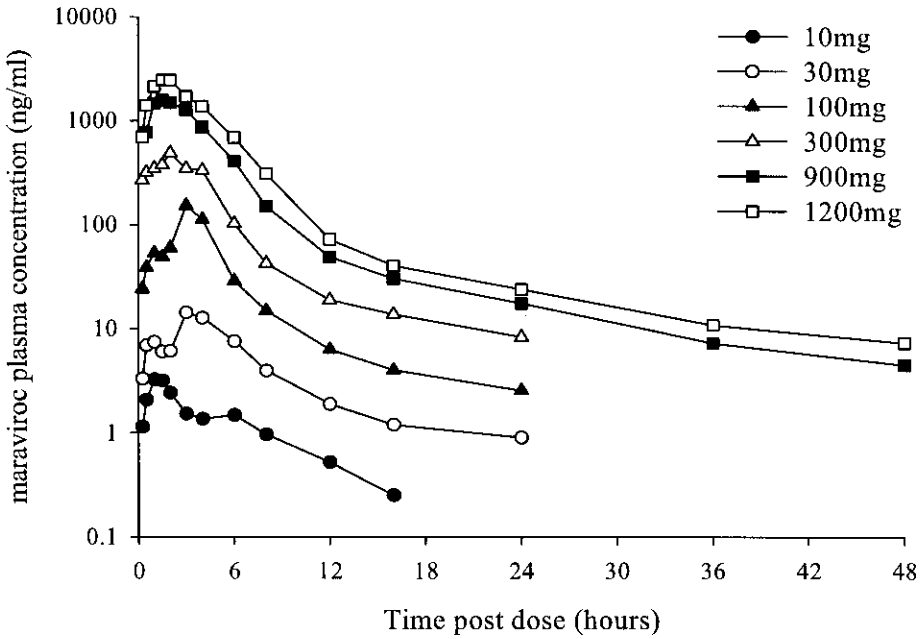


Table 6. Summary of Mean Single-Dose Pharmacokinetic Parameters (A4001001)

Dose (mg)	Mean Maraviroc Parameters (range)					Aet µg (% of dose)
	AUClast [ng·h/mL][a]	Cmax [ng/mL][a]	Tmax [h][b]	t½ [h][b]	CLr [L/h]	
1	0.118	0.318	1.25	n/c	n/c	15
N=2[c]	(0.069-0.201)	(0.275-0.368)	(1.0-1.5)			(1.5%)
3	2.25	0.584	2.06	n/c	n/c	47
N=9	(1.18-3.36)	(0.354-1.25)	(0.5 to 6.0)			(1.6%)
10	17.2	2.92	2.50	n/c	n/c	232
N=9	(10.5-32.5)	(1.24-8.34)	(0.5-6.0)			(2.3%)
30	80.9	15.3	2.89	8.91	10.5	916
N=9	(27.8-178)	(12.1-42.1)	(0.5-6.0)	(7.61-10.1)	(8.82-14.0)	(3.1%)
100	583	172	3.11	9.86	10.3	6098
N=9	(466-758)	(132-229)	(2.0-4.0)	(7.39-14.0)	(7.47-12.0)	(6.1%)
300	2190	621	1.64	10.6	12.9	2140
N=9	(1350-3020)	(417-970)	(0.3-4.0)	(7.88-16.0)	(11.2-14.4)	(2.1%)
900	7280	1630	1.94	11.3	11.5	28400
N=9	(4100-9790)	(881-2550)	(1.0-3.0)	(7.12-14.6)	(2.09-15.4)	(9.5%)
1200	11300	2807	1.78	12.5	12.7	144156
N=9	(8790-17700)	(1980-3960)	(1.0-2.0)	(9.15-16.5)	(10.1-15.9)	(12.0%)
100 mg (fed)	205	19.3	2.88	14.0	12.6	2140
N=12	(133-401)	(13.1-83.7)	(1.5-6.0)	(9.04-18.4)	(8.70-16.7)	(2.14%)

Source:A4001001 CSR Table 5.1.1, 5.1.2, 5.7.1 and 5.7.2
All values are quoted as total concentrations
[a] unadjusted geometric mean,
[b] unadjusted arithmetic mean,
[c] only 2 subjects had detectable concentration
n/c = not calculated

Food reduced exposure of maraviroc with mean AUCinf and Cmax after 100 mg being 63% and 88% lower, respectively when fed than when fasted. The results of the fed/fasted comparison in Cohort A are discussed in more detail in Section 2.7.1.2.3, Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods.

Safety Results: Maraviroc was tolerated up to 900 mg. Treatment related adverse events were mostly confined to subjects who received 1200 mg, the most common of which was asthenia, followed by postural hypotension and headache. The 900 mg dose was considered the maximum tolerated dose, with postural hypotension at 1200 mg being the dose limiting event. Four out of nine subjects had dose limiting postural hypotension recorded after the single 1200 mg maraviroc dose. Events were recorded as orthostatic or postural hypotension when the subject complained of dizziness on standing and had a recorded postural drop in blood pressure (systolic or diastolic blood pressure) on standing. These postural hypotension events appeared temporally related to Cmax and resolved without any specific treatment. These postural hypotension events were considered dose-limiting. Postural hypotension is discussed in this module in section 2.7.2.3.2 and Section 2.7.4.2.1.5, Module 2.7.4 Summary of Clinical Safety.

Study A4001003

Study A4001003 was an open, randomised, five-way crossover study in fifteen healthy volunteers that investigated the pharmacokinetics of single oral doses of maraviroc (50, 100 and 600 mg), the effect of food on a single 600 mg dose (4 x 150 mg tablets) and the relative oral bioavailability of the 100 mg tablet versus a dose of 100 mg oral solution. Fifteen subjects entered the study and were randomised to be fasted for four of the five study periods. Successive treatments were separated by at least 5 days. Dose proportionality was assessed using power law and dose divide methods as described in the statistical section of the clinical study report.

Pharmacokinetic Results: The unadjusted mean pharmacokinetic parameters for maraviroc (50 mg, 100 mg and 600 mg) are presented in Table 7.

Table 7. Summary of Maraviroc Pharmacokinetic Parameters (A4001003)

Parameter	Fasted Maraviroc Dose Mean Parameter Value (range)		
	50 mg N=13	100 mg N=15	600 mg N=15
AUC_{last} (ng.h/mL)[a]	209 (72.0-376)	555 (133-1070)	5636 (4150-9630)
AUC_{inf} (ng.h/mL)[a]	227 (80.2-396)	576 (150-1090)	5703 (4200-9750)
C_{max} (ng/mL)[a]	55.0 (25.9-124)	154 (28.3-470)	1221 (762-1910)
T_{max} (h)[b]	3.0 (1.0-6.0)	2.33 (0.5-4.0)	3.30 (1.0-6.0)
$t_{½}$ (h)[b]	14.4 (10.1-20.5)	13.3 (7.48-17.7)	11.5 (9.32-14.2)

Source: A4001003 CSR Table 5.1.
[a] unadjusted geometric means;
[b] unadjusted arithmetic means

Maraviroc pharmacokinetics are not dose proportional over the dose range 50 to 600 mg. Dose proportionality could not be concluded for C_{max} as the power law analysis indicated a deviation from linearity. The dose proportionality constant for AUC_{inf} was estimated as 1.18 (95% CI; 1.10, 1.26). As this was statistically significantly different from 1, dose proportionality could not be concluded (Table 8).

Table 8. Summary of Dose Proportionality Assessment (A4001003)

Parameter	Maraviroc Dose			Assessment of Dose Proportionality[a]		
	50 mg (fasted)[b]	100 mg (fasted)[b]	600 mg (fasted)[b]	Linearity	Slope	Dose proportionality Estimate (95% CI)
AUC_{last} (ng.h/mL)[c]	4.16	5.55	9.39	0.615	0.142	1.32 (1.21, 1.43)[d]
AUC_{inf} (ng.h/mL)[c]	4.50	5.76	9.51	0.081	0.312	1.18 (1.10, 1.26)[d]
C_{max} (ng/mL)[c]	1.10	1.53	2.04	0.036	-	-

Source: A4001003 CSR Tables 5.3 and 5.4
[a] All pharmacokinetic parameter values (50 mg, 100 mg and 600mg) have been divided by dose in these analyses
[b] adjusted geometric means
[c] dose normalized to 1mg; A dose proportionality constant has only been presented if there is evidence to assume both linearity and a common slope.
[d] 95% confidence intervals are presented here in accordance with the SAP and protocol, whereas 90% confidence intervals were calculated and presented in the CSR for A4001003. The source data for the 95% confidence intervals are available on request.
CI= confidence interval

The results of comparison of the relative bioavailability of the tablet compared to the solution in the fasted state and the effect of food on a single 600 mg dose of maraviroc from Study A4001003 are presented in Sections 2.7.1.2.1 and 2.7.1.2.3, Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods.

Study A4001009

Study A4001009 investigated the pharmacokinetics, safety and tolerability of escalating IV doses of maraviroc, and determined the absolute bioavailability of a 100 mg oral tablet dose of maraviroc in twenty healthy male subjects. This study comprised two cohorts.

Cohort 1 was a double-blind (third party open), randomised, four-way crossover study, where eight subjects received escalating IV doses of maraviroc (3, 10 and 30 mg) with placebo insertion. All IV doses were given as 1 hour infusions. The safety, tolerability and pharmacokinetics of each IV dose in Cohort 1 were assessed prior to the next dose, to allow adjustment of the subsequent doses (up or down as appropriate). The aim was for the maximum IV dose to have an exposure equivalent to that seen following a single oral dose of 100 mg tablet; this IV dose was to be used in Cohort 2.

Cohort 2 was an open, randomised, two-way crossover study involving twelve subjects who received 30 mg maraviroc by IV infusion and 100 mg oral maraviroc tablet.

Pharmacokinetic Results: The adjusted mean pharmacokinetic parameters for maraviroc are shown in Table 9.

Table 9. Mean Single Dose, IV and Oral Maraviroc Pharmacokinetic Parameters (A4001009)

Parameter	Maraviroc Dose Mean Parameter Value (range)				
	Cohort 1			Cohort 2	
	3 mg IV N=8	10 mg IV N=8	30 mg IV N=8	30 mg IV N=12	100 mg oral tablet N=12
AUC_{last} (ng.h/mL)[a]	57.6 (42.1-68.6)	201 (180-252)	670 (534-795)	644 (494-828)	492 (298-1010)
Cmax (ng/mL)[a]	36.9 (23.4-44.6)	122 (104-156)	397 (308-467)	374 (316-439)	122 (64.1-314)
Tmax (h)[b]	0.94 (0.75-1.00)	0.94 (0.50-1.00)	0.91 (0.50-1.00)	0.98 (0.75-1.00)	3.08 (1.0-4.0)
t½ (h)[b]	n/c	n/c	13.2 (10. 3-18.3)	12.0 (9.64-14.9)	12.5 (9.66-15.0)
Vss	n/c	n/c	194 (118-319)	182 (122-284)	n/c
CL (L/h)	n/c	n/c	44.0 (37.4-54.8)	46.2 (35.6-59.3)	n/c
CLr (L/h)	11.2 (8.22-12.7)	10.5 (8.26-12.6)	10.2 (8.00-12.2)	n/c	n/c
F (%)	n/c	n/c	n/c	n/c	23.1

Source: A4001009 CSR Tables 5.1.1.1, 5.1.2, 5.2.1.9 and 5.5.2 All values are quoted as total concentrations
[a]unadjusted geometric means; [b] unadjusted arithmetic means
IV= intravenous, n/c = not calculated

Mean total clearance and steady state volume of distribution for a 30 mg IV dose were 44 L/h and 194 L, respectively (Table 9). Approximately 23% of the total clearance (44 L/h) was accounted for by renal clearance (10.2 L/h) and 77% by non-renal clearance (33.8 L/h). Mean absolute bioavailability of the 100 mg oral dose was 23% (95% CI 19.2, 27.8).

Maraviroc IV pharmacokinetics were essentially linear (dose proportionality constant for AUC_{last} was 1.07 [95% CI: 1.01, 1.12]) and for C_{max} was 1.03 [95% CI: 0.96, 1.11]) suggesting systemic clearance was independent of dose over this dose range (Table 10).

Table 10. Summary of Dose Proportionality Assessment (A4001009)

Parameter	Maraviroc Dose			Assessment of Dose Proportionality[a]		
	3 mg (IV)	10 mg (IV)	30 mg (IV)	Linearity	Slope	Dose proportionality Estimate (95% CI)
AUC_{last} (ng.h/mL)[b,c]	19.2	20.1	22.3	0.500	0.626	1.07 (1.01, 1.12)
C_{max} (ng/mL)[b,c]	12.3	12.2	13.2	0.525	0.383	1.03 (0.96, 1.11)

Source: A4001009 CSR Tables 5.3.1 and 5.4

[a] All pharmacokinetic parameter values (50 mg, 100 mg and 600mg) have been divided by dose in these analyses

[b] adjusted geometric means

[c] dose normalized to 1mg; A dose proportionality constant has only been presented if there is evidence to assume both linearity and a common slope.

CI= confidence interval

The full results from Cohort 2 and absolute bioavailability of the oral tablet (100 mg) are presented in Section 2.7.1.2.1, Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods.

Study A4001010 (Maraviroc Radiolabelled Study)

Study A4001010 was a single centre open study to investigate the absorption, metabolism and excretion of [^{14}C] maraviroc in three healthy male subjects following single oral solution (300 mg) administration. The concentrations of radioactivity in plasma and whole blood, urine and faeces, and the metabolic pathways of [^{14}C] maraviroc were determined.

Pharmacokinetic Results: Maraviroc was rapidly absorbed with low inter-individual variation. The maximum observed maraviroc plasma and whole blood concentrations of radioactivity occurred within a mean of 1.5 hours of dosing and occurred between one and two hours for all subjects (Table 11).

Table 11. Summary of Mean Maraviroc Pharmacokinetic Parameters and Radioactivity (A4001010)

Parameter	Medium	Maraviroc 300 mg (solution) Mean value (range) N=3	Total Radioactivity (ng equiv)[a]	Geometric Mean Blood/Plasma ratio
AUC_{last} (ng.h/mL)[b]	Plasma	2055 (1900 to 2250)	4497 (4260 to 4640)	0.62 (0.48 to 0.79)[d]
	Blood		2251 (1540 to 3630)	n/c
Cmax (ng/mL)[b]	Plasma	496 (429 to 627)	800 (603 to 1060)	0.61 (0.57 to 0.65)
	Blood		489 (343 to 686)	n/c
Tmax (h)[c]	Plasma	0.83 (0.5 to 1.5)	1.33 (1.00 to 2.00)	n/c
	Blood		1.33 (1.00 to 2.00)	n/c

Source: A4001010 CSR Tables 5.1, 5.2, 5.3 and 5.4
[a] Total radioactivity reported as (ng equiv.h/g) for AUC_{last} and as (ng equiv/g) for C_{max}
[b]Geometric means;
[c]arithmetic means,
[d] using time matched AUC_{last} comparisons
n/c = not calculated

There was a higher amount of radioactivity in plasma than in blood. The blood/plasma ratio for total radioactivity for AUC_{last} and Cmax was approximately 0.6 suggesting that maraviroc related material is predominantly confined to the plasma with negligible distribution into red blood cells (Table 11).

High performance liquid chromatography and mass spectrometric analysis of precipitated plasma (0-18 hours) showed that unchanged maraviroc was the major circulating component in plasma, accounting for 42% of the circulating radioactivity. UK-408,027, which resulted from N dealkylation and an analogue of this amine involving oxidation of the methyl group of the triazole moiety, was also identified, accounting for 22% and 11% of the circulating radioactivity respectively. The coefficient of variation for the analytical methods in plasma (as assessed by analysis of six replicates at 3 concentrations) was between 2.2% and 11.3%.

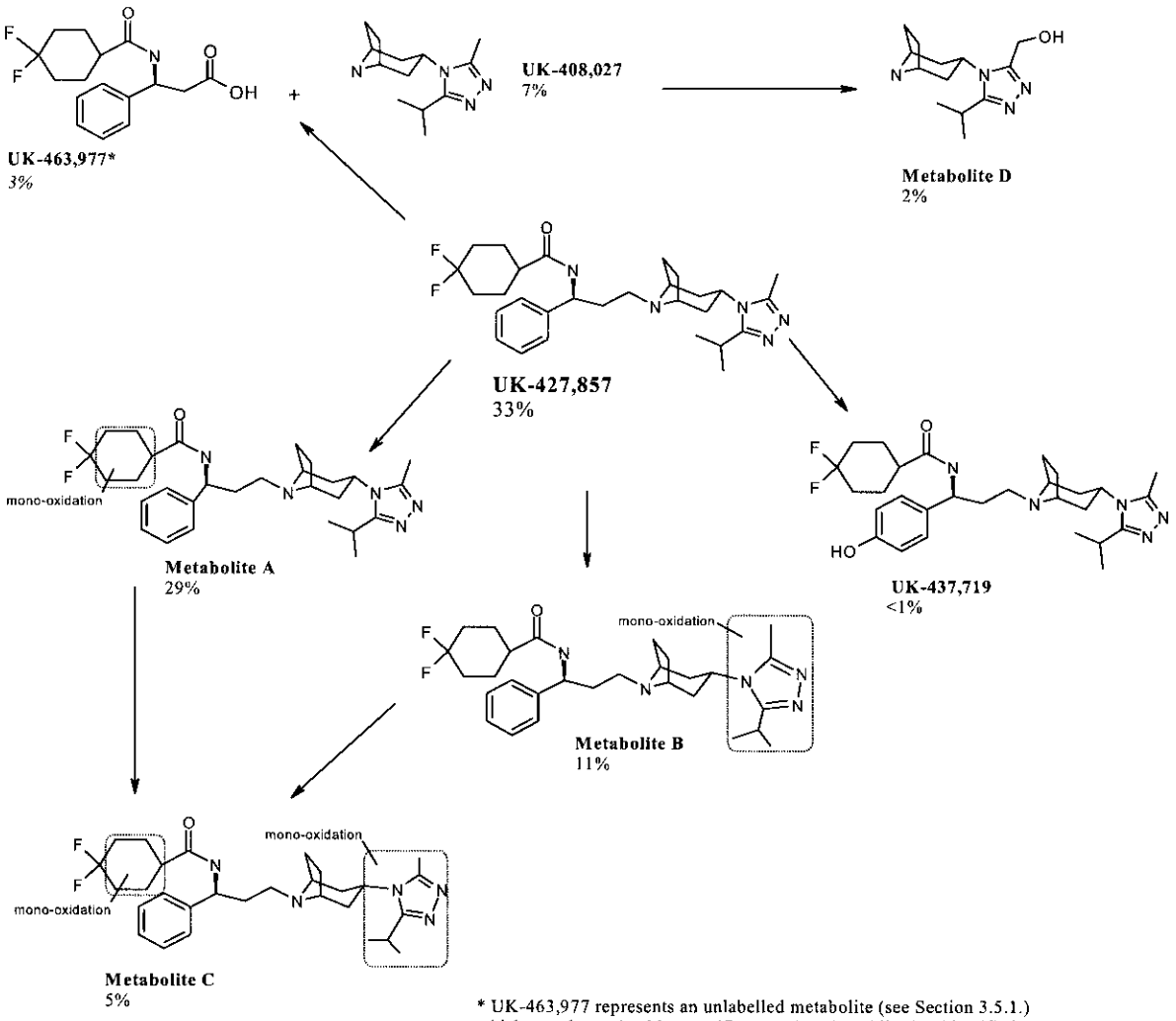
Total mean recovery of radioactivity was 96%. Most radioactivity was excreted via the faeces (76.4%) whilst 19.6% was recovered in urine. Intersubject variability was low in terms of relative quantities of maraviroc and its metabolites in both plasma and excreta.

Excreted human metabolites are illustrated in Figure 3. All human circulating metabolites were present in the plasma of at least one of the toxicology species tested. The metabolism of maraviroc across species is described in further detail in Section 2.4.3.4, Module 2.4, Nonclinical Overview.

Metabolite analysis of urine and faeces showed that maraviroc metabolism was extensive and similar for all subjects. The major metabolite pathways involved oxidation in the difluorocyclohexane ring, oxidation in the triazole group and N-dealkylation adjacent to the tropane moiety. The major excreted components were unchanged maraviroc (33% of total radioactive dose), four metabolites involving mono-oxidation in the difluorocyclohexane ring (each accounting for between 5 and 9%), a metabolite which resulted from oxidation in the triazole group (10%) and a secondary amine (UK-408,027) resulting from N-dealkylation

adjacent to the tropane moiety (7%). The N-dealkylation also yielded an unlabelled carboxylic acid (UK- 463,977; ~ 3%).

Figure 3. Excreted metabolites of Maraviroc (percentage of maraviroc dose) following administration of [14C]-Maraviroc to male human volunteers (n=3).



* UK-463,977 represents an unlabelled metabolite (see Section 3.5.1.) which was determined by specific assay in urine. All other identified metabolites contained the radiolabelled centre.

Mass balance modelling of the data from Study A4001010 is presented in Section 2.7.2.3.1.

2.7.2.2.3. Maraviroc Multiple Dose Pharmacokinetic Studies

Study A4001002

Study A4001002 was a double-blind (3rd party open), randomised, parallel group, placebo-controlled single and multiple oral dose escalation study to investigate the safety, toleration and pharmacokinetics of maraviroc in seventy-two healthy male subjects. One of the secondary objectives was to compare the debrisoquine metabolic ratio in the presence and absence of maraviroc to assess potential cytochrome P450 2D6 isozyme (CYP2D6) inhibition; and to investigate the level of CYP3A4 induction in the presence of maraviroc by using 6⇓-OH-cortisol/cortisol ratio. There were 72 subjects who were screened and assigned to treatment.

The study involved the following treatments,

Cohort 1: 100 mg BID maraviroc or placebo (ratio 3:1)

Cohort 2: 300 mg BID maraviroc or placebo (ratio 3:1)

Cohort 3: 600 mg QD maraviroc or placebo (ratio 3:1)

Cohort 4: 25 mg BID maraviroc or placebo (ratio 3:1)

Cohort 5: 600 mg QD maraviroc or placebo (ratio 3:1)

Cohort 6: 3 mg BID or 10 mg BID maraviroc or placebo (ratio 5:5:2).

All doses used a solution formulation with the exception of the 600 mg dose which was dosed as tablets (4 x 150 mg tablets). For each treatment, a single dose was given on Day 1, followed by QD or BID dosing starting on Day 3 and continuing until the final dose was given on the morning of Day 12.

Between screening and Day -1 (the run in day), subjects in Cohorts 1 to 5 attended the unit for debrisoquine phenotyping. They were given a single dose of 10 mg debrisoquine, and then urine was collected from 0 to 8 hours post-debrisoquine dose. If this was not possible, subjects attended for phenotyping at or after the follow-up visit.

For Cohort 3 only (600 mg QD maraviroc), dosing was stopped on Day 7 due to severe postural hypotension in 3 subjects (2 maraviroc subjects and 1 placebo subject). Additional pharmacokinetic samples were taken up to 72 hours post-dose and urine samples were taken up to 24 hours post-dose, as had been planned for Day 12. Debrisoquine phenotyping was not conducted in this Cohort. After review of blood pressure and pulse rate data, a second cohort (cohort 5) was dosed with 600 mg QD of maraviroc.

Pharmacokinetic Results: Maraviroc was rapidly absorbed after single and multiple dosing with T_{max} occurring between 0.5 and 4 hours (Figure 4 and Table 12).

Figure 4. Mean Plasma Concentration versus Time Profiles (A4001002)

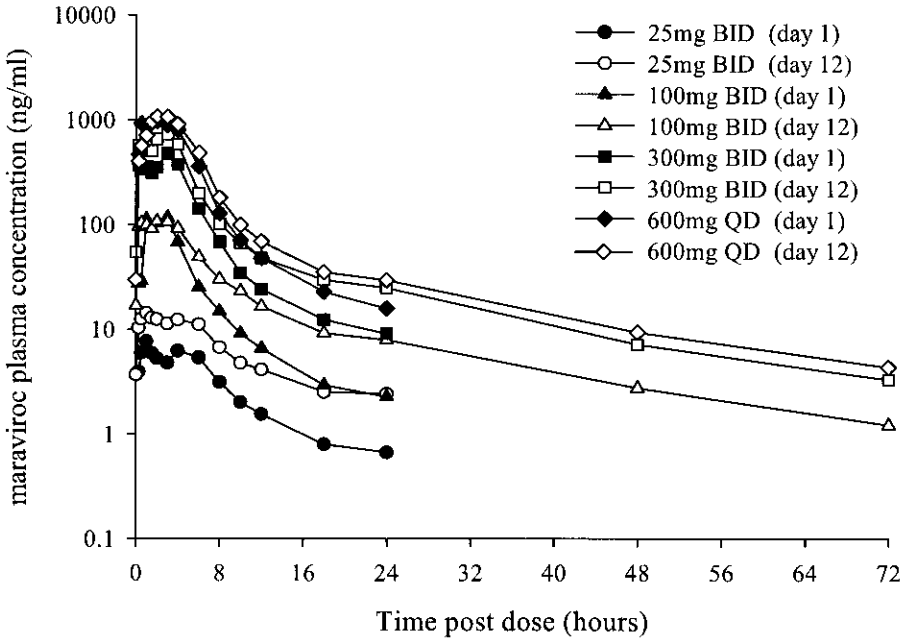


Table 12. Summary of Multiple-Dose Pharmacokinetic Parameters (A4001002)

Maraviroc Dose	Day[a] (n)	Mean Pharmacokinetic Parameters					Aet µg (% of dose)
		AUC_{tau}[b,c] (ng·h/mL)	C_{max}[c] (ng/mL)	T_{max}[d] (h)	$t_{½}$[d] (h)	CL_R[d] (L/h)	
3 mg BID N=5	1 (5)	n/c	0.668 (0.434-1.36)	0.90 (0.50-1.00)	n/c	n/c	n/c
	7 (5)	6.57 (4.39-9.05)	1.32 (0.78-1.79)	1.10 (1.00-1.50)	n/c	n/c	n/c
	12 (4)	4.22 (2.76-9.83)	0.834 (0.54-1.28)	0.56 (0.25-1.00)	n/c	n/c	n/c
10 mg BID N=5	1 (5)	11.8 (7.32-18.3)	2.26 (1.20-3.44)	1.80 (0.50-4.00)	n/c	n/c	n/c
	7 (5)	19.0 (13.3-25.3)	2.71 (2.01-4.35)	1.90 (0.50-6.00)	n/c	n/c	n/c
	12 (5)[e]	22.2 (14.8-29.9)	3.33 (1.78-5.47)	1.30 (0.50-4.00)	15.2 (11.1-18.6)	n/c	n/c
25 mg BID N=8	1 (9)[f]	46.1 (29.0-103)	8.72 (3.88-22.2)	3.33 (1.00-6.00)	10.8 (6.20-13.2)	11.4 (9.44-14.0)	695 (2.8%)
	7 (8)	92.0 (50.2-179)	18.6 (6.44-37.2)	3.13 (1.00-6.00)	n/c	11.1 (8.99-15.5)	1075 (2.2%)
	12 (8)[f]	98.6 (50.9-200)	16.2 (6.35-33.2)	3.25 (1.00-6.00)	13.9 (10.6-15.2)	11.0 (3.99-17.1)	1404 (5.6%)
100 mg BID N=8	1 (9)	512 (344-715)	187 (95.7-367)	2.17 (1.00-3.00)	7.76 (7.11-8.59)	11.3 (10.2-12.5)	6399 (6.4%)
	7 (9)	636 (403-931)	159 (99.9-288)	2.50 (0.50-4.00)	n/c	11.3 (6.08-14.9)	7463 (3.7%)
	12(9)	686 (376-913)	181 (121-307)	2.53 (0.25-6.00)	18.5 (16.1-23.2)	11.1 (2.74-13.3)	9138 (9.1%)
300 mg BID N=9	1 (9)	2157 (1250-4240)	538 (251-1010)	1.64 (0.25-4.0)	8.63 (6.20-13.2)	11.2 (7.46-15.4)	25756 (8.6%)
	7 (9)	2641 (1460-4140)	674 (297-1530)	1.47 (0.25-4.00)	n/c	12.8 (8.55-19.9)	32678 (5.5%)
	12 (9)	3609 (2760-5990)	854 (524-1450)	2.61 (0.25-4.00)	16.4 (12.0-19.9)	10.3 (7.90-12.9)	41733 (13.9%)
600 mg QD (Cohort 3) N=9	1 (9)	5877 (3930-7430)	1317 (638-2400)	3.33 (2.0-4.0)	7.74 (6.17-8.96)	12.0 (9.23-15.3)	70656 (11.8%)
	7 (9)	6982 (4360-11000)	1351 (711-2460)	2.61 (0.50-4.00)	15.3 (12.4-19.8)	11.6 (7.34-15.8)	79544 (13.3%)
	12 (0)[g]	n/c	n/c	n/c	n/c	n/c	n/c
600 mg QD (Cohort 5) N=9	1 (9)	5545 (3380-7910)	1322 (509-2490)	2.08 (0.5-4.0)	7.84 (5.97-10.3)	9.21 (6.89-11.2)	53544 (8.9%)
	7 (9)	n/c	1204 (309-2170)	2.83 (0.50-4.00)	n/c	9.95 (8.83-10.9)	57422 (9.6%)
	12 (9)	6440 (5380-7580)	1361 (821-1720)	2.31 (0.25-4.00)	17.2 (12.2-22.2)	9.55 (7.59-11.9)	61878 (10.3%)

Source: A4001002 CSR Tables 5.1.1, 5.1.2, 5.1.3, 5.1.4, 5.1.5 and 5.1.6..

[a] Days 7 and 12 correspond to 5 and 10 days of multiple dosing respectively

[b] 0 to 12 for BID dosing, 0 to 24 for QD dosing,

[c] unadjusted geometric mean

[d] unadjusted arithmetic mean,

[e] t½ only calculated for 4 subjects

[f] t½ only calculated for 5 subjects

[g] No pharmacokinetic parameters were obtained for Cohort 3 on Day 12 as this cohort was stopped on Day 7 for safety reasons.

n/c= not calculated

Estimates of t½ after a single dose were compromised by the sampling schedule; this is thought to account for the apparent differences in the t½ between single and multiple doses. The terminal half-life at steady state was 14 to 18 hours. Less than 15% of the maraviroc dose was excreted as unchanged maraviroc in urine over 24 hours. Renal clearance did not appear to change across the dose range or with time (Table 12).

Visual assessment of individual trough concentrations suggests that steady state was achieved after seven days of multiple dosing. Plasma maraviroc accumulated after both once- and twice-daily dosing in this study (Table 13). The mean accumulation ratios on day 12, for 300 mg BID and 600 mg QD (cohort 5) were 1.7 and 1.2, respectively.

Table 13. Summary of Statistical Analysis (A4001002)

Maraviroc Dose	Comparison	Ratio (%) of means (95% CI)[a]		
		AUC_{tau}	Cmax	Linearity[b]
3 mg BID	Day 7/Day 1	n/c	197 (125,311)	n/c
	Day 12/ Day 1	n/c	129 (79,212)	n/c
10 mg BID	Day 7/Day 1	162 (119,219)	120 (76,189)	n/c
	Day 12/ Day 1	189 (139,255)	148 (94,232)	n/c
25 mg BID	Day 7/Day 1	193 (152,245)	208 (146,299)	n/c
	Day 12/ Day 1	206 (162,262)	181 (126,259)	129 (97,171)
100 mg BID	Day 7/Day 1	124 (99,155)	85 (61,120)	n/c
	Day 12/ Day 1	134 (107,168)	97 (69,136)	119 (95,148)
300 mg BID	Day 7/Day 1	123 (98,154)	125 (89,176)	n/c
	Day 12/ Day 1	167 (134,210)	159 (113,223)	149 (120,186)
600 mg QD (Cohort3)	Day 7/Day 1	119 (95,149)	103 (73,144)	n/c
	Day 12/ Day 1	n/c	n/c	n/c
600 mg QD (Cohort 5)	Day 7/Day 1	n/c	91 (65,128)	n/c
	Day 12/ Day 1	123 (98,154)	103 (73,145)	113 (90,140)

Source: A4001002 CSR Table 5.3.2
[a] the ratio and corresponding confidence limits are back transformed from the log scale.
[b] Linearity=$AUC_{tau\ (Day\ 12)}$ / $AUC_{(Day\ 1)}$
n/c-=not calculated, no data

There was no evidence of CYP3A4 induction/inhibition (as demonstrated by changes in 6β-hydroxycortisol/cortisol ratio) at unit doses up to 600 mg QD maraviroc (Table 14).

Table 14. Summary of Geometric Mean 6⇓-hydroxycortisol/cortisol Ratio Data (A4001002)

Treatment Group	Mean 6⇓-OH-cortisol/cortisol ratio (range)		Geometric mean ratio % (90% CI)[a]
	Baseline	On Treatment	
25 mg BID	7.01 (3.71-12.1)	6.03 (4.09-10.4)	86.1 (59.6, 124.2)
100 mg BID	4.09 (2.66-7.4)	3.75 (1.97-7.39)	91.6 (67.9, 123.7)
300 mg BID	3.80 (2.25-15.3)	3.90 (2.10-9.50)	102.7 (74.7, 141.1)
600 mg QD (cohort 3)	4.31 (1.81-6.17)	5.48 (2.88-8.42)	127.1 (92.5, 174.6)
600 mg QD (cohort 5)	3.99 (2.91-6.44)	4.78 (3.06-8.90)	119.8 (88.8, 161.7)
Placebo	5.00 (1.97-12.1)	4.55 (2.57-12.6)	92.7 (72.9, 117.9)

Source A4001002 CSR Tables 5.3.4, 5.3.5 and 5.2.7
[a] Ratio of 'on-treatment ratio/baseline ratio'

Maraviroc showed no effect on CYP2D6 activity (as demonstrated by changes in debrisoquine metabolic ratio) at doses up to and including 300 mg BID, but did show the potential for weak inhibition of CYP2D6 following 600 mg QD maraviroc (Table 15). Phenotype analysis defined two subjects as poor 2D6 metabolisers at baseline (metabolic ratio [MR]> 12.6), one maraviroc subject receiving 300 mg BID (MR=16.0) and one placebo subject (MR=15.1). The metabolic ratio of the maraviroc subject decreased to 11.6 on treatment. There was no other evidence that any other subjects were converted to poor metabolisers during the study.

Table 15. Summary of Debrisoquine/ 4-OH Debrisoquine Metabolic Ratio Data

Treatment Group	Mean Debrisoquine/ 4-OH Debrisoquine Metabolic ratio (range)		Geometric mean ratio % (90% CI)[a]
	Baseline	On Treatment	
25 mg BID	0.86 (0.5 to 2.1)	0.72 (0.3 to 2.5)	84.2 (62.9, 112.8)
100 mg BID	0.63 (0.2 to 2.5)	0.65 (0.3 to 3.8)	103.6 (75.8, 141.6)
300 mg BID	1.52 (0.5 to 16.0)	1.13 (0.4 to 11.3)	74.1 (56.3, 97.6)
600 mg QD (cohort 3)[b]	n/c	n/c	n/c
600 mg QD (cohort 5)	1.23 (0.9 to 5.0)	3.36 (1.3 to 7.6)	333.3 (243.8, 455.4)
Placebo	0.96 (0.2 to 15.1)	0.63 (0.2 to 2.8)	88.6 (67.3, 116.7)

Source A4001002 CSR Tables 5.5.1, 5.5.2 and 5.4

[a] Ratio of 'on-treatment ratio/baseline ratio'

[b] No data available for Cohort 3 as this cohort was stopped on Day 7

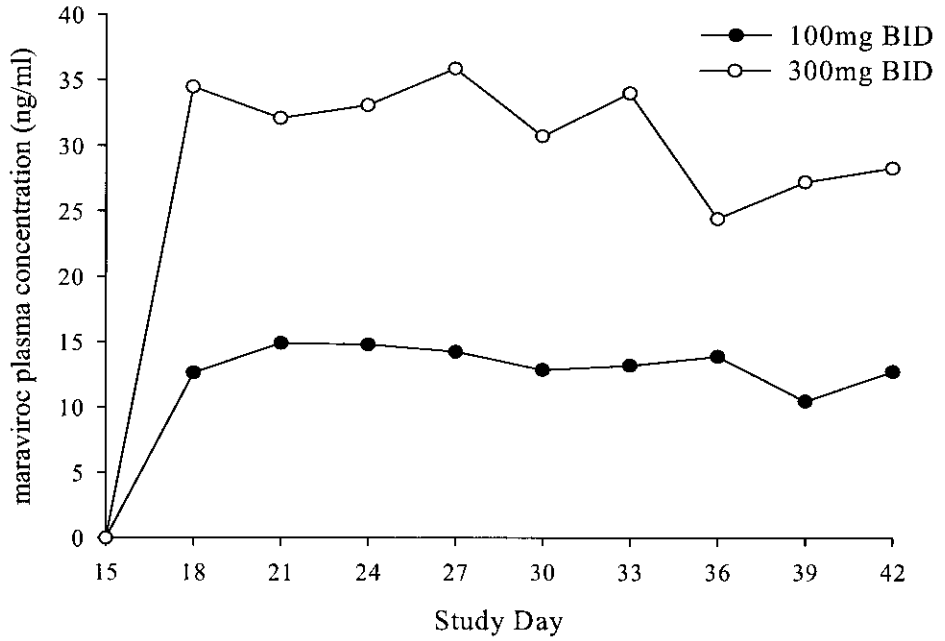
Safety Results: At doses of maraviroc up to and including 300 mg BID, there were few adverse events, most of which were mild or moderate. Cohort 3 reported a higher incidence of adverse events than any other cohort and dosing was terminated for this cohort because three subjects had severe symptomatic postural hypotension four hours post-dose on Day 7 (two after 600 mg QD maraviroc and one after placebo)(Section 2.7.4.2.1.5, Module 2.7.4 Summary of Clinical Safety). After review of the blood pressure and pulse rate data from Cohort 3, this dose was repeated in Cohort 5, and was tolerated in all subjects with no severe adverse events reported and one episode of mild transient postural hypotension that did not result in discontinuation.

Study A4001008

Study A4001008 was a randomised, double-blind, placebo-controlled, multiple-dose study to investigate the safety of maraviroc or placebo for 28 days. Fifty-four subjects entered the study. The study had a placebo run-in phase for 14 days (N=54), followed by a randomised, double-blind, placebo controlled, multiple dose period with maraviroc 100 mg (N=16) or 300 mg BID (N=16) or placebo (N=16). Trough plasma concentration (C_{min}) was the only pharmacokinetic parameter recorded (Days 15-43, every 3 days).

Pharmacokinetic Results: Visual assessment of the individual trough profiles suggested that steady state was reached after seven days of maraviroc dosing (Day 21, either 100 mg or 300 mg daily, Figure 5).

Figure 5. Mean Maraviroc Plasma Trough Concentrations (A4001008)



The geometric C_{min} values on Day 21 were 12.6 ng/mL and 24.8 ng/mL for 100 mg BID and 300 mg BID maraviroc respectively.

Safety Results: Maraviroc was well tolerated following 28 days of dosing at 100 mg and 300 mg twice daily. There was no apparent trend in changes in blood pressure, pulse rate or ECG with dosing. Further information on the safety results from studies can be found in Section 2.7.4.1.1.4.2, Module 2.7.4, Summary of Clinical Safety.

Study A4001019

Study A4001019 was a double-blind, 3rd party open, randomised, placebo-controlled, parallel group, forced titration, multiple dose study of maraviroc in thirty-six healthy male and female subjects to evaluate whether toleration to postural hypotension developed as had been previously noted with anti-hypertensive drugs active through the alpha adrenoreceptor. There were three cohorts of 12 subjects. Cohort 1 received 300 mg BID maraviroc for 7 days followed by 600 mg BID maraviroc for a further 7 days, Cohort 2 received 600 mg BID maraviroc followed by 900 mg BID maraviroc and Cohort 3 received 900 mg QD maraviroc followed by 1200 mg QD maraviroc. Three subjects from each cohort received placebo throughout the study.

Pharmacokinetic Results: Maraviroc was absorbed with the mean T_{max} occurring after approximately 2 hours after single (Day 1) and multiple dosing (Days 7 and 14) in all treatment groups (Table 16). Renal clearance was similar for all maraviroc doses and regimens throughout the study.

Table 16. Summary of Maraviroc Pharmacokinetic Parameters (A4001019)

Maraviroc Dose	Day (n)	Mean Maraviroc Pharmacokinetic Parameters (range)			
		AUC_{12}[a] (ng.h/mL)	Cmax[a] (ng/mL)	Tmax[b] (h)	CLr (L/h)
300mg BID .	1 (9)	1896 (1180-3940)	770 (480-1540)	1.83 (0.5-2.0)	9.70 (5.49-12.4)[d]
	7 (8)	2102 (1510-3050)	807 (512-1370)	2.00 (2.0-2.0)	9.12 (5.09-14.7)[d]
600mg BID[c]	14 (8)	4980 (2940-6990)	1810 (1050-2630)	2.00 (2.0-2.0)	9.44 (7.05-12.7)
600mg BID .	1 (8)	3232 (2720-3950)	1096 (897-1490)	2.00 (2.0-2.0)	12.6 (5.11-17.2)[e]
	7 (8)	3872 (3010-5530)	1177 (880-1730)	2.25 (2.0-4.0)	12.6 (8.90-14.1)[e]
900mg BID[c]	14 (8)	5884 (4970-8740)	1630 (1250-2290)	2.25 (2.0-4.0)	11.8 (5.99-15.5)
900mg QD .	1 (9)	5993 (4320-8580)	1993 (1370-3120)	1.72 (0.5-2.0)	10.8 (5.82-13.9)
	7 (9)	6550 (4770-9380)	1960 (1330-3460)	2.00 (2.0-2.0)	12.2 (9.87-14.9)[f]
1200mg QD[c]	14 (9)	10394 (7520-14000)	2988 (1850-3720)	1.83 (0.5-2.0)	7.58 (1.82-15.6)

Source: A4001019 CSR Tables 5.1.1, 5.1.2 and 5.1.3
[a] unadjusted geometric mean,
[b] unadjusted arithmetic mean,
[c] dose increase on day 8
[d] For clearance, n=8 Day 1 and n=7 on Day 7 for 300-600 mg BID
[e] For clearance, n=7 Day 1 and n=6 on Day 7 for 600-900 mg BID
[f] For clearance, n=7 on Day 7 fro 900-1200 mg BID

Visual inspection of trough concentrations suggested that steady state was reached by Day 7 and, after the dose increase, reached again by Day 14. The mean accumulation ratio was 1.2 after both 300 mg BID and 600 mg BID maraviroc for seven days and Cmax increased by 14 and 7% respectively (Table 17). The mean accumulation ratio was 1.09 after 900 mg QD maraviroc for seven days with no increase in Cmax.

Table 17. Summary of Statistical Analyses for Maraviroc AUC_{12} and Cmax (A4001019)

Maraviroc Dose	Comparison	AUC_{12} ratio (95% CIs)	Cmax ratio (95% CIs)
300mg BID	Day 7/Day 1	1.21 (1.06,1.40)	1.14 (0.932, 1.40)
. 600mg BID	Day 14/ Day 7	2.37 (2.10, 2.67)	2.24 (1.81, 2.77)
600mg BID	Day 7/Day 1	1.20 (1.04, 1.38)	1.07 (0.875, 1.32)
. 900mg BID	Day 14/ Day 7	1.52 (1.35, 1.71)	1.38 (1.12, 1.71)
900mg QD	Day 7/Day 1	1.09 (0.957, 1.25)	0.983 (0.811, 1.19)
. 1200mg QD	Day 14/ Day 7	1.59 (1.42, 1.78)	1.52 (1.25, 1.86)

Source: A4001019 CSR Source: Table 5.5.2

Visual assessment of trough concentrations suggested that steady state for UK-408,027 (primary circulating metabolite) was reached by Day 7, and after the dose increase, reached again by Day 14. The mean accumulation ratio for UK-408,027 was 1.50 and 1.39 after 300 mg BID and 600 mg BID for seven days and Cmax increased by 46 and 26% respectively (Table 18). The mean accumulation ratio was 1.11 after 900 mg QD for seven days with no increase in Cmax.

Table 18. Summary of Statistical Analyses for UK-408,027 AUC_{12} and Cmax (A4001019)

Maraviroc Dose	Comparison	AUC_{12} ratio	Cmax ratio
300mg BID	Day 7/Day 1	1.50	1.46
. 600mg BID	Day 14/ Day 7	2.60	2.28
600mg BID	Day 7/Day 1	1.39	1.26
. 900mg BID	Day 14/ Day 7	1.46	1.32
900mg QD	Day 7/Day 1	1.11	0.97
. 1200mg QD	Day 14/ Day 7	1.50	1.47

Source: A4001019 CSR Tables 5.7.1, 5.7.2 and 5.8.1 and 5.8.2

Safety Results: The adverse event profile for maraviroc doses below 600 mg BID was similar to that of placebo. The adverse event and safety profile for maraviroc 600 mg BID was similar for subjects titrating to this dose from 300 mg BID maraviroc and for subjects who received 600 mg BID maraviroc as a starting dose. Postural hypotension was confined to the 900 mg QD . 1200 mg QD cohort and reported at a similar frequency at both 900 mg QD and 1200 mg QD. Titration from 600 mg BID to 900 mg BID did not result in events of postural hypotension although 6/8 and 7/8 subjects had dizziness and light-headedness respectively in this cohort. Therefore, neither titration nor repeated dosing caused toleration of symptomatology consistent with postural hypotension. Once again as in other studies where postural hypotension had been observed, it was typically found to be temporally associated with Cmax. Postural hypotension is discussed further in Section 2.7.4.2.1.5, Module 2.7.4, Summary of Clinical Safety. The cardiovascular and haemodynamic effects of maraviroc are discussed in sections 2.7.2.2.7 and 2.7.2.3.2 of this module.

2.7.2.2.4. Special Populations

Limited pharmacokinetic data on the effects of age, race and gender was derived from individual Phase 1 and 2a studies. Population pharmacokinetic modelling on the combined Phase 1/2a dataset has been performed to investigate the effect of various special population covariates on the pharmacokinetics of maraviroc. The results of this modelling are presented in section 2.7.2.3.4. No data in subjects with renal or hepatic impairment is currently available.

Study A4001038

Study A4001038 was an open, parallel group, two centre study, to compare the pharmacokinetics of a single oral dose of maraviroc 300 mg in Asian (N = 12) and Caucasian (N = 12) healthy subjects. This study was conducted following observations of higher than expected maraviroc concentrations in 2 studies (A4001022, A4001025) conducted in [redacted] in Singapore in Asian subjects compared with similar studies conducted in Caucasians.

Pharmacokinetic Results: The pharmacokinetics of maraviroc are similar in Asian and Caucasian subjects (Table 19).

Table 19. Summary of Maraviroc Pharmacokinetic Parameters (A4001038)

Parameter	Mean Pharmacokinetic Parameter Value (range)		Geometric Mean Ratio[a] (90% CI)
	Asian N=12	Caucasian N=12	
AUC_{24} (ng.h/mL)[b]	2640 (1840 to 4350)	2680 (2020 to 3830)	0.99 (0.84 to 1.16)
Cmax (ng/mL)[b]	741 (409 to 1070)	666 (318 to 928)	1.11 (0.90 to 1.37)
Tmax (h)[c]	3.54 (0.50 to 5.00)	3.04 (0.50 to 5.00)	n/c
Ae_{24} (mg)[c]	21.7 (12.1 to 36.0)	27.6 (14.9 to 36.7)	n/c
Ae_{24} (%)[c]	7.22 (4.00 to 12.0)	9.19 (5.00 to 12.2)	n/c

Source: CSR A4001038 Tables 13.5.1.1 and 13.5.3.2

[a] comparison of interest was maraviroc 300 mg Asian v maraviroc 300 mg Caucasian

[b] unadjusted geometric mean,

[c] unadjusted arithmetic mean

n/c = not calculated

2.7.2.2.5. Studies in HIV-1 Infected Patients (Phase 2a Studies)

Studies A4001007 and A4001015

Study A4001007 was a randomised, double-blind; placebo-controlled, multicentre study of maraviroc 25 mg QD, 50 mg BID, 100 mg BID and 300 mg BID 10 day monotherapy in asymptomatic HIV-1 infected patients to investigate pharmacodynamics, pharmacokinetics, safety and toleration. Forty-five subjects entered the study.

Study A4001015 was a randomised, double-blind (except the fed 150 mg BID group), placebo-controlled, multicentre, five treatment, parallel group study to investigate the effects of food and dose regimen (150 mg BID fasted and fed, 100 mg QD, 300 mg QD) on viral load response in asymptomatic HIV-1 infected patients on short-term monotherapy with maraviroc. Thirty-seven subjects entered the study.

Pharmacokinetic Results: Maraviroc absorption was variable after single and multiple dosing with mean Cmax generally occurring between 1 and 4 hours post-dose (Tmax) (Figure 6 and Table 20). Exposures were similar to those observed in healthy volunteers excepting that there was no significant accumulation of AUC_{12} or Cmax following 10 days of dosing at any maraviroc dose.

Figure 6. Mean Maraviroc Plasma Profiles in HIV-1 Infected Patients (A4001007)

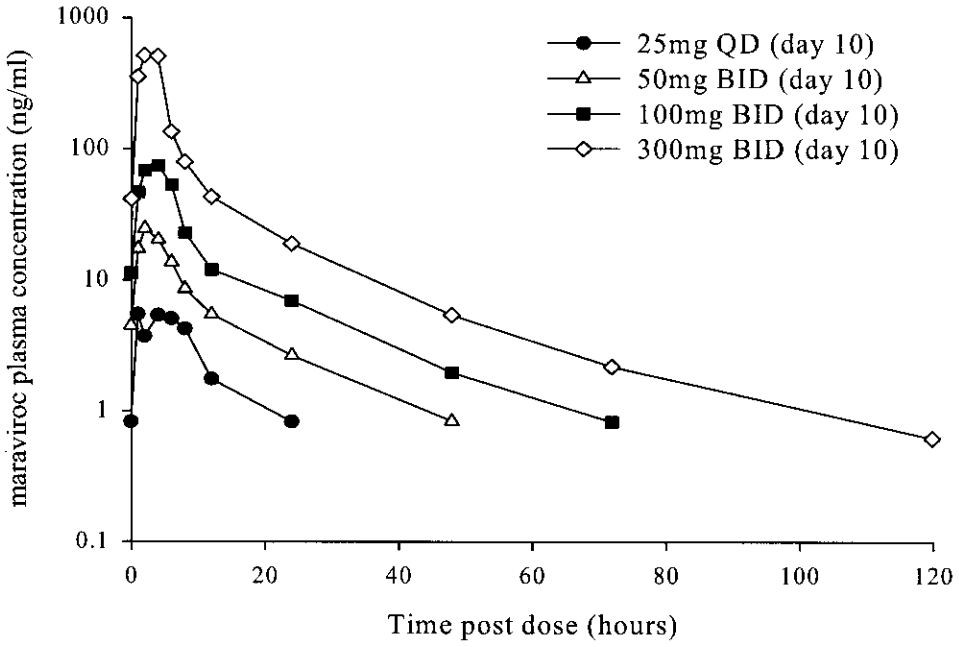


Table 20. Summary of Pharmacokinetic Parameters for HIV-1 Infected Subjects (A4001007, A4001015)

Treatment	Day (n)	Mean Pharmacokinetic Parameter Value (range)					Accumulation Ratio[c]
		AUC_{12}[a] (ng.h/mL)	AUC_{24}[a] (ng.h/mL)	Cmax[a] (ng/mL)	Tmax[b] (h)	t½[b] (h)	
25 mg QD[d] N=9	1 (9)	47.2 (19.0-119)	n/c	9.65 (2.86-31.3)	2.78 (1.0-8.0)	n/c	n/c
	10 (8)	44.1 (26.6-80.5)	n/c	6.87 (3.93-10.6)	4.25 (1.0-8.0)	n/c	0.99
50 mg BID[d]	1 (8)	173 (116-328)	n/c	42.2 (27.9-102)	3.38 (1.0-6.0)	n/c	n/c
	10(8)	142 (56.1-240)	n/c	27.7 (16.9-52.6)	2.88 (1.0-6.0)	15.9 (10.5-26.7)	0.82
100 mg BID[d]	1 (8)	425 (147-658)	n/c	112 (36.0-220)	3.25 (2.0-4.0)	n/c	n/c
	10 (8)	454 (219-771)	n/c	104 (43.2-264)	3.25 (1.0-6.0)	16.2 (13-0-21.9)	1.07
300 mg BID[d]	1 (8)	2262 (1460-3720)	n/c	585 (425-829)	2.88 (1.0-4.0)	n/c	n/c
	10 (8)	2552 (1690-4060)	n/c	618 (328-1020)	3.13 (1.0-4.0)	22.9 (12.0-31.8)	1.13
100 mg QD[e]	10 (9)	n/c	571 (352-1200)	161 (70.0-310)	3.3 (2.0-6.0)	n/c	n/c
150 mg BID[e]	10 (8)	933 (374-1700)	n/c	273 (90.1-658	3.0 (1.0-6.0)	n/c	n/c
150 mg BID (fed)[e]	10 (8)	474 (163-1030)	n/c	110 (39.6-248)	2.3 (1.0-4.0)	n/c	n/c
300 mg QD[e]	10 (8)	n/c	2260 (1470-3820)	484 (246-1020)	3.3 (2.0-4.0)	n/c	n/c

Source: A4001007 CSR Tables 5.1.1, 5.1.2, 5.2.1 and A4001015 CSR Table 5.1

[a] Geometric mean,

[b] Arithmetic mean,

[c] $AUC_{12(day\ 10)}/AUC_{12(day1)}$

[d] A4001007,

[e] A4001015

n/c = not calculated

Comparison of the 150 mg BID fed and fasted data is discussed in Section 2.7.1.3.2, Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods and Section 2.7.3.1.2, Module 2.7.3 Summary of Clinical Efficacy.

2.7.2.2.6. Drug Interactions

Drug interaction studies were conducted primarily using maraviroc doses of 100 mg BID, or 300 mg BID. The 100 mg BID maraviroc dose was used for early studies (A4001005, A4001006 and A4001013) as this was the predicted clinical dose at this stage (based on the in vitro antiviral IC_{90}). After completion of the Phase 2a monotherapy studies and safety Study A4001008, 300 mg QD/BID dose equivalents were the doses selected for evaluation in the Phase 2b/3 clinical programme (Section 2.7.3.1.2, Module 2.7.3 Summary of Clinical Efficacy). Subsequent drug interaction studies therefore used 300 mg BID maraviroc. The results of the early studies are felt to be relevant, despite the use of a lower maraviroc dose, for several reasons;

Pre-clinical data has shown that maraviroc is not an inhibitor of the major cytochrome P450 enzymes at clinically relevant concentrations.

Clinical data has shown that maraviroc did not affect 6β-hydroxycortisol/cortisol ratios at doses up to and including 300 mg BID, and 600 mg QD, suggesting no induction of CYP3A4. Hence, the potential of maraviroc to affect the pharmacokinetics of co-administered agents, which are metabolised by the cytochrome P450 enzymes (including oral contraceptives), is considered to be low.

Further, the effect of Lopinavir/Ritonavir* has been studied with doses of both 100 mg BID and 300 mg BID maraviroc (A4001013 and A4001021). The results from these two studies were similar.

Modelling and simulation has been used to simulate the effect of different interactants on different doses of maraviroc (Section 2.7.2.3.5).

2.7.2.2.6.1. Effect of Maraviroc on 'Other Drugs'

The effect of maraviroc on the pharmacokinetics of 'other drugs' has been investigated in studies A4001005, A4001012 and A4001020.

Study A4001005

Study A4001005 was a randomised, double-blind, placebo-controlled, two-way crossover study to investigate the pharmacokinetics, safety and tolerability of maraviroc in fifteen healthy young women and to investigate the effect of maraviroc on the pharmacokinetics of oral contraceptive steroids. All subjects received either maraviroc 100 mg BID or placebo in both study periods (Days 1-11) with the final dose being given on the morning of Day 11. Subjects also received 30 μg of ethinylestradiol (EE) and 150 μg levonorgestrel (LN, levonorgestrel/ethinylestradiol*) at the same time as their morning dose of maraviroc or placebo on Days 2-8 only.

Pharmacokinetic Results: Maraviroc had no clinically relevant effect on the pharmacokinetics of ethinylestradiol or levonorgestrel (Table 21).

* ：新薬承認情報提供時に置き換えた

Table 21. Summary of Ethinylestradiol and Levonorgestrel Pharmacokinetic Parameters (A4001005)

Co-administered Drug (dose)	MVC Dose	Means (ranges) and ratios (CI) of ethinylestradiol and levonorgestrel pharmacokinetic parameters with/without maraviroc (No effect when ratio= 1.00)					
		+ Placebo	+ Maraviroc	Ratio[a] (90% CI)	+ Placebo	+ Maraviroc	Ratio[a] (90% CI)
		AUC_{last} (pg.h/mL)[b]			Cmax (pg/mL)[b]		
Ethinylestradol (30 µg QD) N=15	100 mg BID	746 (211-1080)	745 (243-1160)	1.00 (0.95, 1.05)	84.8 (53.2-124)	84.0 (42.4-115)	0.98 (0.91, 1.06)
		AUC_{tau} (ng.h/mL)			Cmax (ng/mL)[b]		
Levonorgestrel (150 µg QD) N=15	100 mg BID	72.0 (42.2-112)	71.0 (42.8-102)	0.98 (0.92, 1.04)	7.05 (4.53-10.2)	7.13 (4.63-9.36)	1.00 (0.93, 1.08)

Source A4001005 CSR Tables 5.3, 5.5.2, 5.6 and 5.8.2
[a]The comparison of interest was ethinylestradiol/levonorgestrel + MVC versus ethinylestradiol/levonorgestrel + placebo (Day 8).
[b]unadjusted means
MVC=maraviroc, CI=confidence interval

Study A4001012

Study A4001012 was a randomised, double-blind, placebo-controlled, two-period crossover study in twelve healthy subjects to investigate the effects of steady state maraviroc (300 mg BID) on the pharmacokinetics of a single oral dose of midazolam (probe CYP3A4 substrate). Midazolam is primarily metabolised by the CYP3A4 subfamily of cytochrome P450, and hence its pharmacokinetics could be affected by drugs that inhibit or induce this enzyme. Midazolam is widely accepted as the optimal CYP3A4 probe substrate for investigating potential drug interactions. Midazolam does not appear to be a substrate for P-gp.

Pharmacokinetic Results: Maraviroc had no clinically relevant effect on the pharmacokinetics of midazolam (Table 22). Therefore, these results indicate that maraviroc is not an inhibitor of CYP3A4.

Table 22. Summary of Midazolam Pharmacokinetic Parameters (A4001012)

Co-administered Drug (dose)	MVC Dose	Means (range) and ratios (CI)of midazolam pharmacokinetic parameters with/without maraviroc (No effect when ratio= 1.00)					
		AUCinf (ng.h/mL)[a]			Cmax (ng/mL)[a]		
		+ Placebo	+ Maraviroc	Ratio[b] (90% CI)	+ Placebo	+ Maraviroc	Ratio[b] (90% CI)
Midazolam (7.5 mg SD) N=12	300 mg BID	104 (57.9-162)	122 (74.5-193)	1.18 (1.04, 1.34)	38.7 (16.2-81.2)	46.9 (27.6-119)	1.21 (0.92, 1.60)

Source A4001012 CSR Tables 5.1.1, 5.1.2 and 5.4.1
[a] unadjusted means
[b] The comparison of interest was midazolam + MVC versus midazolam +placebo (day 7).
MVC=maraviroc, CI=confidence interval

Study A4001020

Study A4001020 was a double-blind, third party open, randomised, placebo-controlled, two-period crossover study to investigate the effects of steady state maraviroc 300 mg BID on the steady state pharmacokinetics of Zidovudine/Lamivudine* in twelve healthy subjects. Zidovudine/Lamivudine* was investigated as this combination of NRTIs was the backbone regimen selected for Study A4001026 in treatment naïve HIV-1 infected patients. Zidovudine and lamivudine are cleared predominantly by renal and/or non-P450 metabolic routes. As maraviroc also has some renal clearance (~23% of maraviroc related material is excreted in the urine; see Study A4001010, section 2.7.2.2.2) this interaction study evaluated the potential for both pharmacokinetic and safety interactions between maraviroc and Zidovudine/Lamivudine*.

Pharmacokinetic Results: Maraviroc had no clinically relevant effect on the pharmacokinetics of the components of Zidovudine/Lamivudine* (Table 23).

Table 23. Summary of Lamivudine and Zidovudine Pharmacokinetic Parameters (A4001020)

Co-administered Drug (dose)	MVC Dose	Means (range) and ratios (CI)of lamivudine and zidovudine pharmacokinetic parameters with/without maraviroc (No effect ratio= 1.00)					
		AUC_{12} (ng.h/mL)[a]			C_{max} (ng/mL)[a]		
		+ Placebo	+ Maraviroc	Ratio[b] (90% CI)	+ Placebo	+ Maraviroc	Ratio[b] (90% CI)
Zidovudine (300 mg BID) N=11	300 mg BID	1713 (1120-3220)	1685 (959-2820)	0.98 (0.79, 1.22)	1188 (517-2190)	1108 (596-2630)	0.92 (0.68, 1.24)
Lamivudine (150 mg BID) N= 11	300 mg BID	4852 (2420-6500)	5490 (4580-7270)	1.14 (0.98, 1.32)	1125 (432-2030)	1305 (762-2200)	1.16 (0.88, 1.54)

Source A4001020 CSR Tables 5.1, 5.4.2, 5.5 and 5.8.2
[a] unadjusted means
[b] The comparison of interest was Zidovudine/Lamivudine* + maraviroc versus Zidovudine/Lamivudine* + placebo (day 7).
MVC=maraviroc, CI=confidence interval

2.7.2.2.6.2. Effect of Other Drugs on Maraviroc

A series of studies have been conducted in healthy subjects and HIV-1 infected patients to investigate the effect of CYP3A4 inhibitors (including ketoconazole and protease inhibitors), CYP3A4 inducers (efavirenz and rifampicin) and drugs with mixed CYP3A4/P-gp inhibition/induction potential (tipranavir/r, Lopinavir/Ritonavir* + efavirenz, saquinavir/r + efavirenz), on the steady state pharmacokinetics of maraviroc. Protease inhibitors co-administered with ritonavir (ritonavir boost) will be abbreviated with the suffix of /r after the protease inhibitor. The effect of substrates and inhibitors of renal clearance (tenofovir and Trimethoprim/Sulfamethoxazole*) on the steady state pharmacokinetics of maraviroc have also been investigated.

Effect of CYP3A4 and/or P-gp inhibitors on maraviroc

The effect of CYP3A4/P-gp inhibitors on the pharmacokinetics of maraviroc has been primarily investigated in studies A4001006, A4001013, A4001025 and A4001046.

* ：新薬承認情報提供時に置き換えた

Study A4001006

Study A4001006 was an open, randomised, placebo-controlled, 2-way crossover study to investigate the effect of ketoconazole and saquinavir on the steady state pharmacokinetics, safety and tolerability of maraviroc in twenty-four healthy subjects. Ketoconazole is a potent CYP3A4 inhibitor and is commonly used as a probe compound. Saquinavir is a CYP3A4 inhibitor, which is also clinically relevant as it is a protease inhibitor and may be co-administered with maraviroc. All subjects received maraviroc 100 mg BID in both study periods. In Cohort 1, subjects also received saquinavir (saquinavir*) 1200 mg or placebo three times daily (TID) and Cohort 2 also received ketoconazole 400 mg QD or placebo in both study periods.

Pharmacokinetic Results: Both saquinavir and ketoconazole increased mean maraviroc AUC_{tau} at steady state, but the increase in AUC_{tau} was higher with ketoconazole (5.0 fold) than saquinavir (4.3 fold). Similarly, both saquinavir and ketoconazole increased mean maraviroc C_{max} at steady state by approximately 3.4 fold (Table 24).

Table 24. Summary of the Effect of Ketoconazole/Saquinavir on Maraviroc Pharmacokinetic Parameters (A4001006)

Co-administered Drug (dose)	MVC Dose	Mean (range)and Ratios (CI) of Maraviroc Pharmacokinetic Parameters with/without Ketoconazole/Saquinavir (no effect ratio= 1.00)					
		AUC_{tau} (ng.h/mL)[a]			C_{max} (ng/mL)[a]		
		+ Placebo	+ Drug[b]	Ratio[c] (90% CI)	+ Placebo	+ Drug[b]	Ratio[c] (90% CI)
Ketoconazole (400 mg QD) N=12	100 mg BID	618 (291-1620)	3095 (1730-5440)	5.01 (3.98, 6.29)	155 (53.0-490)	524 (302-1060)	3.38 (2.38, 4.78)
Saquinavir (1200 mg TID) N=12	100 mg BID	487 (242-797)	2068 (1240-4170)	4.25 (3.47, 5.19)	131 (53.9-299)	434 (270-743)	3.32 (2.45, 4.49)

Source A40010106 CSR Tables 5.1.2, 5.3.2, 5.4.2 and 5.6.2.
[a] unadjusted means
[b] Drug was either ketoconazole or saquinavir
[c] Ratio of maraviroc pharmacokinetic parameters with/without co-administered drug; the comparison of interest was for MVC+ saquinavir or ketoconazole versus MVC + placebo (Day 7)
MVC=maraviroc, CI=confidence interval

Study A4001013

Study A4001013 was an open, randomised, placebo-controlled, four treatment, parallel group study to explore the steady state pharmacokinetics of maraviroc when co-administered with the protease inhibitors; ritonavir, saquinavir/r or Lopinavir/Ritonavir*. All of these protease inhibitor combinations are known to inhibit CYP3A4.

Thirty two healthy male and female subjects were randomised to one of the four treatment groups (eight per treatment group) (Table 25).

* ：新薬承認情報提供時に置き換えた

Table 25. Summary of Treatment Groups (A4001013)

Treatment group	Days 1 to 7	Days 8 to 21	Days 22 to 28[a, b]
Maraviroc + ritonavir N=8	Maraviroc 100 mg BID	Maraviroc 100 mg BID + ritonavir 100 mg BID	Maraviroc 50 mg BID + ritonavir 100 mg BID
Maraviroc + saquinavir/r N=8	Maraviroc 100 mg BID	Maraviroc 100 mg BID + Saquinavir/r (1000 mg/100 mg BID)	Maraviroc 25 mg BID + Saquinavir/r (1000 mg/100 mg BID)
Maraviroc + Lopinavir/Ritonavir* N=8	Maraviroc 100 mg BID	Maraviroc 100 mg BID + Lopinavir/Ritonavir* (400 mg/100 mg BID)	Maraviroc 50 mg BID + Lopinavir/Ritonavir* (400 mg/100 mg BID)
Maraviroc + placebo N=8	Maraviroc 100 mg BID	Maraviroc 100 mg BID + placebo BID	Maraviroc 100 mg BID + placebo BID

[a] Only the morning dose was taken on Day 28
[b] maraviroc dose was determined from magnitude of interaction observed during second phase (Days 8-21)

In order to guide maraviroc dose-adjustments for days 22-28 of the study, the average plasma concentration over a 4h period following morning dosing on Days 7 and 17 was calculated.

Pharmacokinetic Results: All agents increased the exposure of steady state maraviroc, with saquinavir/r having the greatest effect, followed by Lopinavir/Ritonavir* and then ritonavir alone. Dose adjustment from 100 mg to 25 mg BID maraviroc in the presence of saquinavir/r, 100 mg to 50 mg BID maraviroc in the presence of Lopinavir/Ritonavir* and ritonavir alone, adequately and from compensated for the increases in AUC_{tau} and more than compensated for increases in C_{max} seen (Table 26, Table 27 and Figure 7).

Table 26. Summary of the Effect of Protease Inhibitors on Maraviroc Pharmacokinetics (A4001013)

Co-administered Drug (dose)	Maraviroc Dose	Study Day	Mean Parameter Value (range)	
			AUC_{tau} [a] (ng.h/mL)	C_{max} [a] (ng/mL)
Ritonavir (100 mg BID) N=8	100 mg	7	547 (402-713)	129 (72.9-272)
	100 mg	21	1277 (943-1917)	228 (118-368)
	50 mg[b]	28	439 (242-911)	67.7 (29.3-242)
Saquinavir/r (1000 mg/ 100 mg BID) N=8	100 mg	7	663 (509-779)	154 (118-222)
	100 mg	21	4920 (3981-6029)	900 (778-1070)
	25 mg[b]	28	839 (561-1322)	133 (90.2-196)
Lopinavir/Ritonavir* (400 mg/100 mg) N=8	100 mg	7	499 (371-600)	121 (81.4-169)
	100 mg	21	1704 (1171-2957)	268 (170-492)
	50 mg[b]	28	695 (360-1244)	88.5 (43.8-169)
Placebo N=8	100 mg	7	597 (413-900)	138 (85.1-195)
	100 mg	21	533 (314-864)	191 (74.0-462)
	100 mg	28	526 (352-1060)	194 (95.6-362)

Source:A4001013 Tables 5.1.1, 5.1.2, 5.1.3 and 5.1.4
a unadjusted geometric means
b Maraviroc dose adjustment determined from magnitude of interaction observed during second phase

* ：新薬承認情報提供時に置き換えた

Table 27. Summary of Statistical Analyses of Maraviroc AUC_{tau} and Cmax Parameters (A4001013)

Co-administered Drug (dose)	Parameter	Comparison	Ratio[a] (90% CI)
Ritonavir (100 mg BID)	AUC_{tau} (ng.h/ml)	Day 21 v Day 7	2.61 (1.92, 3.56)
		Day 28 v Day 7	0.91 (0.65, 1.28)
	Cmax (ng/ml)	Day 21 v Day 7	1.28 (0.79, 2.09)
		Day 28 v Day 7	0.38 (0.23, 0.62)
Saquinavir/r (1000 mg/ 100 mg BID)	AUC_{tau} (ng.h/ml)	Day 21 v Day 7	8.32 (6.11, 11.3)
		Day 28 v Day 7	1.44 (1.03, 2.01)
	Cmax (ng/ml)	Day 21 v Day 7	4.23 (2.60, 6.88)
		Day 28 v Day 7	0.61 (0.37, 1.01)
Lopinavir/Ritonavir* (400 mg/100 mg)	AUC_{tau} (ng.h/ml)	Day 21 v Day 7	3.83 (2.81, 5.21)
		Day 28 v Day 7	1.58 (1.13, 2.22)
	Cmax (ng/ml)	Day 21 v Day 7	1.61 (0.99, 2.63)
		Day 28 v Day 7	0.53 (0.32, 0.86)

Source:A4001013 Table 5.4.1
[a] Ratio for AUC_{tau} and Cmax (Day 28 or Day 21 divided by Day 7)
CI=confidence interval

Figure 7. Mean Maraviroc Plasma Concentration versus Time Profiles (A4001013)

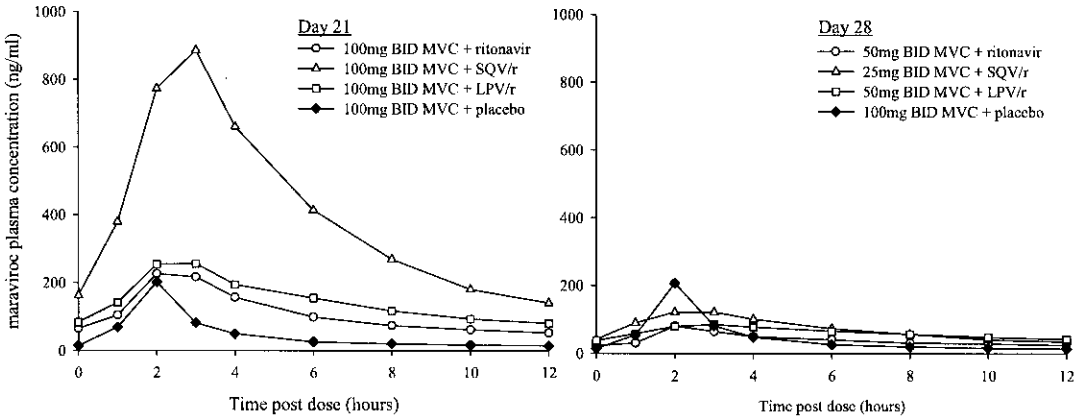
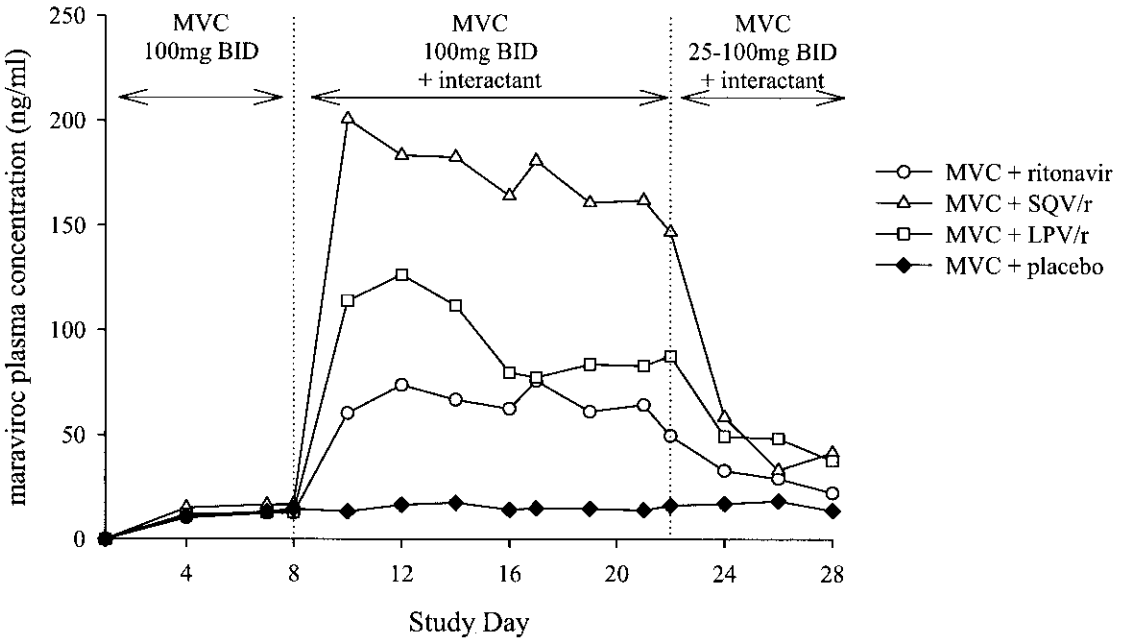


Figure 8. Mean Maraviroc Plasma Trough Concentrations (A4001013)



Study A4001025

Study A4001025 was an open, placebo-controlled, randomized, 2-way crossover study to investigate the effect of co-administration of atazanavir alone (400 mg QD) and boosted atazanavir (atazanavir 300 mg plus ritonavir 100 mg QD) on the steady state pharmacokinetics of maraviroc in twelve healthy subjects. Atazanavir has been shown to be an inhibitor and inducer of P-gp as well as a potent inhibitor of CYP3A in vitro (Perloff ES et al, 2005).

Pharmacokinetic Results: Atazanavir and boosted atazanavir both increased the exposure of steady state maraviroc, with atazanavir/r having the greatest effect (Table 28).

Table 28. Summary of the Effect of Atazanavir on Maraviroc Pharmacokinetic Parameters (A4001025)

Co-administered Drug (dose) N=12	MVC Dose	Mean (range)and Ratios (CI) of Maraviroc Pharmacokinetic Parameters with/without Atazanavir/Atazanavir/r (no effect ratio= 1.00)					
		AUCtau (ng.h/mL)[a]			Cmax (ng/mL)[a]		
		+ Placebo	+ Drug[b]	Ratio[c] (90% CI)	+ Placebo	+ Drug[b]	Ratio[c] (90% CI)
Atazanavir (400 mg QD) N=12	300 mg BID	2790 (1880-3740)	9970 (7260-13900)	3.57 (3.30, 3.87)	915 (478-1350)	1914 (1460-3280)	2.09 (1.72, 2.55)
Atazanavir/r (300mg/100 mg QD) N=12	300 mg BID	2614 (1710-3770)	12800 (9240-16900)	4.88 (4.40, 5.41)	914 (449-1340)	2240 (1750-3250)	2.67 (2.32, 3.08)

Source:A4001025 Tables 13.5.1.1, 13.5.1.2, 13.5.8.3 and 13.5.8.4
[a] unadjusted means
[b] drug is either atazanavir or atazanavir/r
[b] Ratio of maraviroc pharmacokinetic parameters with/without co-administered drug; the comparison of interest was Day 7 maraviroc+ atazanavir versus maraviroc+ placebo and Day 14 maraviroc+ atazanavir/r versus maraviroc+ placebo
MVC=maraviroc, CI=confidence interval

Effects of CYP3A4 and/or P-gp inducers on Maraviroc

The effect of maraviroc on the pharmacokinetics of CYP3A4/P-gp inducers has been primarily investigated in study A4001011.

Study A4001011

Study A4001011 was an open, randomised, parallel group study to investigate the effect of rifampicin and efavirenz on the steady state pharmacokinetics of maraviroc in thirty-six healthy subjects. The treatment regimens and dosing sequences are summarised in Table 29.

Table 29. Treatments Groups in Study A4001011

Group	Study Days			
	1 to 7	8 to 21	22 to 27	28
1	Maraviroc 100 mg BID	Maraviroc 100 mg BID + Rifampicin 600 mg QD	Maraviroc 200 mg BID + Rifampicin 600 mg QD	Maraviroc 200 mg QD + Rifampicin 600 mg QD
2	Maraviroc 100 mg BID	Maraviroc 100 mg BID + Efavirenz 600 mg QD	Maraviroc 200 mg BID + Efavirenz 600 mg QD	Maraviroc 200 mg QD + Efavirenz 600 mg QD
3	Maraviroc 100 mg BID	Maraviroc 100 mg BID + Placebo QD	Maraviroc 100 mg BID + Placebo QD	Maraviroc 100 mg QD + Placebo QD

Maraviroc plasma concentrations were investigated on days 7, 21 and 28. In addition, the primary metabolite UK-408,027 was also assayed in samples taken on Days 7, 21 and 28 from subjects who received maraviroc and placebo or rifampicin only. Urine was collected up to 12 hours post-dose on Days 7 and 21 to determine the 6⇓-OH-cortisol/cortisol ratio to investigate the level of CYP3A4 induction in the presence of rifampicin and efavirenz.

Pharmacokinetic Results: Increases in the placebo adjusted 6⇓-OH cortisol/ cortisol ratio between Days 7 and 21 indicated that rifampicin strongly induced CYP3A4 activity (5.2 fold increase) whilst efavirenz moderately induced CYP3A4 activity (1.9 fold increase) (Table 30). As a consequence, rifampicin and efavirenz reduced the exposure of steady state maraviroc; however, this effect was adequately compensated for by adjusting the maraviroc dose (Table 30). This is also illustrated in Figure 9 and Figure 10.

Table 30. Summary of the Effect of Rifampicin and Efavirenz on Maraviroc Pharmacokinetics (A4001011)

Co-administered Drug Days 8 to 28 only (dose)	Maraviroc Dose	Study Day	Mean Parameter Value (range)		
			AUCtau[a] (ng.h/mL)	Cmax[a] (ng/mL)	6⇓-OH ratio[a]
Rifampicin	100 mg	7	695 (505-1100)	182 (129-501)	5.72 (2.57-9.15)
(600 mg QD)	100 mg	21	256 (163-450)	60.9 (27.6-152)	28.7 (15.1-50.3)
N=12	200 mg	28	723 (444-1020)	176 (110-267)	n/c
Efavirenz	100 mg	7	543 (410-900)	140 (101-327)	5.82 (4.16-9.85)
(600 mg QD)	100 mg	21	300 (178-459)	68.1 (27.3-131)	11.2 (6.09-23.0)
N=12	200 mg	28	624 (226-919)	163 (75.3-391)	-
Placebo	100 mg	7	550 (368-770)	138 (68.6-286)	5.47 (1.99-13.5)
N=12	100 mg	21	624 (382-1140)	153 (71.4-328)	4.42 (2.72-7.03)
	200 mg	28	580 (269-1470)	138 (48.6-581)	n/c

Source:A4001011 Tables 5.1.1, 5.1.2, 5.1.3 and 5.3
[b]unadjusted geometric means
n/c=not calculated, 6⇓-OH ratio=6⇓-OH cortisol/ cortisol ratio

Figure 9. Mean Maraviroc Plasma Concentration versus Time Profiles (A4001011)

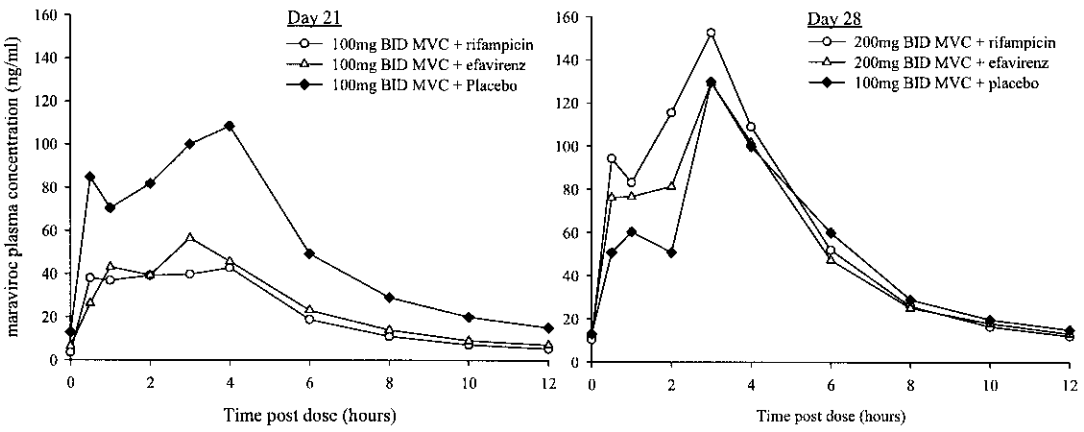
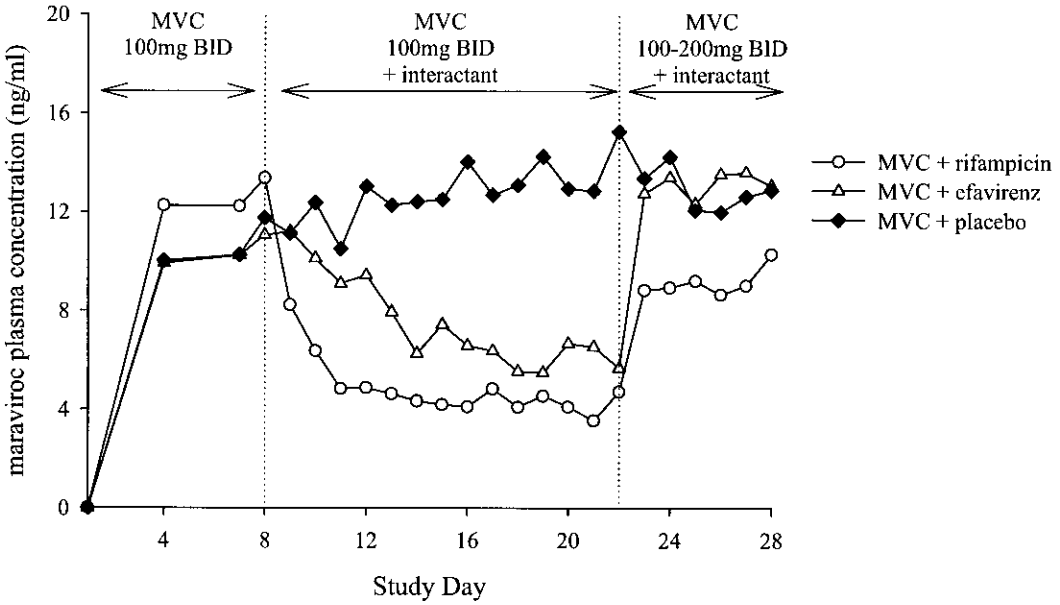


Figure 10. Mean Maraviroc Plasma Trough Concentrations (A4001011)



Statistical analysis of AUC_{tau} and Cmax between Days 21 and 7 and Days 28 and 7 for each study drug group confirmed that doubling the maraviroc dose compensated for metabolic induction by efavirenz and rifampicin (Table 31).

Table 31. Summary of Statistical Analyses of AUC_{tau} and Cmax Parameters (A4001011)

Co-administered Drug (dose)	Parameter	Comparison	Ratio[a] (90% CI)
Rifampicin (600 mg QD)	AUCtau (ng.h/ml)	Day 21 v Day 7	0.368 (0.328, 0.413)
		Day 28 v Day 7	1.04 (0.885, 1.22)
	Cmax (ng/ml)	Day 21 v Day 7	0.335 (0.260, 0.431)
		Day 28 v Day 7	0.996 (0.724, 1.29)
Efavirenz (600 mg QD)	AUCtau (ng.h/ml)	Day 21 v Day 7	0.552 (0.492, 0.620)
		Day 28 v Day 7	1.15 (0.977, 1.35)
	Cmax (ng/ml)	Day 21 v Day 7	0.486 (0.377, 0.626)
		Day 28 v Day 7	1.16 (0.871, 1.55)
Placebo	AUCtau (ng.h/ml)	Day 21 v Day 7	1.13 (1.01, 1.27)
		Day 28 v Day 7	1.05 (0.895, 1.24)
	Cmax (ng/ml)	Day 21 v Day 7	1.12 (0.865, 1.44)
		Day 28 v Day 7	0.999 (0.749, 1.33)

Source: A4001011 Table 5.5.1
[a] geometric mean ratio for AUC_{tau} and Cmax (Day 28 or Day 21 divided by Day 7)
CI=confidence interval

As expected, the mean exposure of the metabolite UK-408,027 increased from Days 7 to 21 in the maraviroc plus rifampicin group due to induced maraviroc metabolism and increased further from Days 21 to 28 due to doubling of the maraviroc dose. Mean exposure to

UK-408,027 in the maraviroc plus placebo group was similar throughout the time course of the study (Table 32). As previously stated, concentrations of UK-408,027 were only assayed for subjects who received maraviroc with either rifampicin or placebo.

Table 32. Summary of the Effect of Rifampicin on UK-408,027 Pharmacokinetics (A4001011)

Co-administered Drug Days 8 to 28 only (dose)	Maraviroc Dose	Study Day	Mean Parameter Value (range)	
			AUCtau[a] (ng.h/ml)	Cmax[a] (ng/ml)
Rifampicin	100 mg	7	148 (97.6-208)	19.6 (13.3-31.9)
(600 mg QD)	100 mg	21	214 (162-294)	28.5 (17.0-46.3)
N=12	200 mg	28	489 (354-650)	63.1(42.9-96.6)
Placebo	100 mg	7	142 (78.5-187)	18.5 (11.2-29.0)
N=12	100 mg	21	136 (79.4-259)	18.4 (12.4-41.1)
	100 mg	28	129 (72.8-234)	15.7 (8.27-30.8)

Source:A4001011 CSR Tables 5.1.4 and 5.1.5
[b]unadjusted geometric means

Effects of combinations of CYP3A4 and/or P-gp Inhibitors and Inducers on Maraviroc.

The effects of combinations of CYP3A4/P-gp inhibitors and inducers have been investigated in Studies A4001021 and A4001042.

Study A4001021

Study A4001021 was an open, randomised, placebo-controlled, 2-way crossover study to investigate the effect of co-administration of efavirenz with Lopinavir/Ritonavir*, efavirenz with saquinavir/r and efavirenz with both Lopinavir/Ritonavir* and saquinavir on the pharmacokinetics of maraviroc 100 mg BID or 300 mg BID in thirty six healthy subjects.

Table 33. Treatments Groups In Study A4001021

	Period 1[a]	Period 2[a]
Cohort 1 (N=12)	Maraviroc 300 mg BID + Lopinavir/Ritonavir* BID (Days 1-21) plus efavirenz 600 mg QD (Days 8-21)	Maraviroc 300 mg BID + placebo BID (Days 1-21) plus placebo QD (Days 8-21)
Cohort 2 (N=12)	Maraviroc 100 mg BID + saquinavir/r BID (Days 1-21) plus efavirenz 600 mg QD (Days 8-21)	Maraviroc 100 mg BID + placebo BID (Days 1-21) plus placebo QD (Days 8-21)
Cohort 3 (N=12)	Maraviroc 100 mg BID + saquinavir 1000 mg BID + Lopinavir/Ritonavir* BID (Days 1-21) plus efavirenz 600 mg QD (Days 8-21)	Maraviroc 100 mg BID + placebo BID (Days 1-21) plus placebo QD (Days 8-21)

[a] Subjects were randomised to treatment sequence and could receive the treatments in either order
Lopinavir/Ritonavir* = lopinavir 400 mg + ritonavir 100 mg , Saquinavir/r = saquinavir 1000 mg + ritonavir 100mg

Pharmacokinetic Results: Co-administration of Lopinavir/Ritonavir* increased exposure of maraviroc, AUC_{12} was 4.0-fold higher and Cmax was 2.0-fold higher compared with placebo. Co-administration of saquinavir/r increased maraviroc exposure, AUC_{12} was 9.8-fold higher and Cmax was 4.8-fold higher compared to placebo. The addition of efavirenz for 14 days reduced the effect of Lopinavir/Ritonavir* and saquinavir/r but the net effect was still a higher maraviroc exposure; 2.5- and 1.3-fold higher AUC_{12} and Cmax respectively for Lopinavir/Ritonavir* and efavirenz,

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and 5.0- and 2.3-fold higher AUC_{12} and Cmax respectively for saquinavir/r and efavirenz (Table 34 and Table 35).

Table 34. Summary of Maraviroc Pharmacokinetic Parameters on Days 7 and 21 (A4001021)

Cohort (N)	Treatment	Maraviroc Dose	Day	Mean Pharmacokinetic Parameter (range)	
				AUC_{12} (ng.h/ml)[a]	C_{max} (ng/ml)[a]
1	Lopinavir/Ritonavir* (400 mg/100 mg BID)	300 mg BID	7	10030 (7990-155000)	1810 (1000-2260)
	Lopinavir/Ritonavir* (400 mg/ 100 mg BID) + Efavirenz 600g QD		21	6198 (4540-11400)	1070 (635-1870)
	Placebo	300 mg BID	7	2500 (1890-4180)	914 (660-1410)
	Placebo		21	2450 (1500-4180)	854 (390-1540)
2	Saquinavir/r (1000 mg/100 mg BID)	100 mg BID	7	4852 (3110-7480)	888 (562-1400)
	Saquinavir/r (1000 mg/100 mg BID) + efavirenz (600 mg QD		21	2714 (1810-4850)	194 (77.5-541)
	Placebo	100 mg BID	7	486 (266-1040)	187 (86.1-379)
	Placebo		21	543 (306-1410)	194 (77.5-541)

Source: A4001021 CSR Tables 13.5.1.1-13.5.1.2.2.
[a] geometric mean

Table 35. Summary of Statistical Analysis of Maraviroc Pharmacokinetic Parameters (A4001021)

Cohort (N)	Treatment Comparison	Day	Ratios (90% CI)	
			AUC_{12}	C_{max}
1	Maraviroc 300 mg BID + Lopinavir/Ritonavir* versus maraviroc 300 mg BID + placebo	7	3.95 (3.43, 4.56)	1.97 (1.66, 2.34)
	Maraviroc 300 mg BID + Lopinavir/Ritonavir* +Efavirenz versus maraviroc 300 mg BID placebo	21	2.53 (2.24, 2.87)	1.25 (1.01,1.55)
2	Maraviroc 100 mg BID Saquinavir/r versus maraviroc 100 mg BID placebo	7	9.77 (7.87, 12.14)	4.78 (3.41, 6.71)
	Maraviroc 100 mg BID Saquinavir/r plus efavirenz versus maraviroc 100 mg BID placebo	21	5.00 (4.26, 5.87)	2.26 (1.64, 3.11)

Source: A4001021 CSR Tables 13.5.12.3 to 13.5.12.6 and 13.5.13.3 to 13.5.13.6
CI=confidence interval

Safety Results: In Cohort 3 (maraviroc 100 mg BID plus saquinavir/ Lopinavir/Ritonavir*/efavirenz), two subjects missed study doses of maraviroc, saquinavir and Lopinavir/Ritonavir* in the first seven days of treatment period 1 due to treatment-related adverse events of moderate abdominal pain, nausea and vomiting and severe nausea and moderate vomiting. Two subjects permanently discontinued due to hyperbilirubinaemia. Subjects 10[redacted] and 10[redacted] discontinued on Days 4 and 6 respectively with highest total bilirubin value of 43.8 µmol/l and 49.5 µmol/l respectively. These events are defined as mild and moderate respectively according to the AIDS Clinical Trial Group (ACTG) rating. All subjects in this cohort were permanently discontinued on Day 7 when the cohort was stopped by the sponsor due to treatment related gastrointestinal adverse events related to poor tolerability of the combination (saquinavir and Lopinavir/Ritonavir*) in this healthy volunteer population.

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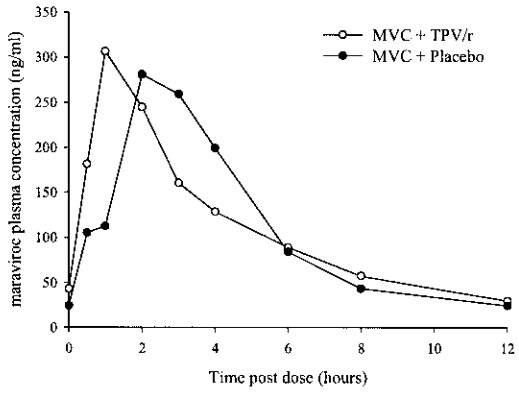
Study A4001042

Study A4001042 was an open, randomised, 2 way crossover study to investigate the effect of tipranavir/r (500 mg tipranavir plus 200 mg ritonavir BID) on the pharmacokinetics of maraviroc (150 mg BID) in twelve healthy subjects. Both tipranavir and ritonavir are substrates, inhibitors and inducers of CYP3A4/P-gp, but when administered in combination, the net effect is thought to be CYP3A4 inhibition and P-gp induction.

Pharmacokinetic Results: Tipranavir/r did not affect the steady state (Day 8) pharmacokinetics of maraviroc (AUC_{tau} and C_{max}), suggesting that the CYP3A4 inhibition and P-gp induction are compensated for producing no net effect (Table 41 and Figure 11A).

Figure 11. Mean Maraviroc Pharmacokinetic Profiles (A) and Trough Concentrations (B) by Treatment Group (A4001042)

A



B

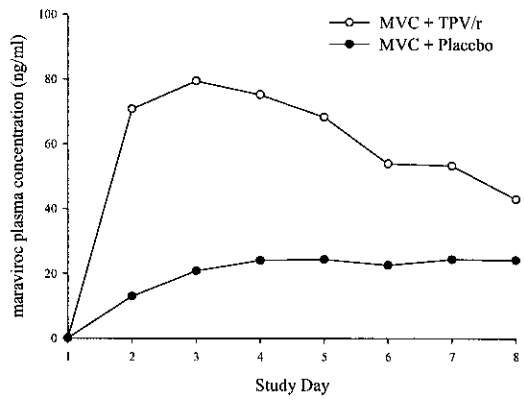


Figure A is mean plasma profiles; Figure B is mean trough concentration for each treatment group

Table 36. Summary of the Effect of Tipranavir/r on Maraviroc Pharmacokinetics (A4001042)

Co-administered Drug (dose)	MVC Dose	Mean (range) and Ratio (CI) of Maraviroc Pharmacokinetic Parameters with/without Tipranavir/r (No effect ratio= 1.00)					
		AUC_{tau} (ng.h/mL)			Cmax (ng/mL)		
		+ Placebo	+ Tipranavir/r	Ratio[a] (90% CI)	+ Placebo	+ Tipranavir/r	Ratio[a] (90% CI)
Tipranavir/r (500 mg/ 200 mg BID) N=12	150 mg BID	1260 (890-1790)	1282 (814-1750)	1.02 (0.85, 1.23)	347 (144-432)	298 (144-461)	0.86 (0.61, 1.21)

Source: A4001042 CSR Tables 13.5.1.1 and 13.5.3.2
[a]The comparison of interest was maraviroc+ boosted tipranavir (Day 8) versus MVC + placebo (Day 8).
MVC=maraviroc, CI=confidence Interval

Inspection of individual maraviroc trough concentrations suggest that steady state was achieved later when maraviroc was administered with boosted tipranavir. Mean maraviroc trough concentrations on Day 8 were higher in the presence of tipranavir/r compared to placebo. Overall, the profile of trough concentrations of maraviroc plus tipranavir/r increased over Days 1 to 4 and decreased thereafter suggesting that there was initial inhibition followed by induction of maraviroc metabolism and is consistent with the known effects of boosted tipranavir (Figure 11B).

Effects of Renal Substrates/Inhibitors on Maraviroc

The effect of renal substrates/renal cation inhibitors has been investigated in studies A4001018 and A4001022.

Study A4001018

Study A4001018 was an open, randomised, placebo-controlled, two-period crossover study to investigate the effects of Trimethoprim/sulfamethoxazole* (960 mg) on the steady-state pharmacokinetics of maraviroc (300 mg) in sixteen healthy volunteers. Trimethoprim/sulfamethoxazole* is a combination antibacterial agent (trimethoprim 160 mg and sulfamethoxazole 800 mg) and a common prophylactic treatment for the prevention of *Pneumocystis jiroveci pneumonia* (PCP) (formerly *Pneumocystis carinii pneumonia*) and toxoplasmosis infections in HIV-1 infected patients. Trimethoprim is an inhibitor of the renal cation transporter and as maraviroc has some renal clearance (~23%), this study evaluated the potential for Trimethoprim/sulfamethoxazole* to affect maraviroc pharmacokinetics.

Pharmacokinetic Results: Concomitant administration of Trimethoprim/sulfamethoxazole* did not appear to affect systemic exposure of maraviroc (Table 37). Indeed, renal clearance of maraviroc was similar when maraviroc was administered with Trimethoprim/sulfamethoxazole* (7.92 L/h) compared to placebo (8.51 L/h).

Table 37. Summary of the Effect of Trimethoprim/sulfamethoxazole* on Maraviroc Pharmacokinetics (A4001018)

Co-administered Drug (dose)	MVC Dose	Mean (range) and Ratio (CI) of Maraviroc Pharmacokinetic Parameters with/without Trimethoprim/sulfamethoxazole*(no effect ratio= 1.00)					
		AUCtau (ng.h/mL)[a]			Cmax (ng/mL)[a]		
		+ Placebo	+Trimethoprim/ sulfamethoxazole*	Ratio[b] (90% CI)	+ Placebo	+Trimethoprim/ sulfamethoxazole*	Ratio[b] (90% CI)
Trimethoprim/ sulfamethoxazole* (800 mg/160 mg BID) N=13	300 mg BID	3060 (1900-3910)	3388 (2210-4640)	1.11 (1.01, 1.21)	705 (372-1180)	849 (535-1400)	1.19 (1.04, 1.37)

Source:A4001018 Tables 5.1 and 5.4.2
[a]unadjusted means
[b]The comparison of interest was maraviroc+ Trimethoprim/sulfamethoxazole* (day7) versus maraviroc + placebo (day 7)
MVC=maraviroc, CI=confidence interval

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Study A4001022

Study A4001022 was an open, randomised, 2-way crossover study to investigate the effect of co-administration of tenofovir (300 mg QD) on the steady state pharmacokinetics of maraviroc (300 mg BID) in twelve healthy subjects. Tenofovir is a commonly prescribed NRTI as part of HAART, which is primarily renally cleared involving both passive and active processes. As maraviroc has some renal clearance (~23%), and tenofovir has had some unpredicted interactions with other HIV agents, this study evaluated the potential for tenofovir to affect maraviroc pharmacokinetics.

Pharmacokinetic Results: Concomitant administration of tenofovir did not appear to affect systemic exposure of maraviroc (Table 38). Renal clearance of maraviroc was similar when maraviroc was administered with tenofovir (7.81 L/h) compared to placebo (8.50 L/h).

Table 38. Summary of the Effect of Tenofovir on Maraviroc Pharmacokinetics (A4001022)

Co-administered Drug (dose)	MVC Dose	Mean (range) and Ratio (CI) of Maraviroc Pharmacokinetic Parameters with/without Tenofovir (No effect ratio=1)					
		AUCtau (ng.h/mL)[a]			Cmax (ng/mL)[a]		
		+ Placebo	+ Tenofovir	Ratio[b] (90% CI)	+ Placebo	+ Tenofovir	Ratio[b] (90% CI)
Tenofovir (300 mg BID) N=12[c]	300 mg BID	3536 (2330-6080)	3613 (2550-5890)	1.03 (0.98, 1.09)	1214 (677-2420)	1245 (615-1880)	1.04 (0.90, 1.19)

Source: A4001022 Table 13.5.1 and 13.5.4.2.
[a] unadjusted means
[b] The comparison of interest was maraviroc plus tenofovir (Day 7) versus maraviroc and placebo (Day 7).
[c] N=12 for maraviroc plus tenofovir AUCtau and Cmax and N=11 for maraviroc plus placebo AUCtau and Cmax.
MVC=maraviroc, CI=confidence Interval

Effect of selected antiretroviral combinations on Maraviroc in HIV-1 infected patients

Study A4001017

Study A4001017 was an open, single period, single centre probe study to investigate the effect of selected antiretroviral combinations on the pharmacokinetics of a single oral dose of maraviroc (300 mg) in HIV-1 infected patients who were already receiving these regimens. The data generated in this study were compared with historical data from Study A4001007 in which asymptomatic HIV-1 infected subjects not taking antiretroviral therapy received 300 mg BID maraviroc monotherapy. Twenty-nine subjects entered the study. Subjects continued their own antiretroviral therapy medication as follows:

Table 39. Summary of Treatment Groups (A4001017)

Cohort	Antiretroviral Therapy
Cohort 1:	Efavirenz 600 mg (QD), Zidovudine/Lamivudine* (lamivudine 150 mg + zidovudine 300 mg) (BID).
Cohort 2:	Efavirenz 600 mg QD, didanosine 250 mg enteric coated QD, tenofovir 300 mg QD.
Cohort 3:	Nevirapine 200 mg BID, lamivudine 150 mg BID, tenofovir 300 mg QD.
Cohort 4:	Lopinavir/Ritonavir* (lopinavir + ritonavir) 400 mg BID, stavudine 40 mg BID, lamivudine 150 mg BID.

Nevirapine is a NNRTI which can cause liver damage particularly in patients with high CD4 counts, therefore an interaction study with nevirapine was not conducted in healthy volunteers. Nevirapine was included in this probe study in HIV-1 infected patients to evaluate any potential effect of nevirapine on maraviroc pharmacokinetics.

Pharmacokinetic Results: Co-administration of efavirenz-containing regimens (cohorts 1 and 2) resulted in an approximate 50% reductions in exposure of maraviroc, with geometric mean ratios of approximately 0.5 fold for AUC_{12}, compared to the historical control group (A4001007) (Table 40 and Table 41).

Table 40. Summary of the Effect of Selected Antiviral Regimens on Maraviroc Pharmacokinetic Parameters (A4001017)

Treatment Group	Mean Maraviroc Pharmacokinetic Parameters (range)	
	AUC_{12} (ng.h/mL)	C_{max}[a] (ng/mL)
Cohort 1 Zidovudine/Lamivudine* + Efavirenz (N=8)	1060 (523-1800)	389 (142-625)
Cohort 2 Didanosine +Efavirenz + Tenofovir (N=8)	1093 (405-4140)	447 (144-1810)
Cohort 3 Nevirapine+ lamivudine +Tenofovir (N=8)	2273 (1160-5110)	900 (384-2610)
Cohort 4 Lopinavir/Ritonavir* + stavudine + lamivudine (N=5)	5987 (3250-8430)	1050 (493-2040)
Day 1 300 mg BID (A4001007, N=8)[b]	2262 (1460-3720)	585 (425-829)

Source A4001017 CSR Tables 5.1, 5.2.1,5.2.2, 5.2.3 and 5.4
[a] unadjusted geometric mean;
[b] data generated in this study were compared with historical data from Study A4001007, in which asymptomatic HIV-infected subjects received 300mg maraviroc monotherapy

Maraviroc exposure (AUC_{12}) was similar in the regimen including nevirapine (Cohort 3) though the geometric mean ratio for C_{max} was 1.5 fold higher compared with the historical control group. The regimen including Lopinavir/Ritonavir* (Cohort 4) resulted in a 2.6 fold higher AUC_{12} and 1.8 higher for C_{max}, compared with the historical control group (Table 41).

* ：新薬承認情報提供時に置き換えた

Table 41. Summary of Statistical Analyses of AUC_{12} and Cmax Parameters (A4001017)

Treatment Group	Parameter	Ratio of Means[a] (90% CI)
Cohort 1: Zidovudine/Lamivudine* + Efavirenz (N=8)	AUC_{12} (ng.h/ml)	0.469 (0.303, 0.724)
	Cmax (ng/ml)	0.665 (0.408, 1.09)
Cohort 2: Didanosine +Efavirenz + Tenofovir (N=8)	AUC_{12} (ng.h/ml)	0.483 (0.313, 0.746)
	Cmax (ng/ml)	0.764 (0.468, 1.25)
Cohort 3: Nevirapine+ lamivudine +Tenofovir (N=8)	AUC_{12} (ng.h/ml)	1.01 (0.651, 1.55)
	Cmax (ng/ml)	1.54 (0.943, 2.51)
Cohort 4 : Lopinavir/Ritonavir* + stavudine + lamivudine (N=5)	AUC_{12} (ng.h/ml)	2.65 (1.61, 4.35)
	Cmax (ng/ml)	1.80 (1.03, 3.14)

Source: A4001017 Tables 5.5.1 and 5.5.2
[a] the comparison of interest was maraviroc 300mg + *antiretroviral therapy* (A4001017) – maraviroc 300mg (A4001007)]. Maraviroc 300mg Day 1 (A4001007) was the reference treatment.[a]
CI=confidence interval

These findings in patients following a single dose of maraviroc are consistent with the data generated from formal multiple dose drug-drug interactions studies (A4001013, A4001021).

Study A4001046

Study A40010046 was an open, single period, single centre study to investigate the range of maraviroc exposures following a 150 mg single dose of maraviroc in eight HIV-1 infected patients receiving antiretroviral therapy containing saquinavir/r.

Prior to this study, no data was available on the exposure of maraviroc at clinically relevant doses (150 mg) in combination with saquinavir/r. Hence this study was conducted to gather some information at this dose in a clinically relevant population i.e. HIV-1 infected patients.

Pharmacokinetic Results: The mean AUC_{inf} and Cmax following maraviroc in the presence of Saquinavir/ritonavir was 4588 ng.h/mL (range: 2470 to 12000) and 756 ng/mL (range: 498 to 1550), respectively. In seven of the patients, the Cmax and AUC_{inf} ranged from 498-1210 ng/mL and 2470-4820 ng.h/mL respectively. One further subject had an outlying value for AUC_{inf} of 12000 ng.h/mL (Cmax 1550 ng/mL). The inter-subject variability for the pharmacokinetic parameters was consistent with that seen in previous studies with maraviroc in HIV-1 infected patients. No formal statistical comparisons were made between the data in this study and historical controls.

There was no relationship between saquinavir formulation and maraviroc exposure (Table 42).

Table 42. Summary of Maraviroc Pharmacokinetic Parameters (A4001046)

Subject	AUC_{inf} (ng.h.mL)	Cmax (ng.mL)	Saquinavir Formulation[a]	Concomitant ART
100[redacted]	5590	739	Saquinavir* Tablet	Ritonavir, Abacavir, Zidovudine
100[redacted]	5350	670	Saquinavir* Capsule	Ritonavir, Emtricitabine, Tenofovir
100[redacted]	2960	600	Saquinavir* Capsule	Ritonavir, Abacavir, Lamivudine
100[redacted]	3500	650	Saquinavir* Capsule	Ritonavir, Aciclovir, Lamivudine, Zidovudine
100[redacted]	5230	1210	Saquinavir* Capsule	Ritonavir, Stavudine, Tenofovir
100[redacted]	12000	1550	Saquinavir* Tablets	Ritonavir, Didanosine, Tenofovir
100[redacted]	2470	498	Saquinavir* Capsule	Ritonavir, Abacavir, Lamivudine,
100[redacted]	4090	594	Saquinavir* Tablets	Ritonavir, Abacavir, Tenofovir
Geometric Mean	4588	756		

Source: A4001046 CSR Tables 13.5.1 and B.3.4

[a] The protocol did not specify the dose of saquinavir or the formulation to be used. All patients received 1000 mg Saquinavir* and 100 mg ritonavir. Saquinavir was taken either as Saquinavir* hard gel capsules (200 mg), Saquinavir* tablets (500 mg) or Saquinavir* soft gel capsules (200 mg)

The Cmax concentrations from A4001046 are comparable to those seen in HIV-1 infected patients following multiple dosing of 300 mg BID (A4001007; mean Cmax 585 ng/mL [range 425-829]. As expected, the mean AUC_{inf} values were generally higher in A4001046 than those observed in HIV-1 infected patients following 300 mg BID maraviroc alone (A4001007 mean AUC_{tau} 2262 ng.h/mL [range 1460-3720]).

2.7.2.2.7. Cardiovascular Pharmacodynamic Studies

The effect of maraviroc on QTc interval and haemodynamic parameters was evaluated in Studies A4001016 and A4001033. This is discussed in section 2.7.2.3.2 of this module and also Section 2.7.4.2.1.5, Module 2.7.4, Summary of Clinical Safety.

Study A4001016

A4001016 was a single-dose, placebo- and active-controlled, 5-way crossover study in sixty-one healthy male (N=30) and female (N=31) subjects specifically designed to assess the potential to prolong QTc interval for active drug (maraviroc or moxifloxacin) compared with placebo control to account for procedural and study variables. The study was double blind with respect to the maraviroc and placebo doses but open label with respect to the moxifloxacin dose. The rationale for performing this prospectively designed QTc study is presented in section 2.7.2.3.2.

The study comprised a screening visit, five study periods, each separated by at least seven days, and a follow-up visit. In study period 3, subjects had a run-in day the day before dosing on Day 1 during which assessments were made to correspond with the time of day that they were taken on study treatment days. On the run-in day subjects received placebo single blinded for maraviroc. This dose of placebo was independent of the randomised study treatments.

A separate heart rate correction formula for QT was determined for each subject using data from pre-dose resting ECG recordings in each study period, the run-in day recordings and the

additional ECG recordings (described below). This formula was used to derive a corrected individual subject QT value (QTcI) for each timepoint, which best described their QT-RR relationship.

Resting ECG: The ECG measurements were recorded at the exact protocol times before the pharmacokinetic blood samples were collected (within 5 minutes of the ECG), after subjects had been resting semi-recumbent for at least 30 minutes. The ECG print outs were reviewed immediately to ensure they were of suitable quality for QTc assessment. If they were of insufficient quality then the ECG was repeated immediately.

Additional ECGs (Run-in day, study period 3 only): On the run-in day, during study period 3, six additional 12-lead ECGs were recorded when subjects had an increased heart rate due to exercise. During the exercise period three ECGs were recorded as subject's heart rate was increasing and three ECGs were recorded when the subject's heart rate was decreasing back to baseline. The measurements were taken at approximately equal intervals between subject's resting heart rate and up to a rate of 90 beats per minute.

For each subject, the QT:RR relationship was evaluated from measurements made pre-dose in the five study periods and on the *run-in* day of study period 3. A non-linear mixed effect model was used to estimate the correction factor for each subject (b_s). QTcI was calculated using these correction factors, $QTcI_s = QT/(RR)^{b_s}$

Pharmacokinetic results: A summary of the pharmacokinetic data are presented below in Table 43.

Table 43. Summary of Maraviroc Pharmacokinetic Parameters (A4001016)

Parameter	Mean Values (range)		
	Maraviroc 100 mg N=60	**Maraviroc 300 mg** N=59	**Maraviroc 900 mg** N=58
AUC_{last} (ng.h/mL)[a]	396 (89.7 to 872)	1840 (515 to 3620)	5259 (3090 to 10300)
Cmax (ng/mL)[a]	111 (17.7 to 391)	464 (92.7 to 956)	1148 (431 to 2360)
Tmax (h)[b]	2.8 (1.0 to 4.0)	2.6 (1.0 to 4.0)	2.2 (1.0 to 4.0)

Source: A4001016 CSR Tables 5.11. 5.1.2, 5.1.3
[a] unadjusted geometric means for AUC and Cmax,
[b] unadjusted arithmetic means for Tmax

Pharmacodynamic Results: Table 44 summarises a comparison of the active treatments against placebo for the three primary pharmacodynamic endpoints of the study.

Table 44. Summary of the Statistical Analysis of Pharmacodynamic Results (A4001016)

Endpoint	Comparison	N	Adjusted Means (milliseconds)		Mean Difference[a] (90% CI)
			Active	Placebo	
QTcI at median Tmax	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)

Source: A4001016 CSR Table 5.4
[a] Difference between active and placebo
[b] Median Tmax for Maraviroc 100 mg = 3 hours, for Maraviroc 300mg = 3 hours, for Maraviroc 900mg = 2 hours, for Moxifloxacin 400mg = 2 hours.

The mean maximum difference from placebo in QTcI at median Tmax and between 1 and 4 hours after dosing, was less than 4 msec for all 3 doses of maraviroc (100, 300, and 900 mg as single doses). Furthermore, the upper limits of the 90% CI were below 7 msec for all endpoints. By contrast, the active comparator, moxifloxacin, resulted in a mean difference in QTcI for all three endpoints of between 12 and 14 msec. There did not appear to be any gender differences in the magnitude of the effects of maraviroc and moxifloxacin. No subject in the maraviroc treatment groups had a maximum QTcI interval =450 (for males) or 470 msec (for females), or a maximum increase from baseline of =60 msec, after dosing. In conclusion, there was no evidence of maraviroc (at 3 times the nominal dose of 300 mg) having any clinically meaningful effect on QTc prolongation.

Study A4001033

Study A4001033 was a 2 part study to investigate the effect of maraviroc on the cardiovascular function of sixteen healthy male subjects.

Part 1 was an open, randomized, two-period (periods 1 and 2) crossover assessment of a single sublingual spray of 0.4 mg glyceryl trinitrate (GTN) versus no-treatment (placebo). Treatments were separated by at least 24 hours. Part 2 was a double blind, randomized, placebo-controlled, two period (periods 3 and 4) crossover assessment of a single oral dose of maraviroc 900 mg versus placebo. Parts 1 and 2 of the study were separated by at least 5 days. Subjects were assigned to one of four treatment sequences as shown in Table 45.

Table 45. Summary of Treatment Groups (A4001033)

Sequence	Part 1		Part 2	
	Period 1	Period 2	Period 3	Period 4
1 (N=16)	GTN	No treatment	Maraviroc 900 mg	Placebo
2 (N=16)	GTN	No treatment	Placebo	Maraviroc 900 mg
3 (N=16)	No treatment	GTN	Maraviroc 900 mg	Placebo
4 (N=16)	No treatment	GTN	Placebo	Maraviroc 900 mg

The relationship between maraviroc plasma concentration and pharmacodynamics was investigated using impedence cardiography, blood pressure, ECG and cardiac monitoring.

Blood sampling was performed during Part 2 of the study of the study only, with sample collection at 0.5 hours and every 30 minutes until 4 hours post-dose. No pharmacokinetic parameters were calculated.

Impedence Cardiography Monitoring: ICG is based on measurement of the thoracic electrical impedence and allows non-invasive real-time monitoring of cardiac stroke volume trends beat by beat. Subjects were familiarized with the ICG machine which was used to measure stroke index, cardiac index and systemic vascular resistance. For Part 1 of the study, subjects had ICG, twice over 30 beats, at pre-dose and every three minutes up to 60 minutes post-dose. For Part 2 of the study, subjects had ICG pre-dose and every 30 minutes until 4 hours post-dose. Subjects lay supine for at least 15 minutes before each ICG assessment.

Blood Pressure Monitoring: For Part 1 of the study, subjects first had supine blood pressure and pulse rate measured pre-dose on period 1 to familiarize them with the procedure. Further measurements were taken at pre-dose and every three minutes up to 60 minutes post-dose. For Part 2 of the study, subjects also had supine measurements pre-dose and every 30 minutes until 4 hours post-dose.

Cardiac Monitoring: For both periods of Part 1 of the study, subjects had cardiac monitoring by a Holter monitor from immediately pre-dose until one hour post-dose. For both periods of Part 2 of the study, subjects were monitored from immediately pre-dose until four hours post-dose.

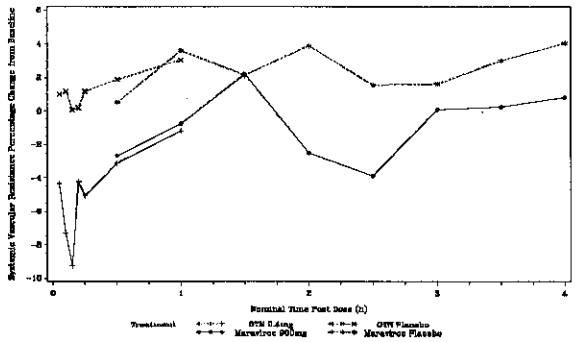
ECG Monitoring: Subjects had a single ECG at screening, Day 0 on period 1 and at the follow-up visit. For Part 1 of the study, subjects had triplicate ECGs (2 to 4 mins apart), pre-dose, one hour post-dose and before leaving the study centre. For Part 2 of the study, subjects had triplicate ECGs (2 to 4 mins apart), pre-dose, 1, 2 and 4 hours post-dose and before leaving the study centre.

Pharmacodynamic Results: GTN decreased systemic vascular resistance (largest mean decrease –9.2%), stroke index (largest mean decrease –8.6%) and supine diastolic blood pressure and increased cardiac index (largest mean increase 6.2%) and pulse rate. These effects peaked approximately six to nine minutes post-dose. In contrast, maraviroc 900 mg did not cause a clinically significant change in supine systolic or diastolic blood pressure but did, to a lesser extent than GTN, decrease systemic vascular resistance (largest mean

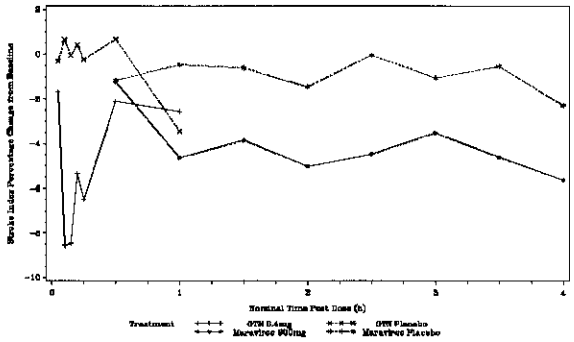
decrease –3.9%) and stroke index (largest mean decrease –5.6%) and increased cardiac index (largest mean increase 6.8%) and pulse rate. These effects were mostly sustained over the four hours post-dose measurement period (Figure 12).

Figure 12. Mean Profiles of Vascular Resistance (A) and Stroke Index (B), % Change from Baseline versus Time by Treatment

A Vascular Resistance



B Stroke Index



The pharmacodynamic results following maraviroc are consistent with those expected of a mild vasodilator with a fully compensated haemodynamic response maintaining supine blood pressure. However the 3/16 subjects experiencing postural hypotension imply that there was not always complete compensation for orthostatic changes.

There was no apparent relationship between the percentage change from baseline in ICG parameters or change from baseline in supine blood pressure and pulse rate and maraviroc plasma concentration. There were no clinically significant findings in the ECG measurements.

2.7.2.3. Comparison and Analyses of Results across Studies

The results of population modelling analysis of Phase 1, 2a and 2b/3 studies are integrated into all subsections within the comparison across studies. An introduction to the objectives and data included in these analyses are provided in section 2.7.2.1.3. Full details of the reports can be found in Modules 5.3.3.5, 5.3.4.1 and 5.3.4.2.

2.7.2.3.1. Pharmacokinetics of Maraviroc

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 (Table 1). The coefficient of variation for Cmax and AUC variables at doses of 100 mg and above was generally between 20-40% for most studies.

After oral administration, maraviroc Cmax is achieved generally between 0.5 and 4 hours after single and multiple dosing and steady state after multiple dosing is achieved by 7 days. Plasma maraviroc accumulates to a limited extent after both once- and twice-daily dosing

(Study A4001002). The mean accumulation ratio for 300 mg BID is 1.23, although significant accumulation was not seen in HIV-1 infected patients (1.13 at 300 mg BID maraviroc, A4001007).

Mean total clearance of maraviroc was estimated as 44L/h for 30 mg IV dose, with renal clearance (mean CLr 10.2L/h), accounting for ~23% of total clearance. A renal clearance of 10.2 L/h (170 mL/min) equates to 680 mL/min unbound which is considerably higher than glomerular filtration rate (approximately 120 mL/min), indicating the role of active processes in the renal clearance of maraviroc. Nonlinear mixed effects pharmacokinetic modelling of the IV data from Study A4001009 estimated the population clearance to be 48.0 L/h (95% CI 46.3 – 50.4) with low inter-subject variability (10.8%, 95% CI 7.9 – 13.1%) in clearance. The IV data was best described by a four-compartment model. This analysis also showed that over the IV dose range of 3 mg to 30 mg maraviroc, the disposition of maraviroc is linear (Module 5.3.3.5 Population Pharmacokinetics Analysis of Maraviroc IV Data from Phase 1 Study A4001009). The results of this pharmacokinetic analysis are in close agreement with the clinical data from Study A4001009.

Maraviroc has multiphasic elimination with a terminal half-life estimate from population pharmacokinetic modelling of data from oral tablet dosing of approximately 15 hours (Module 5.3.3.5, Population Pharmacokinetics of Maraviroc after Oral Tablet Administration – A Pooled Analysis of Phase 1/2a Data). The clinical relevance of the maraviroc terminal half-life is limited due to it being primarily determined by drug leaving deep compartments (Module 5.3.3.5 Population Pharmacokinetics Analysis of Maraviroc IV Data from Phase 1 Study A4001009).

Population effects of clearance changes on IV plasma profiles arising from potential induction or inhibition of metabolic clearance were predicted. This analysis indicates that changes in clearance from concomitant inhibitors or inducers that significantly impact maraviroc AUC would have a relatively minor effect (less than 2 fold change) on measured terminal half-lives (predicted range 12-21 hours for 8-fold clearance changes) (Module 5.3.3.5 Population Pharmacokinetics Analysis of Maraviroc IV Data from Phase 1 Study A4001009). A subsequent population pharmacokinetic analysis of oral data from Phase 1 studies estimated that in the presence of CYP3A4 and/or P-gp inhibitors, the median terminal half life ($t_{1/2\Downarrow}$) increased from 15.3 hours to a range of 15.55-25.25 hours, with median fraction of area under the terminal phase ($F_{Area\Downarrow}$) increasing from 0.28 to a range of 0.3-0.58. In contrast, in the presence of CYP3A4 inducers, the median $t_{1/2\Downarrow}$ decreased to a range of 12.29-13.93 hours with the median $F_{Area\Downarrow}$ decreased to 0.21 with rifampicin and 0.27 for efavirenz (Module 5.3.3.5, The Impact of Interacting Antiretroviral Drugs on Maraviroc Pharmacokinetics After Oral Tablet Administration – A Pooled Population Pharmacokinetic Analysis of Phase 1 Data).

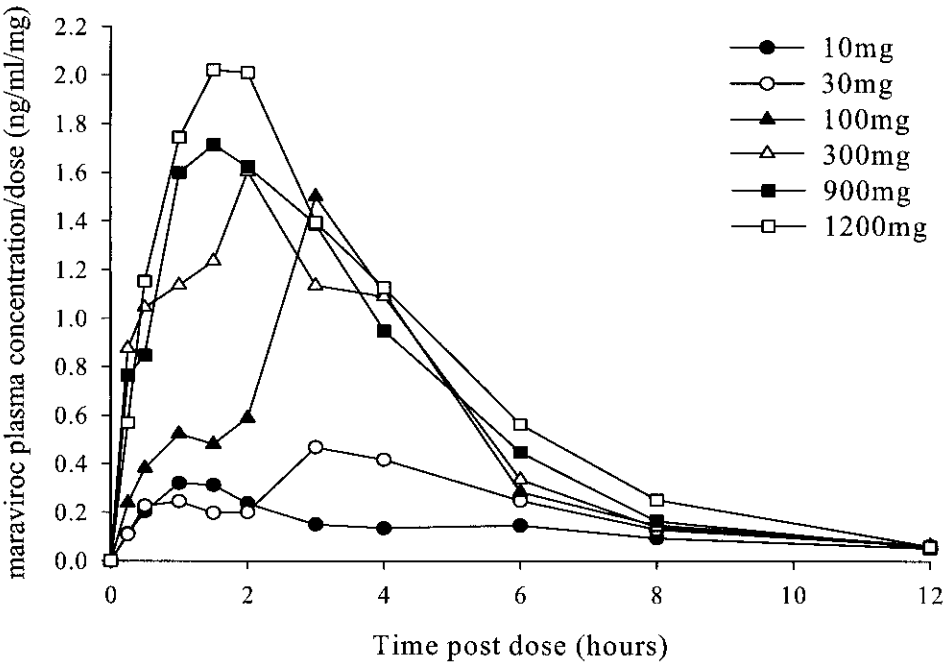
Absorption

After single and multiple oral dosing, maraviroc C_{max} generally occurs between 0.5 to 4 hours in both healthy subjects and HIV-1 infected patients.

A pooled population pharmacokinetic analysis of all available data for maraviroc administered alone as the tablet formulation at doses of 100 mg or greater (single and multiple doses) across Phase 1 and 2a studies was performed to describe rich maraviroc pharmacokinetic data (Module 5.3.3.5; Population Pharmacokinetics of Maraviroc after Oral Tablet Administration – A Pooled Analysis of Phase 1/2a Data). Using nonlinear mixed effects modelling a 2-compartment model was adapted to incorporate separate absorption and clearance components on bioavailability (referred to as the partition model). Bioavailability (F) was modelled as a product of extent of absorption (F_{ABS}) and fraction surviving first-pass elimination (F_{HEP}) with hepatic plasma flow fixed to 59.59 L/h and renal clearance fixed to 12 L/h according to previous findings. The model included a sigmoid Emax function to describe the dose effect on F_{ABS} and a power function of dose for the absorption rate constant (ka) and incorporated the concentration data from all Phase 1/2a studies with tablet doses of 100 mg or greater. This analysis estimated that the rate of maraviroc absorption was dose dependent, with a small increase in the rate of absorption with increasing maraviroc dose. The extent of maraviroc absorption was also dose-dependent with bioavailability increasing with increasing maraviroc dose. For the maraviroc tablet formulation, pharmacokinetic modelling estimated that the oral bioavailability of unit doses of maraviroc would be 24% at 100 mg, 31% at 300 mg and approximately 33% for unit doses of 600 mg and above (Module 5.3.3.5; Population Pharmacokinetics of Maraviroc after Oral Tablet Administration – A Pooled Analysis of Phase 1/2a Data). Predictions for bioavailability of maraviroc at a 100 mg unit dose are very similar across the modelling analyses and are consistent with the calculated oral absolute bioavailability (23%) from Study A4001009.

The oral pharmacokinetics of maraviroc are non-proportional (Figure 13).

Figure 13. Mean Dose-Normalised Maraviroc Plasma Concentration versus Time Profiles (A4001001)



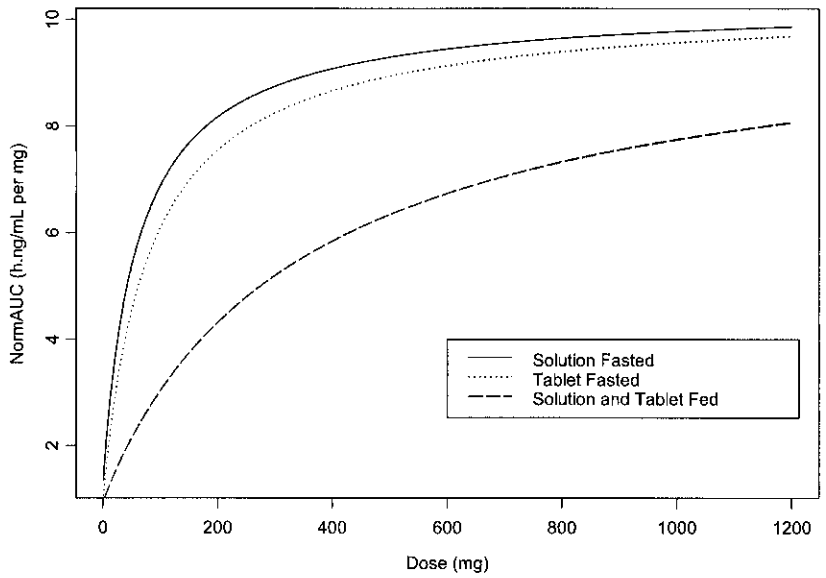
Formal assessment of dose proportionality following single doses of 50, 100, and 600 mg in Study A4001003, confirmed that the pharmacokinetics of maraviroc were not dose proportional over this unit dose range (section 2.7.2.2.2). It is estimated that a doubling in dose will lead to a 2.3-fold increase (95% CI; 2.2, 2.4) in mean AUC over this dose range.

The IV kinetics of maraviroc are linear over the 3-30 mg IV dose range (Study A4001009), On the assumption that disposition remains linear across the concentration range, the dose non-proportionality is likely to arise from factors influencing the extent of absorption. A postulated mechanism for the non-proportionality of maraviroc pharmacokinetics is the action of gut transporters (predominantly P-gp) returning maraviroc to the lumen of the intestine, thus reducing the bioavailability of maraviroc. These transporters may become saturated at higher doses resulting in a return to dose proportionality.

A population pharmacokinetic analysis of dose normalised AUC and C_{max} using the nonlinear mixed effect modelling approach expressed the dose non-proportionality in quantitative terms to allow predictions for doses not studied (Module 5.3.3.5, Population Analysis of Phase 1 non-compartmental pharmacokinetic data). Studies included in this analysis covered doses from 3 to 1200 mg for both maraviroc tablet and solution. Exploratory graphical analysis indicated a nonlinear relationship and hence an Emax model was fitted to the normalised AUC (AUC divided by dose) versus dose data. These results showed that the dose non-proportional behaviour of maraviroc is most apparent at maraviroc doses below 300 mg. Above 300 mg (administered in a fasted state), the dose non-proportionality is much less marked as the normalised AUC dose relationship begins to

reach a maximum (i.e. maximal absorption) Figure 14. Above 600 mg unit doses of maraviroc, dose proportional kinetics for maraviroc would be expected.

Figure 14. Maraviroc Dose-Normalised Steady State



In the pooled analysis of Phase 1/2a studies, the influence of food was modelled using fractional models with fed/fasting status affecting maximal extent of absorption and influencing the dose effect on extent of absorption. Food (high fat meal) taken at the same time as maraviroc doses caused a dose dependent reduction in the bioavailability of maraviroc, with less of a food effect at higher maraviroc doses. Pharmacokinetic modelling predicted that the food effect reduces to about 30% reduction at 300 mg and is more or less a constant 25% reduction at doses of 600 mg and above (Module 5.3.3.5, Population Pharmacokinetics of Maraviroc After Oral Tablet Administration – A Pooled Analysis of Phase 1/2a Data). The effect of food on bioavailability is discussed in Section 2.7.1.3, Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods.

Distribution

The steady state volume of distribution of maraviroc is approximately 194L (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]-labelled 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

In vitro studies have shown that the major route of metabolism of maraviroc is via CYP3A4 and that formation of the primary metabolite UK-408,027 is governed by CYP3A4 (section

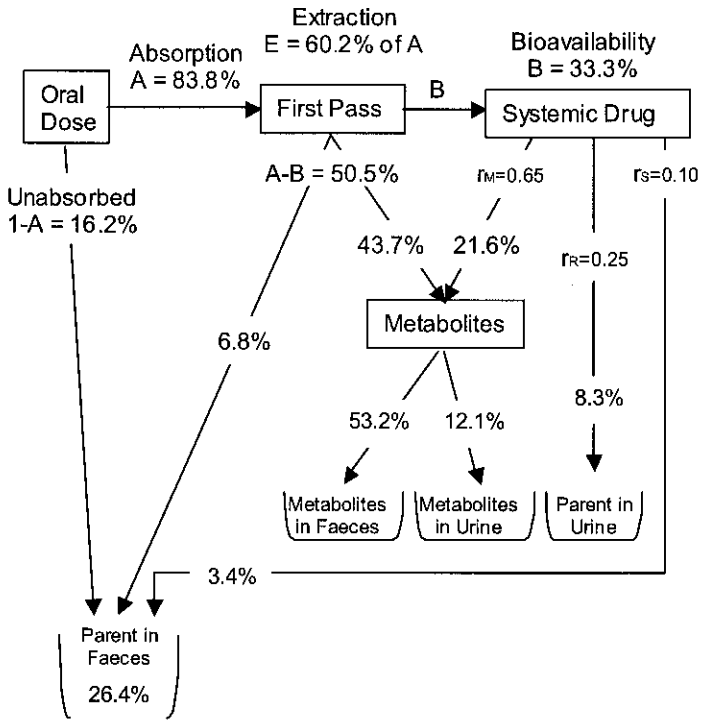
2.7.2.2.1). In clinical studies, potent CYP3A4 inhibitors and inducers were shown to modulate the kinetics of both maraviroc and its primary metabolite. Whilst initial screening identified a potential role for CYP2D6, more definitive studies in human liver microsomes have shown no CYP2D6 involvement in the metabolism of maraviroc (section 2.7.2.2.1). Furthermore, in Study A4001002, CYP2D6 phenotyping was conducted and there was no evidence that being a CYP2D6 poor metaboliser affected maraviroc exposure.

A single dose of 300 mg [^{14}C]-labelled maraviroc was administered to three subjects to assess mass balance and obtain metabolic profiles (Study A4001010, section 2.7.2.2.2). Cumulatively, 76% of the radioactivity was recovered in the faeces while 20% was recovered in the urine. HPLC profiling of human urine and extracted faecal homogenates showed similar and extensive metabolism in all subjects. The major metabolite pathways involved oxidation in the difluorocyclohexane ring, oxidation in the triazole group and N-dealkylation adjacent to the tropane moiety.

Unchanged maraviroc was the major plasma circulating component (42% of plasma radioactivity) and the metabolites UK-408,027 (22%), an amine analogue (11%) and UK-463,977 (5%) were also identified in the plasma. UK-408,027 and UK-463,977 have been evaluated in vitro against a range of 74 receptors, ion channels and enzymes and these metabolites are considered to be devoid of activity of any biological relevance. All human metabolites have been identified as circulating metabolites in one or more toxicology species tested (Sections 2.4.2.5.6 and 2.4.3.4.2, Module 2.4 Non clinical Overview). The metabolic pathways of maraviroc are discussed in Section 2.6.4.5, Module 2.6.4 Pharmacokinetics Written Summary.

Using data from Study A4001010, combined with predictions of absorption of 83.8% for a 300 mg dose of maraviroc (Module 5.3.3.5, Population Analysis of Maraviroc Phase 1 Non-compartmental Pharmacokinetic Data) and the population modelled value of systemic clearance from IV data (Study A4001009), mass balance was used to apportion the relative amounts of parent maraviroc and (combined) metabolites observed in Study A4001010, to various pathways, including first pass effects, renal clearance and metabolic and other (secretion) clearance. A detailed diagram of the disposition of maraviroc and metabolites after a 300 mg oral solution dose of maraviroc is shown in Figure 15. Full details of this report can be found in Module 5.3.3.5, Clearance and Mass Balance Model for Maraviroc.

Figure 15. Clearance and Mass Balance of Maraviroc after 300 mg Oral Dose



This mass balance indicated that with hepatic extraction of 60.2% (of 83.8% of the dose absorbed), the predicted maximum possible systemic bioavailability would be approximately 40% for a sufficiently high dose of maraviroc that was 100% absorbed.

2.7.2.3.2. Pharmacodynamic Results from Studies

Various pharmacodynamic assessments (visual nearpoint, pupillometry, salivary flow, CCR5 receptor occupancy, immune function effectors, blood pressure and ECG) were carried out in selected Phase 1 and Phase 2a studies. The results from pertinent studies are discussed below.

Visual nearpoint, Pupillometry and Salivary Flow

Pupillometry visual near point testing and salivary flow measurements were performed in the first two studies conducted in man (A4001001 and A4001002) due to findings in an early toxicology study in dogs. In the 2-week oral study in dogs at daily doses of 10, 50 or 250 mg/kg, mydriasis (dilated pupils) occurred in all drug-treated groups. A diminished pupillary light response test with the mydriasis was also observed in some of these animals. Other ocular signs were observed sporadically and included reddened conjunctiva (from 10 mg/kg), partial eye closure and protruding nictitating membrane (from 50 mg/kg) and lacrimation (at 250mg/kg). Salivation occurred in all drug-treated groups, immediately after dosing. The sponsor postulated that some of these clinical signs could be related to the non-selective pharmacology of the compound at high doses, such as actions on μ opioid or muscarinic receptors (Section, 2.4.4.3.3, Module 2.4, Nonclinical Overview).

Visual near-point, pupil diameter and salivary flow measurements were compared at each maraviroc dose to placebo in Studies A4001001 and A4001002. Though there were isolated changes in these measurements across doses, the changes were highly variable between doses with no evidence of a dose response.

Overall, as there was no clear pattern to these pharmacodynamic effects and they were not considered clinically relevant, these results provide no clinical evidence of maraviroc activity at the muscarinic and μ-opioid receptors.

Immune Function Effectors

As a consequence of binding to CCR5, maraviroc may have pharmacological effects that are not related to its antiviral activity. Maraviroc blocks binding of endogenous ligands of the CCR5 receptor and acts as an antagonist of subsequent signalling processes. There is therefore a theoretical risk that a CCR5 antagonist may affect immune function and this was investigated in in vitro assays, animal and human studies.

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. In a 4-week oral immunotoxicology study in the cynomolgus macaque monkey, maraviroc administration for 4 weeks at doses of 30, 100 and 300 mg/kg/day BID did not affect lymphocyte subset distribution, natural killer cell activity, phagocytosis activity or oxidative burst (Study No. 911/096). All animals were able to mount a humoral primary (IgM) and secondary (IgG) immune response against the antigen KLH, and there were no adverse pathological changes to the immune system (Sections 2.4.2.4.1 and 2.4.4.7, Module 2.4 Nonclinical Overview). Preclinical assessment of immune function suggests that inhibition of CCR5 function is unlikely to affect immune processes.

The clinical strategy for evaluating any potential effect of maraviroc on immune function included detailed monitoring of immune effectors in several Phase 1 studies in healthy volunteers and Phase 2a studies in asymptomatic HIV-1 infected patients. Volunteers and patients were monitored for effects on T lymphocyte subsets, (CD4 and CD8 cells, markers of cellular activation [CD38/HLADR]), macrophages [CD14], NK cells [CD56], B-lymphocytes [CD19] and dendritic cells [CD21, CD 86]). Effects on humoral immune response was evaluated by monitoring of immunoglobulins (A,D, E, G subtypes 1-4 and IgM) in some Phase 1 studies. Finally routine monitoring of full blood count with differential counts were performed for all the subjects included in the Phase 1 and 2a studies.

In both healthy volunteers and HIV-1-infected patients, no clear effect on haematological parameters was observed. In addition no clinically relevant changes in immunoglobulin and lymphocyte subset data, including CD4 and CD8 cells were observed in groups receiving maraviroc versus placebo. Although these data are reassuring, it is limited by the fact that the treatment periods in these studies were limited, with a maximum treatment period of 28 days and the majority of subjects receiving 7-12 days of therapy. Furthermore, interpretation of changes in many of these parameters is limited due to their wide normal variability, which can be further increased in the context of HIV-infection.

During the Phase 2b/3 studies, the sponsor monitored immunological status by assessment of CD4 and CD8 lymphocyte counts and full blood counts with differential counts. It was considered that many of the immune function parameters evaluated in the Phase 1 and 2a studies were of limited use as there were no apparent trends in any of the parameters studied. These parameters would therefore not be useful as defined markers of effects of immune function in the context of the treatment experienced HIV-1 patients. Further detail can be found in the Safety Review of Immunotox Potential of Maraviroc in Module 5.3.5.3.

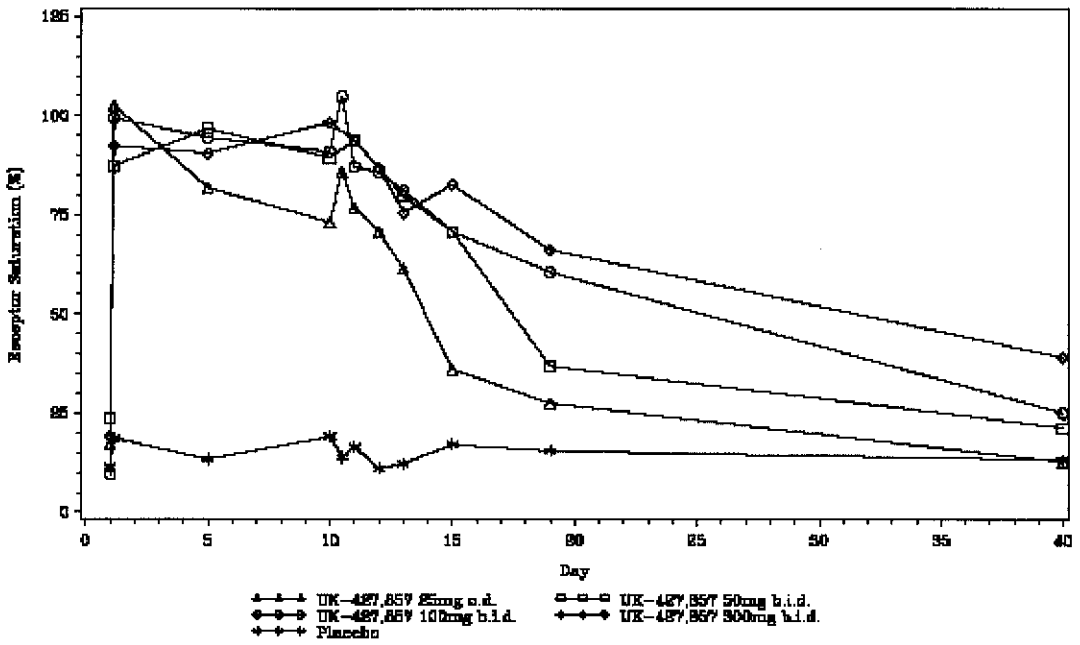
Receptor Occupancy

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 (DI/012/1 & CG/015/02, Section 2.6.2.2.1.1 Module 2.6.2 Pharmacology Written Summary). CCR5 receptor occupancy (or saturation) was investigated in healthy volunteers at doses of 3 mg to 100 mg BID (A4001002, A4001005, etc) and in HIV-1 infected patients (A4001007 and A4001015) at doses of 25 mg OD to 300 mg BID.

In healthy volunteers, receptor occupancy increased rapidly, reaching a plateau by 24 hours in most subjects. Mean receptor saturation at 24 hours post-dose on Day 12 was approximately 65%, 85%, 85% and 95% for the maraviroc doses of 3 mg BID, 10 mg BID, 25 mg BID and 100 mg BID respectively (A4001002). In Study A4001005, receptor saturation was greater than 75% for 100 mg BID maraviroc on Days 1 and 11.

In the Phase 2a studies in HIV-1 infected patients (A4001007 and A4001015) receptor occupancy increased rapidly and remained constant over the 10 day course of maraviroc monotherapy for doses of 50 mg BID and above. Mean receptor occupancy was high (>74%), even at doses of maraviroc that did not demonstrate clinically significant viral load reductions. In Study A4001007, mean CCR5 occupancy was >75% for 25 mg QD and >85% for 50 mg BID and 100 mg BID over the time course of 10 days of maraviroc monotherapy which was concurrent with reductions of -0.4, -0.7 and -1.2 $\log_{10}$ copies/mL in viral load respectively. At 300 mg BID which resulted in a 1.6 $\log_{10}$ copies/mL reduction in viral load, receptor occupancy was 90% over the 10 days of monotherapy. Mean receptor occupancy (saturation) did not notably start to decline until 5-10 days after cessation of maraviroc administration for doses of 100 mg and above as shown in Figure 16.

Figure 16. Mean CCR5 Receptor Saturation by Treatment Group (A4001007)



In study A4001015, mean CCR5 saturation was maintained above 80% throughout the dosing period (10 days) for all maraviroc groups (100 mg QD, 150 mg BID (fed and fasted) and 300 mg). A comparison of the receptor occupancy and viral load drop from baseline in Study A4001007 showed no association between degree of CCR5 occupancy and viral load reduction and that a maraviroc receptor occupancy close to the maximum (higher than 80%) is required before a significant decrease in viral load occurred (e.g. $\log_{10}$ drop of 1 within 10 days). A possible explanation for this observation is that very high levels of receptor occupancy are needed for optimal antiviral activity, and that the inherent variability of the experimental assay may result in an inability to detect small differences in receptor saturation. Furthermore, the assay measures only peripheral blood receptor saturation and gives no indication of the degree of tissue receptor occupancy (Fatkenheuer G, 2005). The relationship between ex vivo receptor occupancy, as measured by this assay, and functional in vivo receptor occupancy is therefore unclear.

The relationship between maraviroc plasma concentration, CCR5 receptor occupancy and viral dynamics was further explored using pharmacokinetic/pharmacodynamic modelling.

A population pharmacokinetic/pharmacodynamic model has been developed with data obtained after multiple dose administration of maraviroc in healthy volunteers (A4001002) and patients (cohort 1 in study A4001007) in order to simultaneously analyse the dose-concentration-CCR5 receptor occupancy relationship in vivo (Module 5.3.4.2., Pharmacokinetic/pharmacodynamic modelling of CCR5 receptor occupancy by Maraviroc in healthy subjects and HIV positive patients). The population pharmacokinetic model was a two-compartment model with first order absorption rate and a lag-time. It took into account the apparent non-proportionality in bioavailability and absorption/distribution observed for maraviroc in the dose range 10 to 600 mg. The pharmacodynamic model was a receptor

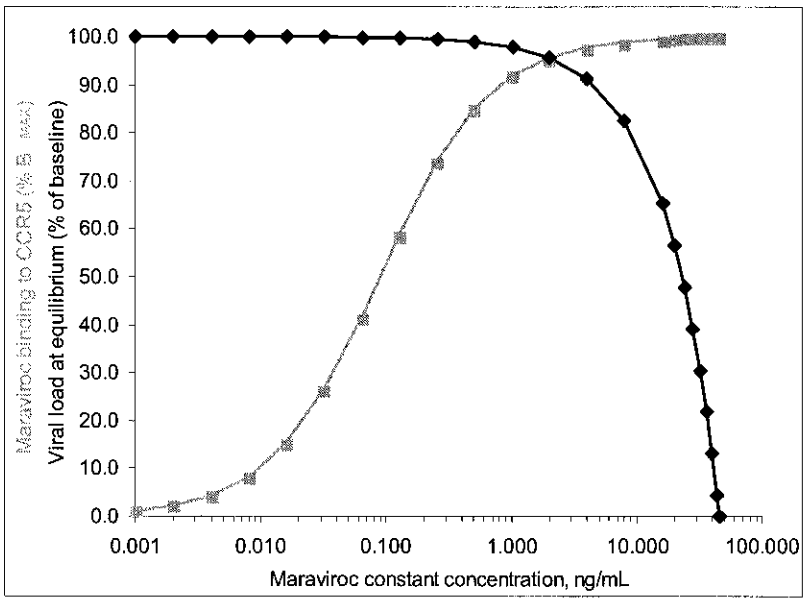
binding model with baseline that directly linked the plasma concentration of maraviroc to the receptor occupancy. The model gave a reasonable fit of the receptor occupancy-time data and revealed that the in vivo affinity of maraviroc for the CCR5 receptor was high (KD =0.089 ng/mL). This high affinity explained why at the lowest dose (i.e. 3 mg BID) in the healthy volunteer study, high median steady state CCR5 receptor occupancy (between 54 and 77%) was already observed. This high affinity also explains why at high doses the decrease in CCR5 receptor occupancy was delayed in time with respect to the maraviroc plasma concentration-time profile, requiring the plasma concentrations to drop below a certain value before receptor occupancy began to decrease significantly.

To further explore receptor occupancy and explain the apparent discrepancy between the estimated values of KD (0.089 ng/mL), in vitro IC_{50} (0.38 ng/mL) and in vivo IC_{50} (7.65 ng/mL), a common theoretical framework based on receptor theory and operational model of (ant-)agonism was developed for maraviroc (Module 5.3.4.2. Semi-mechanistic Pharmacodynamic Model for CCR5 Antagonist based on Receptor Theory). The in vivo IC_{50} value (7.65 ng/mL) was obtained based on the prey and predator principle introduced by Volterra and adapted for viral dynamics by Bonhoeffer (Funk et al, 2001). This viral dynamic model describes the interaction between the virus and the target cells by means of differential equations (full report in Module 5.3.4.2, Modelling and Simulation of Maraviroc to Support Phase III Trial Decisions. October 2003-February 2004).

The viral replication process can also be seen as a binding-stimulus-response cascade in which the virus is an agonist. Therefore, receptor theory and an operational model of agonism (antagonism in the case of maraviroc) have tentatively been applied to the dynamics of the HIV virus. Contrary to the viral dynamic model, the operational model of agonism can only describe the viral load at equilibrium (after long term treatment). Within this restriction, the circular form of the operational model of agonism (COMA) gives predictions that are very similar to those obtained with the viral dynamic model. Relationships between the percentage inhibition or the constant inhibitor concentration with the decrease in viral load are identical to those obtained with the viral dynamic model. In addition, this approach tends to indicate that the replication process is very efficient with a significant amount of unused spare capacity to replicate virus.

Combining the viral dynamic model with an operational model of (ant-) agonism that takes into account the working mechanism of the antiviral drug offers interesting insights. With this combined model, viral load after both short and long term treatment can be predicted and the effect of drugs (with different mechanisms of action) on various viral replication steps could be better mechanistically described. This combined model has been developed for maraviroc, a CCR5 non-competitive antagonist. The anchor point of the operational model in the differential equations of the viral dynamic model is the infection rate constant, which is assumed to be dependent on the number of free activated receptors on each target cell. With this combined model it is now possible to simulate simultaneously the binding of maraviroc to the CCR5 receptor and the viral load after short and long term treatment (Figure 17).

Figure 17. Simultaneous Simulation of Maraviroc Binding to CCR5 receptor and Effect on Viral Load at Equilibrium using a Combined Operational Model of (Ant-)agonism and Viral Dynamic Model



The model also makes it possible to provide an explanation for the apparent discrepancy between the in vivo binding of maraviroc to the CCR5 receptor (K_D=0.089 ng/mL) and the estimated in vivo inhibition (IC_{50}=7.65 ng/mL) of the infection rate. The operational model introduces the assumption that the target cells, when activated, express more receptors (spare receptors) than needed. In the presence of an antagonist, these spare receptors need to be blocked first before any decrease of the infection rate (and the viral load) can be detected. The estimated K_E (operational constant or concentration of receptors occupied by an'agonist' that elicits 50% of the maximum response/effect) value indicates that only 1.2 % of the activated receptors are necessary to elicit 50% of the maximum infection rate. Therefore it is concluded the CCR5 receptor occupancy assay has insufficient discriminatory power to aid dose selection.

Cardiovascular Pharmacodynamic Effects

QT Interval

Results from hERG channel and dog isolated Purkinje fibre studies suggest that maraviroc has the potential to block the I_{Kr} current and affect cardiac repolarisation in vivo at unbound plasma concentrations greater than 3 μM (1541 ng/mL), which represents a margin of approximately 10-fold versus the mean unbound C_{max} in HIV-1 infected patients at a dose of 300 mg BID. Monitoring of ECG parameters was advised during early clinical studies with maraviroc (Section 2.6.2, Module 2.6.2 Pharmacology Written Summary).

Results from Study A4001001, the single-dose escalation study, demonstrated a treatment-related increase of 10.7 msec in the QTc interval (QTcF Fridericia's correction) at 2 hours after dosing with 1200 mg maraviroc. However, QTcF did not appear to optimally correct

for heart rate in this population and a study-specific population correction factor (QTcP) was therefore derived using the before dosing and placebo data. Using this population correction, two hours after a single dose of 1200 mg maraviroc, there was a mean increase in QTcP of 7.8 msec. Following multiple dosing, of between 25 mg BID and 600 mg QD (A4001002), there was no evidence of a clinically significant treatment-related effect on the QTc interval over the dose range studied (mean free C_{max} at steady state after 600 mg QD was 333 ng/mL).

In order to assess the potential clinical significance of the results seen in A4001001, a prospectively designed QT study (A4001016) was conducted. No clear relationship between maraviroc plasma concentration and maximum increase in QTcI was observed at the time of the maximum increase from placebo, even at the 900-mg dose (corresponding to 3 times the 300 mg unit dose to be used in the Phase 2b/3 studies, and approximately 2· the mean free C_{max} seen in HIV-1 infected patients receiving 300 mg BID in Study A4001007). Similarly, there was no clear relationship between the change from placebo in QTcI versus the maraviroc plasma concentrations at an individual's T_{max}.

A population analysis using mixed effects modelling was employed to explore and characterise the plasma concentration-QTc response relationship (Module 5.3.4.1, Exposure-Response Modelling Report for Maraviroc Exposure on QT interval corrected for heart rate. Phase 1 Data [Protocol A4001016]). 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 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 unbound 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.

In conclusion, there were no clinically significant increases in QT interval at maraviroc doses up to and including 900 mg. The effect of maraviroc on the QTc interval is described in Section 2.7.4.2.1.5, Module 2.7.4, Summary of Clinical Safety.

Cardiovascular Function

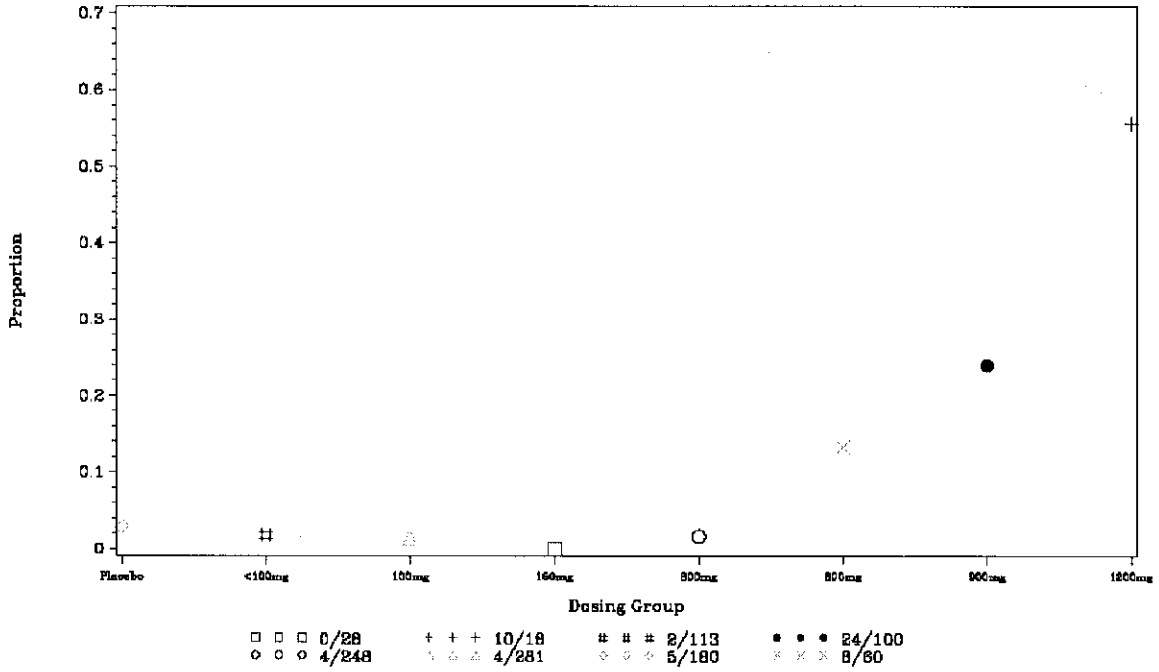
Maraviroc is a weak inhibitor of agonist binding to the human α_{2A} adrenergic receptor and is an antagonist at alpha adrenergic receptors in canine venous tissue giving rise, in vitro, to vasodilatation (Section 2.7.2.2.1). In Study A4001001, 4/9 subjects had dose limiting postural hypotension after a single maraviroc dose of 1200 mg. In Phase 1 studies, the majority of events of postural hypotension occurred during protocol defined postural blood pressure measurements. Events of postural hypotension were recorded as orthostatic or postural hypotension when the subject complained of symptoms of dizziness or light-headedness on standing and had a recorded (where possible) postural drop in blood pressure of greater than 20mmHg systolic or 10mmHg diastolic (Section 2.7.4.2.1.5, Module 2.7.4 Summary of Clinical Safety). Extensive profiling of the interaction of maraviroc with

adrenergic receptors was performed, but there was no consistent adrenergic mediated activity by maraviroc (Section 2.4.5.1.3, Module 2.4, Nonclinical Overview).

In clinical studies, all events of postural hypotension are rare at doses =300 mg where the incidence is similar to placebo, but the frequency increases at doses >300 mg. In Study A4001019, 5/9 subjects had postural hypotension after multiple doses of maraviroc 900 mg QD, as did 6/9 of the same cohort, following dose escalation to multiple doses of maraviroc 1200 mg once daily. Postural hypotension did not occur after 900 mg BID following dose escalation from 600 mg BID, although 7/8 had dizziness and light-headedness.

The observed incidence of postural hypotension across Phase 1/2a studies was plotted against unit dose as shown in Figure 18, indicating that the incidence of postural hypotension increased above that of placebo at unit doses of =600 mg maraviroc.

Figure 18. 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.

In order to investigate the haemodynamic changes that occur with maraviroc, a specific pharmacodynamic study was performed in healthy male subjects (Study A4001033). The sponsor chose 900 mg for this study as it was the maximum tolerated single dose of maraviroc. The pharmacodynamic changes observed in Study A4001033 following maraviroc 900 mg are consistent with those expected of a mild vasodilator with a fully compensated haemodynamic response maintaining supine blood pressure. However, 3/16 subjects experienced postural hypotension, suggesting that there was not always complete compensation for orthostatic changes. There was no relationship between percentage change

from baseline in ICG parameters or change from baseline in supine blood pressure and pulse rate compared with maraviroc plasma concentration.

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 modelling was employed. No significant placebo effect was identified in the baseline models and in the final model, 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) (Module 5.3.4.1, Population Pharmacokinetic/Pharmacodynamic Analysis of Blood Pressure for A4001002 and A4001006 Data from Phase I of Maraviroc).

In conclusion, events of postural hypotension are rare at the therapeutic dose, 300 mg QD or BID of maraviroc. The effect of maraviroc on postural hypotension and cardiac function is described in Section 2.7.4.2.1.5, Module 2.7.4 Summary of Clinical Safety.

2.7.2.3.3. Maraviroc Dose Selection and Exposure/Response Relationship

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 this population in Phase 2b/3 was based on 10 day monotherapy data, pharmacokinetic/pharmacodynamic modelling, clinical trial simulations, drug-drug interaction studies, preclinical serial passage resistance studies and a safety database of over 400 subjects followed for up to 4 weeks.

Two monotherapy studies (A4001007 and A4001015), have been performed in treatment naïve patients or patients who had not received antiretroviral treatment in the previous eight weeks. These studies investigated the antiviral effects, pharmacokinetics, safety and toleration of various doses and regimens of maraviroc administered for 10 days as monotherapy. The conclusions from these studies were that antiviral effects were related to daily dose/exposure, such that maximal short-term anti-viral effects were seen for total daily doses above 200 mg, administered as a once or twice a day regimen.

A model-based decision-making approach was used during the development programme of maraviroc to inform dosing decisions. The model had been developed for maraviroc prior to any clinical data being available for maraviroc (Rosario MC et al, 2005) and then updated when clinical data from Study A4001007 became available. The model was then successfully used to predict short term monotherapy results for study A4001015 which assessed once daily dosage regimens and the effect of food (Rosario MC et al, 2006). Simulations for short term monotherapy predicted that once daily regimens would be equivalent to twice daily regimens at half the dose, that is, the viral load decline for 150 mg twice daily is equivalent to 300 mg once daily.

Whilst a significant and similar drop in viral load was demonstrated for a number of doses in the monotherapy studies this does not necessarily translate to equivalent long term efficacy (24 or 48 weeks) for all doses. A model based (semi-mechanistic) approach which incorporates viral dynamics is necessary for the translation of short term monotherapy to long term dose predictions. Therefore, subsequent to the updating of model parameters from the analysis of concentration and viral load data from both short term monotherapy studies, a fully integrated pharmacokinetic-pharmacodynamic viral load model (incorporating resistance, adherence, other drugs and dropout components) was developed for clinical trial simulation (Module 5.3.4.2, Modelling and Simulation of Maraviroc [UK-427,857] to Support Phase 3 Trial Decisions). An Equivalent Constant Concentration (ECC) varying by maraviroc regimen was used as the maraviroc exposure input for simulations. The adjustments to ECC (dose dependency, fed/fasted status and once versus twice daily) were derived from the concentration data from monotherapy studies A4001007 and A4001015. Given that at that time there was no long-term combination data available for any CCR5 antagonist, a number of assumptions around resistance, compliance, adherence and baseline viral load were explored. Simulations were performed for the outcome of Phase 2b/3 trials in a) treatment naïve patients receiving zidovudine/lamivudine in combination with maraviroc and b) treatment experienced patients on OBT with and without maraviroc.

Population simulations of viral load over 48 weeks were performed for maraviroc exposures for doses of 100 and 300 mg BID (plus zidovudine/lamivudine) under different resistance and baseline viral load assumptions. With the outcome expressed as a success rate (proportion of patients with <400 copies/mL), the simulations predicted a 71% success rate at 48 weeks in an intention-to-treat population (11% dropout) for a 300 mg BID maraviroc dose in treatment naïve patients with a mean baseline viral load of 4.8 $\log_{10}$ copies/mL. These results and thus this dose would be expected to match efavirenz in response. Doses of 100 mg BID were predicted to give substantially lower efficacy (36% at 48 weeks). The effect of taking maraviroc with and without food was also explored with the simulation model. Thus if every dose of maraviroc was taken at the same time as a high fat meal for 48 weeks (25% reduction in ECC compared with fasted state, based on 150 mg fed/fasted data from study A4001015), a reduction in efficacy (proportion of subjects with viral load of <400 copies/mL) of 4 and 7% for BID and QD 300 mg maraviroc would be expected when compared with always taking doses in a fully fasted state. This is likely to be the "worst case" food effect that might be observed with maraviroc in long term studies at these doses (Module 5.3.4.2, Modelling and Simulation of Maraviroc (UK-427,857) to Support Phase 3 Trial Decisions, Addendum).

Notwithstanding the difficulties of making assumptions about OBT, clinical trial simulations were also performed for the treatment-experienced population. Assumptions included that baseline viral load would be higher (5 versus 4.8 $\log_{10}$ copies/mL) and would have a higher standard deviation in this population compared with treatment naïve subjects and that OBT performance would be similar to the enfuvirtide pivotal studies (Module 5.3.4.2, Modelling and Simulation of Maraviroc (UK-427,857) to Support Phase 3 Trial Decisions). Assuming no resistance to maraviroc and no pharmacokinetic drug interactions affecting maraviroc exposure, the population simulations for 300 mg BID maraviroc predicted a change from baseline in viral load of -2.39 versus -0.78 $\log_{10}$ copies/mL for OBT alone (before dropout). The success rate (<400 copies/mL) at 24 weeks for OBT alone and maraviroc 300 mg BID

plus OBT was predicted to be 18% and 70% (approximately 62% intention- to-treat) respectively. Maraviroc regimens which produce similar daily exposure to that of 300 mg BID in the monotherapy studies (i.e. an ECC of approximately 87 ng/mL) would be expected to give similar mean responses to those predicted for the 300 mg BID regimen above. Similar to predictions for treatment naïve subjects, doses of 100 mg BID were predicted to give less efficacy overall, however, when added to inadequate regimens, doses of 300 mg daily or lower would be expected to induce substantial drops in viral load. Thus in both treatment naïve and treatment experienced subjects the simulation results suggested a substantial advantage of 300 mg BID maraviroc doses over 100 mg BID doses (or their daily exposure equivalents). However, the anti-viral effects seen in the maraviroc 10 day monotherapy studies at daily doses of 200 mg and above were in line with those seen with short term monotherapy for other anti-retroviral agents, which have subsequently shown robust long term anti-viral effects in combination with other anti-retroviral agents in treatment experienced patients. Thus a 300 mg once daily dose (or 150 mg maraviroc with PI) was also tested in the Phase 2b/3 programme.

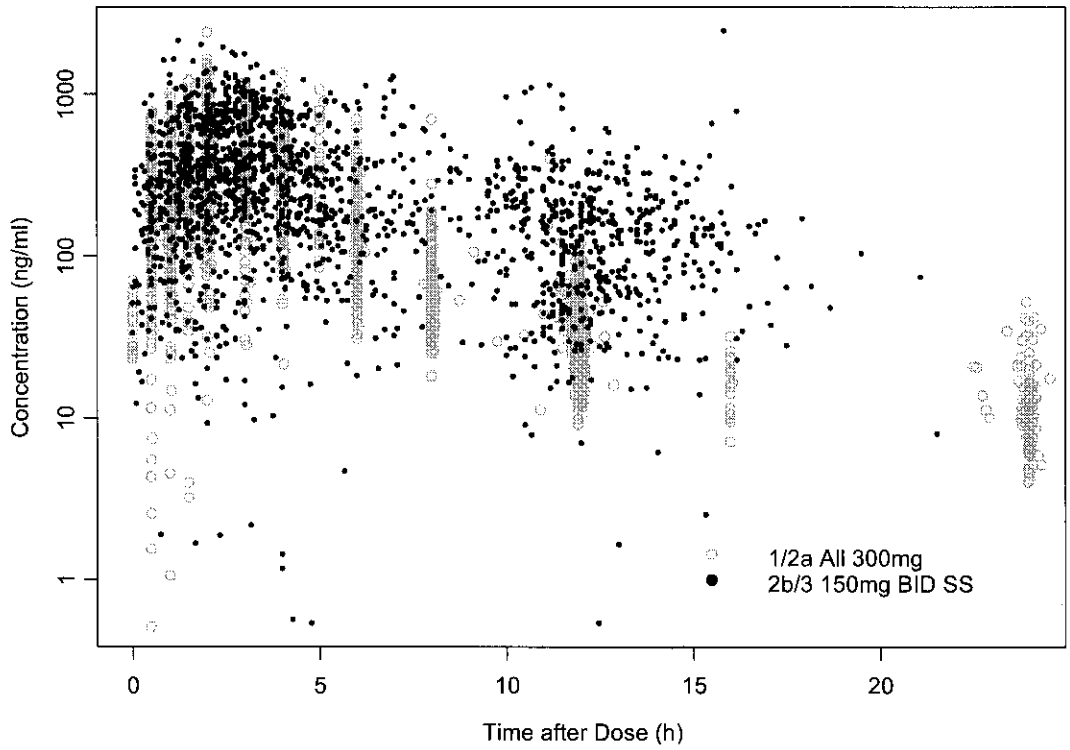
Evaluation of safety data from the Phase 1/2a studies identified postural hypotension as the dose limiting adverse event, occurring at a frequency greater than placebo at unit doses of >300 mg. These events were temporally related to C_{max}. The extensive Phase 1 programme did not elucidate any apparent AUC driven adverse events. Based on these data, it was decided that dose adjustments to compensate for interactions with co-administered agents, should be based on maintaining a C_{max} equivalent to 300 mg doses given alone. Controlling for the peak concentration, whilst potentially allowing total exposure to exceed that of 300 mg alone, was deemed to give an optimal balance between safety and efficacy.

Since maraviroc is a substrate for both CYP3A4 and P-gp, 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 optimized background therapy. 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. The exception to this was saquinavir/r which led to a 4-5 fold and 8-10 fold increase in C_{max} and AUC respectively. 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 singe 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. CYP3A4 inducers (including efavirenz) have been shown to reduce maraviroc exposure, although when given with protease inhibitors, the net effect was shown to be inhibition, and hence the downward dose adjustment of maraviroc is still recommended even if both efavirenz and PIs are contained within the OBT.

Results from the population pharmacokinetic analysis of data from Study A4001029 and 500 patients from studies A4001027 and A4001028 showed that the expectations of the pharmacokinetic behaviour of maraviroc were consistent with observations in Phase 2b/3

(Module 5.3.3.5 Preliminary Population Pharmacokinetic Analysis of Maraviroc in Pooled Phase 2b/3 Studies of Treatment Experienced Patients on Optimized Background Therapy). The dose adjustment strategy for CYP3A4 and P-gp inhibitors appears appropriate, in that in patients receiving 150 mg maraviroc where samples for maraviroc concentrations were taken around C_{max} (sampled in 150 mg BID arm), measured concentrations were similar to those seen with 300 mg doses in Phase 1 and 2a studies (Figure 19). The interacting drugs with least effect on maraviroc exposure (amprenavir, fosamprenavir, delavirdine and some of their combinations with other PIs) produced average maraviroc exposure similar to the 300 mg dose in monotherapy studies. For other PIs, their rank order of effect on maraviroc exposure was similar to the Phase 1 predictions (section 2.7.2.3.5).

Figure 19 150 mg BID Maraviroc Concentrations from Combined Phase 2b/3 Overlaid with all 300 mg Phase 1/2a Maraviroc Concentrations

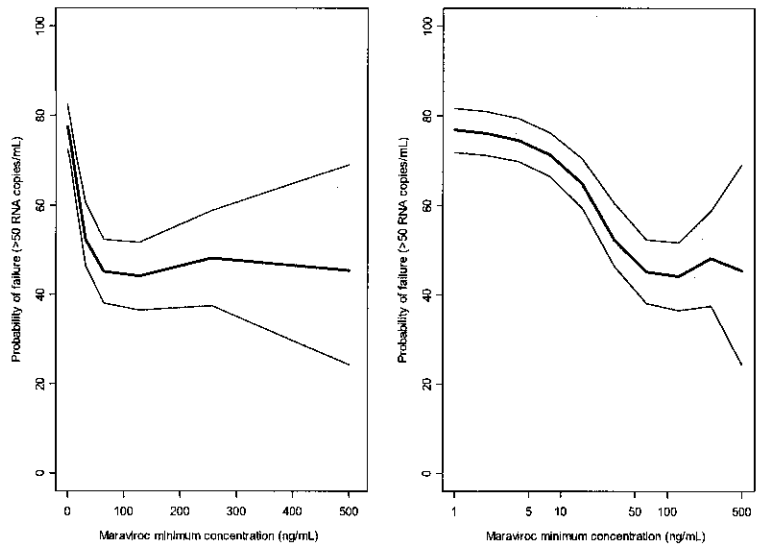


Taken together, these data indicate that the maraviroc dose modification recommendations for the Phase 2b/3 clinical studies were successful in limiting C_{max} so as not to significantly exceed that seen with 300 mg in the absence of interacting agents, while maintaining an average plasma exposure (C_{ave}) that was at or above that seen with 300 mg in the absence of interacting agents (median estimated increase in C_{ave} over 300 mg reference of 1.56 fold for maraviroc QD and 1.73 for maraviroc BID).

A preliminary exposure response analysis was performed with exposure and efficacy data pooled from the first 500 subjects from studies A4001027 and A40010128 (Module 5.3.4.2,

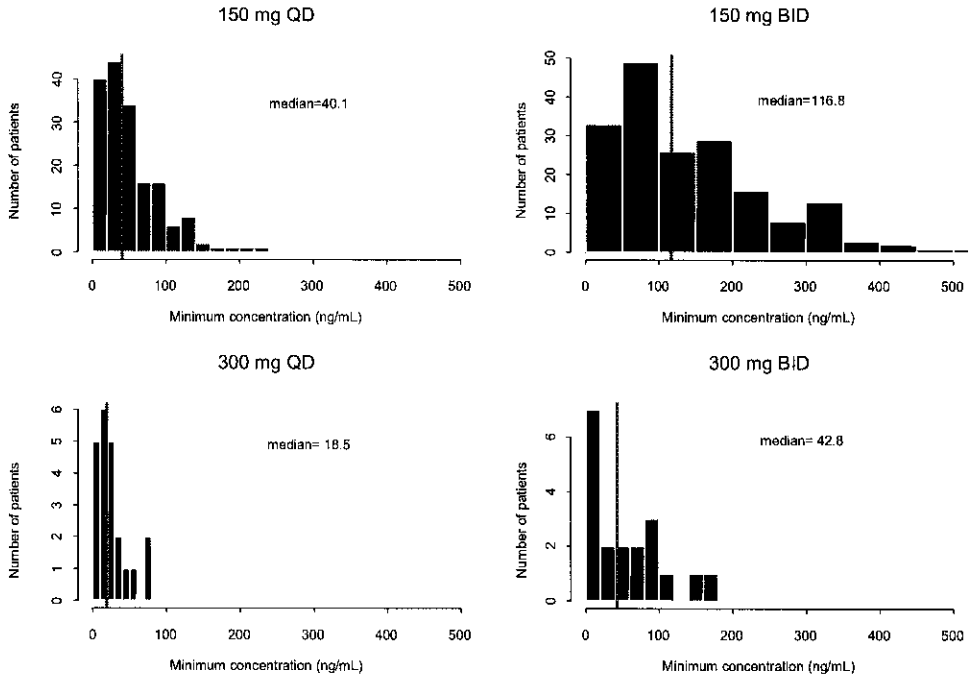
Preliminary Population Pharmacokinetic Analysis of Maraviroc in Pooled Phase 2b/3 Studies of Treatment Experienced Patients on Optimized Background Therapy). The effect of maraviroc exposure and various prognostic factors on binary viral load endpoints and CD4 count change from baseline at week 24 in treatment-experienced HIV-1-infected patients with OBT has been analysed using generalized additive models (GAM). For all 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 exposure response relationship for maraviroc for the most rigorous efficacy endpoint (failure as >50 copies/ml) derived from the GAM modelling is illustrated in Figure 20.

Figure 20. 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.

Figure 21. Distribution of the Maraviroc Individual Minimum Concentration (C_{min}) in the 4 Treatment Groups of Studies A4001027 and A4001028 (data subset at week 24).



The planned interim analyses for studies A4001027 and A4001028, have demonstrated statistical superiority of both maraviroc QD and maraviroc BID over placebo. In addition, all of the secondary endpoint results at Week 24 are 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 (Figure 21) due to the pharmacokinetic interactions of maraviroc with OBT. This has resulted in similar median exposure in patients who received 150 mg QD (with a PI and/or delavirdine) as was observed (and would be expected) in patients taking 300 mg BID. Based on the exposure response relationships (such as Figure 20) and with no safety or tolerability issues identified in the Phase 2b/3 treatment experienced HIV patient programme, maraviroc regimens of 150 QD and BID (with a PI and/or delavirdine) and 300 mg maraviroc BID would produce concentrations expected to be near maximally efficacious in the majority of patients. However, the risk of under exposure with 150 mg maraviroc QD increased when maraviroc was combined with low and moderate CYP3A4 inhibitors in the OBT (amprenavir, atazanavir, fosamprenavir, delavirdine, nelfinavir and some of their combinations with other PIs), based on matching or exceeding exposure observed for 300 mg BID without interacting agents in Study A4001007 (Module 5.3.4.2, Preliminary Population Pharmacokinetic Analysis of Maraviroc in Pooled Phase 2b/3 Studies of Treatment Experienced Patients on Optimized Background Therapy).

2.7.2.3.4. Studies in Special Populations (Intrinsic Factors)

Studies with maraviroc have not yet been conducted in paediatric patients.

Women comprise approximately 11% of the Phase 2b/3 study population and similar to the number of women recruited in other recent anti-retroviral trials (Lalezari JP et al, 2003), and is reasonable representative of a heavily treatment-experienced HIV-1 population. The Phase 2b/3 study population is approximately 80% white and of a similar racial distribution to other recent trials. The population was required to be heavily treatment-experienced and so the ethnic characteristics of the study population may reflect, in part, the degree of access to health care within the developed world (Section 4.2.2, Risk Management Plan, Module 1.8 Information Relating to Pharmacovigilance).

Therefore, population modelling across Phase 1 and 2a studies was used to try to evaluate the effects of intrinsic factors on maraviroc pharmacokinetics (Module 5.3.3.5, Population Pharmacokinetics of Maraviroc After Oral Tablet Administration – A Pooled Analysis of Phase 1/2a Data). Plasma maraviroc concentration-time data from 413 subjects from 17 studies (single and multiple dose) were included in the population pharmacokinetic analysis (section 2.7.2.1.3). Most of the concentration-time profiles were obtained after doses of 100 mg (40.4%) and 300 mg (38%). Median age was 30 (range 18-53) years. There were 317 males (76.8%), 48 (11.6%) HIV-1 infected subjects, 95 Asian subjects (23%) and 14 Black subjects (3.4%). In the final covariate search the race effect was tested as binary (Asians versus reference of all non-Asians). Maraviroc concentrations were modelled with a 2-

compartment model, with first-order absorption and a lag time on the absorption. The resulting models and parameter estimates have been used to support the modelling of sparse data collected in the Phase 2b/3 studies.

2.7.2.3.4.1. Age

Phase 1/2a studies enrolled healthy subjects and HIV-1 infected patients within the age range of 18 to 55 years; therefore the effect of age on maraviroc pharmacokinetics was assessed in the population pharmacokinetic analysis of pooled Phase 1/2a data (section 2.7.2.1.3). Although a statistically significant age effect was found on inter-compartmental clearance (Q), age was not found to have any effect on maraviroc pharmacokinetic parameters that impact upon maraviroc exposure (namely bioavailability or clearance).

2.7.2.3.4.2. Gender

There were no significant gender effects on maraviroc pharmacokinetic parameters as assessed in the population pharmacokinetic analysis of pooled Phase 1/2a data (section 2.7.2.1.3).

2.7.2.3.4.3. Race

The population pharmacokinetic analysis of pooled Phase 1/2a data found the typical Asian subject to have a 26.5% increase in AUC compared to the typical non-Asian subject, independent of dose. This 0.265 fold higher maraviroc exposure is not considered clinically significant and no dose adjustment would be recommended for this difference.

However, Study A4001038 was specifically designed to compare Asians (N=12) versus Caucasians (N=12), the pharmacokinetics of maraviroc were found to be similar in the two groups of subjects. Geometric mean ratios of AUC_{24} and C_{max} were 0.99 (90% CI 0.84 to 1.16) and 1.11 (90% CI 0.90 to 1.37) respectively (Table 19).

2.7.2.3.4.4. Renal/Hepatic Impairment

The pharmacokinetics of maraviroc have not been studied in patients with renal impairment. Renal elimination is a minor route of elimination for maraviroc and therefore no effects of mild to moderate renal impairment the pharmacokinetics of maraviroc would be expected.

A single dose study in patients with mild or moderate hepatic impairment is currently ongoing.

2.7.2.3.4.5. HIV-1 Infection

The effect of HIV-1 infection on maraviroc pharmacokinetics was assessed in the population pharmacokinetic analysis of pooled Phase 1/2a data (section 2.7.2.1.3). This analysis included 365 healthy subjects and 48 HIV-1 infected patients. No effect of HIV status (i.e. whether a subject was infected with HIV-1 or not) on maraviroc pharmacokinetic parameters was found.

2.7.2.3.5. Drug Interactions (Extrinsic factors)

The effects of drug interactions on maraviroc pharmacokinetics have been evaluated by both clinical studies and pharmacokinetic modelling of Phase 1, 2a and 2b/3 studies.

In vitro studies have confirmed that the metabolism of maraviroc, and generation of the primary metabolite UK-408,027, is primarily governed by CYP3A4. No other cytochrome P450 enzymes have been shown to contribute significantly to maraviroc's metabolism. Caco-2 cell work has also suggested that maraviroc is a substrate for P-gp. Maraviroc does not appear to inhibit any of the major cytochrome P450's in vitro (IC_{50}'s > 30 μM). Clinical data suggests that maraviroc does not induce CYP3A4 at doses up to and including 300 mg BID and 600 mg QD (as determined by urinary 6β-hydroxycortisol/cortisol ratios). Investigation of debrisoquine metabolic ratios, suggest that maraviroc does not inhibit CYP2D6 at doses up to and including 300 mg BID. At 600 mg QD, there was an increase in debrisoquine metabolic ratio, suggesting some potential for inhibition at this dose, however no subjects were converted from 'extensive metabolisers' to 'poor metabolisers'.

The drug interaction strategy has focussed on 1) the effect of maraviroc on 'other drugs', and 2) the effect of 'other drugs' on maraviroc.

Effect on maraviroc on 'other drugs'.

The effect of maraviroc on the pharmacokinetics of a midazolam (sensitive probe CYP3A4 substrate), oral contraceptives and Zidovudine/Lamivudine* (lamivudine/zidovudine) have been investigated (section 2.7.2.2.6.1). A summary of the results is presented in Table 46.

Table 46. 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}	Cmax
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)

Source: A4001005 CSR Tables 5.5.2 and 5.8.2, A4001012 CSR Table 5.4.1, A4001020 CSR Table 5.4.2 and 5.8.2.

The data demonstrates that maraviroc does not have a clinically significant effect on the pharmacokinetics of midazolam, ethinylestradiol, levonorgestrel, zidovudine and lamivudine. As maraviroc did not affect the pharmacokinetics of midazolam, it is unlikely that maraviroc will affect the pharmacokinetics of other CYP3A4 substrates of importance to the HIV-1 infected population, such as methadone.

* : 新薬承認情報提供時に置き換えた

Effect 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 (~ 23% of total clearance), with a significant contribution of active processes (section 2.7.2.3.1), the effect of substrates and inhibitors of renal clearance (tenofovir and Trimethoprim/Sulfamethoxazole*) 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 47.

* ：新薬承認情報提供時に置き換えた

Table 47. 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}	Cmax
CYP3A4 and/or P-gp Inhibitors				
Ketoconazole 400 mg QD	12	100 mg BID	5.00 (3.98, 6.29)	3.38 (2.38, 4.78)
Saquinavir (Saquinavir*) 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 (Saquinavir*)/r 1000 mg/100 mg BID	8	100 mg BID	8.32 (6.11, 11.3)	4.23 (2.60, 6.88)
Saquinavir (Saquinavir*) /r 1000 mg/100 mg BID	11	100 mg BID	9.77 (7.87, 12.14)	4.78 (3.41, 6.71)
Lopinavir/Ritonavir* 400 mg/100 mg BID	8	100 mg BID	3.83 (2.81, 5.21)	1.61 (0.99, 2.63)
Lopinavir/Ritonavir* 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				
Lopinavir/Ritonavir* + 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(Saquinavir*) /r + efavirenz 1000 mg/100 mg BID + 600mg QD	11	100 mg BID	5.00 (4.26, 5.87)	2.26 (1.64, 3.11)
Tipranavir/r 500 mg/200 mg BID	12	150 mg BID	1.02 (0.850, 1.23)	0.86 (0.61, 1.21)
Lopinavir/Ritonavir* + 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)
Renal Substrates and/or Inhibitors				
Trimethoprim/Sulfamethoxazole* 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)

Effect of CYP3A4 and/or P-gp inhibitors/inducers on maraviroc

A range of clinically relevant and probe CYP3A4/P-gp inhibitor/inducers have been investigated.

* ：新薬承認情報提供時に置き換えた

As predicted from in vitro data, drugs that inhibit CYP3A4 and/or P-gp lead to increases in maraviroc exposure. In general CYP3A4 and/or P-gp inhibitors increase C_{max} and AUC by 2-3 fold, and 3-5 fold respectively (Table 47). The exception to this was saquinavir/r (1000 mg saquinavir/100 mg ritonavir BID) which led to a 4-5 fold and 8-10 fold increase in C_{max} and AUC respectively (Table 47). The reason for this much larger interaction is not understood. Decreasing the maraviroc dose appeared to compensate for the increases caused by metabolic inhibition.

The CYP3A4 and/or P-gp inducers (efavirenz and rifampicin) reduced maraviroc exposure by approximately 0.5 to 0.7 fold (Table 47). Increasing the maraviroc dose appeared to compensate for the reductions caused by metabolic induction.

Co-administration of an inducer (efavirenz) and protease inhibitors (Lopinavir/Ritonavir* and saquinavir/r), reduced the magnitude of the inhibition, but still led to a net increase in maraviroc exposure remained (Table 34 and Table 35). These results confirm the data previously generated in healthy volunteers and support the proposed dose adjustments for maraviroc.

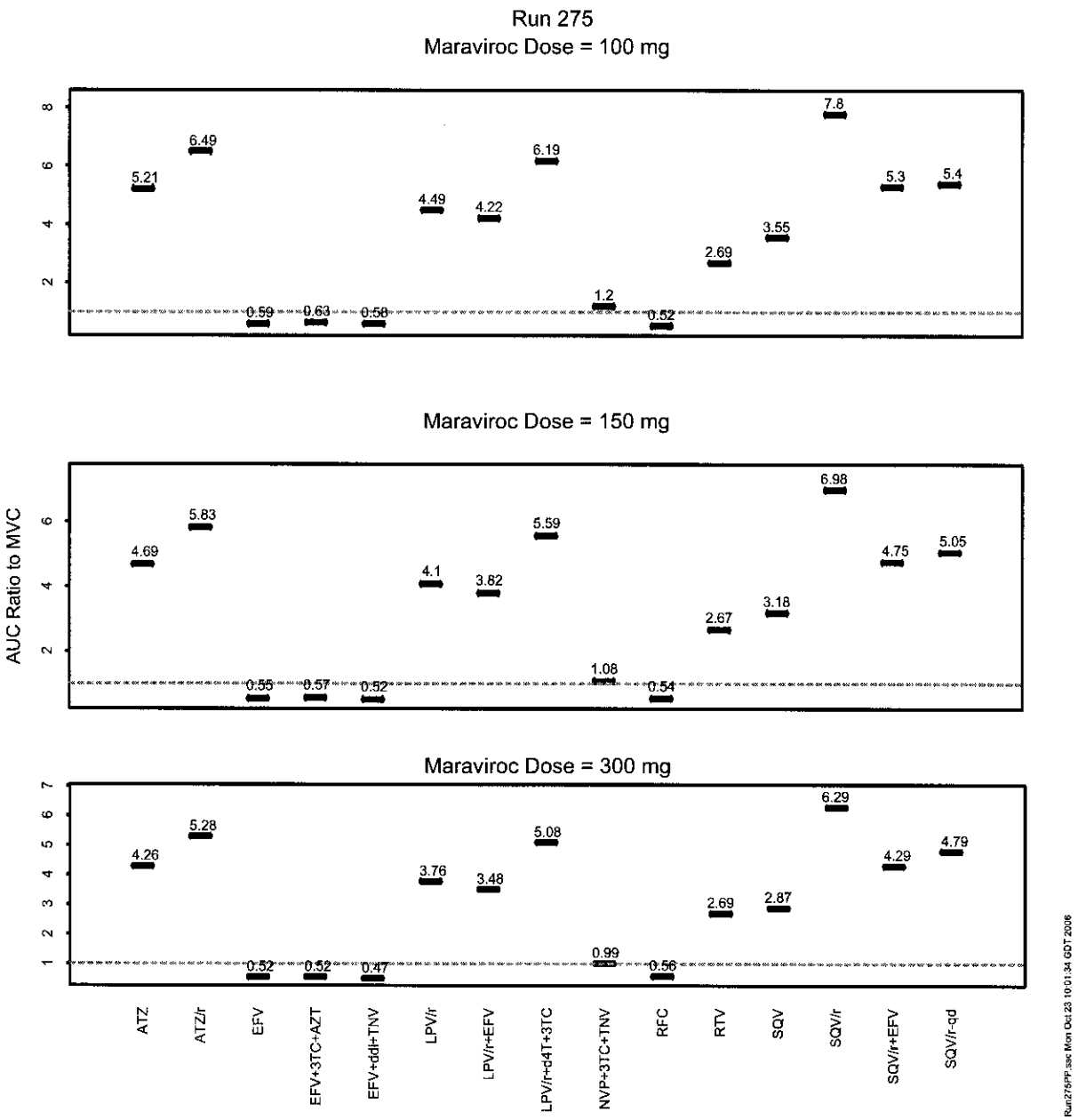
Tipranavir/r (tipranavir 500 mg/ ritonavir 200 mg BID) is thought to lead to net CYP3A4 inhibition and P-gp induction. These opposing effects resulted in no apparent change in the steady state pharmacokinetics of maraviroc.

The population analysis of Phase 1 drug-drug interaction data used a previously developed 2-compartment partition model based on Phase 1/2a healthy subjects and HIV-infected patients to describe the parent maraviroc concentrations obtained in the presence of the different concomitant antiretroviral drugs. All parameters were fixed to their population estimates from the Pooled Phase 1/2a analysis except for E_H (extraction ratio) and $F_{ABS\text{-}ED50}$ (dose at which 50% of absolute bioavailability was achieved), their inter-subject variability and residual variability parameters which were estimated (Module 5.3.3.5, The Impact of Interacting Antiretroviral Drugs on Maraviroc Pharmacokinetics After Oral Tablet Administration – A Pooled Population Pharmacokinetic Analysis of Phase 1 Data).

The predicted AUC ratios for different doses of maraviroc with CYP3A4 and/or P-gp inhibitors or inducers are shown in Figure 22. In general, the predicted AUC ratios are consistent with those reported in clinical studies, some of which are presented in Table 47.

* ：新薬承認情報提供時に置き換えた

Figure 22. Predicted AUC Ratios Stratified by Combination of Concomitant Antiretroviral Drugs and Maraviroc (MVC) Dose.



Subsequent to this a population pharmacokinetic analysis was performed on treatment-experienced HIV-1 infected patients from Phase 2b/3 studies. Exploration of the interactions was performed with graphical (box and whisker plot) analysis and comparative summary statistics for OBT groupings of particular interest and tree regression analysis of maraviroc average concentration (C_{ave}) normalised for maraviroc dosing regimen. The *Post hoc* Bayesian estimates of pharmacokinetic parameters, obtained from the application of the 2-compartment partition model to the sparse data, gave reasonable individual pharmacokinetic profiles and exposure variables, suitable for exposure response analysis.

Full details of this analysis can be found in Module 5.3.3.5 (Preliminary Population Pharmacokinetic Analysis of Maraviroc in Pooled Phase 2b/3 Studies of Treatment Experienced Patients on Optimized Background Therapy).

Different protease inhibitors produced differential effects on maraviroc pharmacokinetics the rank order of which is broadly consistent with the Phase 1 data (Table 47 and Figure 22). 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.

Overall, 300 mg doses (in the absence of PIs) gave comparable exposure and median C_{ave} in the Phase 2b/3 studies to those seen in the monotherapy studies. Dose correction for PIs (i.e. reduction to 150 mg) appeared to have corrected C_{max} to the 300 mg dose equivalent but as predicted, did not generally fully correct concentrations in the terminal phase of the concentration curve. The ratios of the median in C_{ave} for the 150 mg groups, compared with the Phase 2a monotherapy 300 mg groups, were 1.73 and 1.56 fold those for BID and QD, respectively.

In summary, the results from this analysis support the dose adjustment strategy determined from Phase 1 studies, i.e. the downwards dose adjustment to 150 mg maraviroc when delavirdine and PIs are included in the OBT. This dose adjustment strategy achieved appropriate correction of maraviroc C_{max} (similar to that of 300 mg dose equivalent in Phase 2a monotherapy studies) even with interactants with the strongest effects on maraviroc exposure (saquinavir/r and Lopinavir/Ritonavir*).

Effect of Substrates and Inhibitors of Renal Clearance on maraviroc

As renal clearance accounts for ~23% of total clearance of maraviroc and involves active process, the effect of compounds that are substrates (tenofovir) and inhibitors (Trimethoprim/Sulfamethoxazole*) of renal clearance on the pharmacokinetics of maraviroc were investigated. Neither tenofovir nor Trimethoprim/Sulfamethoxazole* resulted in a clinically significant change in the steady state pharmacokinetics of maraviroc (Table 37 and Table 38).

2.7.2.3.5.1. Dosing Recommendations for Drug Interactions

The pharmacokinetic data from treatment-experienced HIV-1 patients in Phase 2b/3 studies confirm the findings from Phase 1 studies and support the dose adjustments used for co-administration of maraviroc with inhibitors of CYP3A4 and/or P-gp.

Given the drug interaction data available, a dose adjustment of half the maraviroc dose (i.e. 150 mg instead of 300 mg) is recommended for maraviroc in the presence of protease inhibitors (except tipranavir/r) and other potent CYP3A4 inhibitors including delavirdine. This dose adjustment is also recommended when protease inhibitors are given with CYP3A4 inducers. It is accepted that this proposed dose adjustment may not adequately adjust for increases in overall systemic exposure (AUC) in all instances, particularly for those subjects receiving regimens that include boosted saquinavir. However, whilst anti-viral efficacy appears to be driven by exposure, adverse events appear to be driven by Cmax and as such it

is hoped that this adjustment strategy will optimise efficacy, whilst minimising side effects and the complexity of dose adjustments (Sections 2.7.3.1.4.1.5, Module 2.7.3, Module of Clinical Efficacy and Section 2.7.4.2.1.1, Module 2.7.4, Summary of Clinical Safety).

Drug interaction data have shown CYP3A4 inducing drugs such as efavirenz, in the absence of CYP3A4 inhibitors, reduce the steady state exposure of maraviroc. This finding appears to be supported by the population pharmacokinetic analysis of the Phase 2b/3 studies, although the data are limited. Very limited data are available on the effect of nevirapine on the pharmacokinetics of maraviroc. Comparison of maraviroc AUCs in HIV-1 infected patients (n=8) taking nevirapine as part of their antiretroviral therapy, compared to historical controls (patients receiving maraviroc monotherapy) suggested that nevirapine did not effect the pharmacokinetics of maraviroc. However, again very limited data in the population pharmacokinetic analysis of the Phase 2b/3 studies seems to suggest that maraviroc exposure may be reduced by nevirapine. Although limited, these data are more consistent with the known inducing capabilities of nevirapine. Therefore, it is recommended that patients on a regimen containing CYP3A4 inducers (including efavirenz, nevirapine, rifampicin and rifabutin) in the absence of CYP3A4 inhibitors should double their dose of maraviroc to 600 mg.

Patients on regimens containing boosted tipranavir and NRTIs do not need to adjust the dose of maraviroc and should receive maraviroc 300 mg.

No dose adjustments are required for other drugs when co-administered with maraviroc.

The drug interaction dosing recommendations for maraviroc are summarised in Table 48.

Table 48. Summary of Maraviroc Dosing Recommendations

Concomitant Antiretroviral	Recommended Maraviroc Dose
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 • rifampicin and rifabutin,	600 mg BID
Other concomitant medications, including all other antiretrovirals including tipranavir/ritonavir	300 mg BID

2.7.2.4. Special Studies

There are no special studies to be included in this section.

Conclusions

The recommended dose of maraviroc is 300 mg BID.

The dose should be reduced to 150 mg BID when co-administered with CYP3A4 inhibitors (including protease inhibitors (except tipranavir/ritonavir), delavirdine, ketoconazole, intraconazole, clarithromycin, nefazadone and telithromycin).

The dose should be increased to 600 mg BID when co-administered with CYP3A4 inducers (including efavirenz, nevirapine, rifampicin and rifabutin) in the absence of CYP3A4 inhibitors.

No dose adjustments are recommended on the basis of age, sex or race.

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2.7.2.5. Appendix

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters				
				AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001009 (Belgium)	To investigate the safety and toleration of intravenous (IV) maraviroc and to determine the absolute bioavailability of a 100 mg oral dose.	Cohort 1: double-blind (third party open), four-way crossover study Cohort 2: open, two-way crossover study COHORT 1 Subjects: 8 Sex: 8 M/0 F Mean Age (min/max): 34.5 (27/40) years						
		Evaluated for: PK: 8; Safety: 8	3 mg maraviroc IV (fasted)	57.6	n/c	36.9	0.94	n/c
		Evaluated for: PK: 8, Safety: 8	10 mg maraviroc IV (fasted)	201	n/c	122	0.94	n/c
		Evaluated for: PK: 8; Safety: 8	30 mg maraviroc IV (fasted)	670	687	397	0.91	13.2
		COHORT 2 Subjects: 12 Sex: 12 M/0 F Mean Age (min/max): 32 (22/42) years						
		Evaluated for: PK: 12; Safety: 12	30 mg maraviroc IV (fasted)	645	656	374	0.98	12.0
		Evaluated for: PK: 12: Safety: 12	1x100 mg maraviroc tablet (fasted)	492	506	122	3.08	12.5

Source: Clinical Study Report A4001009 and Tables 1.1, 2.1, 5.1.1.1 and 5.1.2.
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated, t=tlast, the last time with a quantifiable concentration.

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters				
				AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001001 (Belgium)	To determine the safety and toleration of single oral doses of maraviroc.	Double-blind (3rd party open), placebo-controlled, dose escalating, crossover study <u>COHORT A</u> Subjects: 12 Sex: 12 M/0 F Mean Age (min/max): 28.1 (21/45) years						
		Evaluated for: PK: 9; Safety: 9	1 mg maraviroc solution (fasted)	n/c	n/c	n/c	n/c	n/c
		Evaluated for: PK: 9; Safety: 9	10 mg maraviroc solution (fasted)	17.2	n/c	2.92	2.50	n/c
		Evaluated for: PK: 9; Safety: 9	100 mg maraviroc solution (fasted)	583	619	172	3.11	9.86
		Evaluated for: PK: 12; Safety: 12	100 mg maraviroc solution (fed)	205	222	19.3	2.88	14.0
		Evaluated for: PK: 9; Safety: 9	900 mg maraviroc solution (fasted)	7279	7358	1632	1.94	11.3
		<u>COHORT B</u> Subjects: 12 Sex: 12 M/0 F Mean Age (min/max): 29.1 (22/41) years						
		Evaluated for: PK: 9; Safety: 9	3 mg maraviroc solution (fasted)	2.25	n/c	0.58	2.06	n/c

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters				
				AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001001 continued		Evaluated for: PK: 9; Safety: 9	30 mg maraviroc solution (fasted)	80.9	117	15.3	2.89	8.91
		Evaluated for: PK: 9; Safety: 9	300 mg maraviroc solution (fasted)	2187	2313	621	1.64	10.6
		Evaluated for: PK: 9; Safety: 9	1200 mg maraviroc solution (fasted))	11321	11432	2807	1.78	12.5

Source: Clinical Study Report A4001001; Tables 1.1, 2.1, 5.1.1 and 5.1.2.
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated.
t=tlast, the last time with a quantifiable concentration.

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001002 (Belgium)	To investigate the safety, toleration and pharmacokinetics of multiple oral doses of maraviroc in healthy male subjects,	Double-blind (3rd party open), parallel group, placebo controlled single dose and multiple escalating oral dose study						
		Subjects: 5 Sex: 5 M/0 F Mean Age (min/max): 27.8 (19/40) years Evaluated for: PK: 5; Safety: 5	3 mg BID maraviroc Day 1 Day 7 Day 12	 2.66 6.57 5.3	 n/c n/c n/c	 0.67 1.32 0.83	 0.90 1.10 0.56	 n/c n/c n/c
		Subjects: 5 Sex: 5 M/0 F Mean Age (min/max): 23.4 (20/29) years Evaluated for: PK: 5; Safety: 5	10 mg BID maraviroc Day 1 Day 7 Day 12	 11.8 19.0 38.4	 n/c n/c 44.8	 2.26 2.71 3.33	 0.38 1.90 1.30	 n/c n/c 15.20
		Subjects: 9 Sex: 9 M/0 F Mean Age (min/max): 31.6 (24/37) years Evaluated for: PK: 9; Safety: 9	25 mg BID maraviroc Day 1 Day 7 Day 12	 55.2 92.0 147	 74.6 n/c 236	 8.72 18.6 16.2	 3.33 3.13 3.25	 10.8 n/c 13.9
		Subjects: 9 Sex: 9 M/0 F Mean Age (min/max): 30.1 (21/40) years Evaluated for: PK: 9; Safety: 9	100 mg BID maraviroc Day 1 Day 7 Day 12	 556 636 987	 579 n/c 1018	 187 159 181	 2.17 2.50 2.53	 7.76 n/c 18.5

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001002 continued		Subjects: 9 Sex: 9 M/0 F Mean Age (min/max): 32.6 (22/39) years Evaluated for: PK: 9; Safety: 9	300 mg BID maraviroc Day 1 Day 7 Day 12	 2322 2641 4490	 2422 n/c 4561	 538 674 854	 1.64 1.47 2.61	 8.63 n/c 16.4
		Subjects: 9 Sex: 9 M/0 F Mean Age (min/max): 27.9 (21/36) years Evaluated for: PK: 9; Safety: 9	600 mg QD maraviroc Day 1 Day 7 Day 12	 5877 7576 7069	 6074 7650 7177	 1317 1351 1361	 3.33 2.61 2.31	 7.74 15.3 17.2
		Subjects: 9 Sex: 9 M/0 F Mean Age (min/max): 25.1 (22/28) years Evaluated for: PK: 9; Safety: 9	600 mg QD maraviroc Day 1 Day 7 Day 12	 5545 5227 n/c	 5717 n/c n/c	 1322 1204 n/c	 2.08 2.83 n/c	 7.84 n/c n/c

Source: Clinical Study Report A4001002; Tables 1.1, 2.1 and 5.1.1, 5.1.2 and 5.1.3.
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated.
t=tlast, the last time with a quantifiable concentration.

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters				
				AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001003 (Belgium)	To investigate the pharmacokinetics of single oral tablet doses of maraviroc 50, 100 and 600 mg, the effect of food on a single 600 mg tablet dose, the relative oral bioavailability of the 100 mg tablet versus 100 mg oral solution doses and the safety and tolerability of single oral 50, 100 and 600 mg doses.	Open, randomised, five-way crossover study. Subjects: 15 Sex: 15 M/0 F Mean Age (min/max): 31.3 (20/44) years						
		Evaluated for: PK: 13; Safety: 15	1 x 50 mg maraviroc tablet (fasted)	209	227	55	3.00	14.4
		Evaluated for: PK: 15; Safety: 15	1 x 100 mg maraviroc tablet (fasted)	555	576	154	2.33	13.3
		Evaluated for: PK: 15; Safety: 15	100 mg maraviroc solution (fasted)	638	654	170	2.77	12.6
		Evaluated for: PK: 15; Safety: 15	600 mg (4 x 150 mg tablets) maraviroc (fasted)	5636	5703	1221	3.30	11.5
		Evaluated for: PK: 15; Safety: 15	600 mg (4 x 150 mg tablets) maraviroc (fed)	3715	3805	783	3.07	13.6

Source: Clinical Study Report A4001003; Tables 1.1, 2.1 and 5.1.
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated.
t=tlast, the last time with a quantifiable concentration.

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001008 (U.K.)	To investigate the safety of multiple oral doses of maraviroc for 28 days in healthy subjects.	Randomised, double-blind, placebo-controlled, multiple dose study Subjects: 54 Sex: 39 M/15 F Mean Age (min/max): 31.4 (18/52) years						
		Evaluated for: PK: 16; Safety: 16	100 mg BID maraviroc	n/c	n/c	n/c	n/c	n/c
		Evaluated for: PK: 16; Safety: 16	300 mg BID maraviroc	n/c	n/c	n/c	n/c	n/c

Source: Clinical Study Report A4001008; Tables 1.1 and 2.1.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated..
Only trough plasma concentrations (C_{min}) were calculated for this study which can be found in Tables 5.1 and 5.2.

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001010 (U.K.)	To quantify drug related radioactivity in whole blood and plasma and cumulative amount of radioactivity excreted in urine and faeces; to quantify plasma maraviroc concentrations and any metabolites where possible and to characterise faecal and urinary radioactivity and identify metabolites of maraviroc where possible.	Single centre, open study Subjects: 3 Sex: 3 M/0 F Mean Age (min/max): 49.0 (45/53) years Evaluated for: PK: 3; Safety: 3	300 mg maraviroc ^{14}C solution	2055	2086	496	0.83	23.0

Source: Clinical Study Report A4001010; Tables 1.1, 2.1 and 5.1..
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated,
t=tlast, the last time with a quantifiable concentration.

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001019 (U.K.)	To investigate the safety, toleration and pharmacokinetics of multiple oral doses of maraviroc and the effect of dose escalation on toleration.	Randomised, double blind, 3rd party open, placebo-controlled, parallel group study with three cohorts of 12 subjects (9 active treatment, 3 placebo per cohort). Subjects: 36 Sex: 19 M/17 F Mean Age (min/max): 28.1 (18/44) years COHORT 1						
		Evaluated for: PK: 9; Safety: 9	MVC 300 mg BID (days 1-7)	2102	n/c	807	2.00	n/c
		Evaluated for: PK: 8; Safety: 8	MVC 600 mg BID days 8-14	4980	n/c	1808	2.00	n/c
		COHORT 2						
		Evaluated for: PK: 8; Safety: 9	MVC 600 mg BID (days 1-7)	3872	n/c	1177	2.25	n/c
		Evaluated for: PK: 8; Safety: 8	MVC 900 mg BID (days 8-14)	5884	n/c	1629	2.25	n/c
		COHORT 3						
		Evaluated for: PK: 9; Safety: 9	MVC 900 mg QD (days 1-7)	6549	n/c	1960	2.00	n/c
		Evaluated for: PK: 9; Safety: 9	MVC 1200 mg QD (days 8-14)	10394	n/c	2987	1.83	n/c

Source: Clinical Study Report A4001019; Tables 1.1, 2.1 and 5.1.2 and 5.1.3.
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated,
AUC (0-t) is actually AUC (0-12)

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001038 (Belgium, Singapore)	To compare the pharmacokinetics of a single 300 mg dose of maraviroc between Asian and Caucasian healthy male subjects.	An open, single dose study Subjects: 24 Sex: 24 M/0 F Mean Age (min/max): 28.3 (22/40) years						
		Evaluated for: PK: 12; Safety: 12	300 mg Maraviroc (Asian)	2642	n/c	741	3.54	n/c
		Evaluated for: PK: 12; Safety: 12	300 mg Maraviroc (Caucasian)	2675	n/c	666	3.04	n/c

Source: Clinical Study Report A4001038; Tables 13.1.1,13.2.1 and 13.5.1.1 and 13.5.1.2.
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated,
AUC (0-t) is actually AUC (0-24)

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001005 (U.K.)	To investigate the effect of maraviroc compared with placebo on the pharmacokinetics of ethinyloestradiol and levonorgestrel, to assess the pharmacokinetics, safety and tolerability of maraviroc in healthy women.	Randomised, double blind, placebo-controlled, two way crossover study Subjects: 15 Sex: 0 M/15 F Mean Age (min/max): 38.0 (32/45) years Evaluated for: PK: 15; Safety: 15	100 mg maraviroc (plus ethinyloestradiol 30microgram / levonorgestrel 150microgram)	668	n/c	186	2.63	23.9

Source: Clinical Study Report A4001005; Tables 1.1, 2.1 and 5.1.1.
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means for Day 11
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated,
AUC (0-t) is actually AUCtau
Day 11 pharmacokinetic parameters are presented.

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters				
				AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001006 (Belgium)	To investigate the effect of ketoconazole and saquinavir on the steady state pharmacokinetics of maraviroc. To investigate the safety and toleration of maraviroc in the presence of ketoconazole and saquinavir.	An open, randomised, placebo controlled, 2 way crossover study Subjects: 24 Sex: 24 M/0 F Mean Age (min/max): 30.3 (18/43) years <u>COHORT 1</u>						
		Evaluated for: PK: 12; Safety: 12	100 mg maraviroc (+saquinavir 1200 mg TID)	3004	3074	434	2.58	15.73
		Evaluated for: PK: 12; Safety: 12	100 mg maraviroc (+ placebo TID)	742	762	131	2.38	16.12
		<u>COHORT 2</u> Evaluated for: PK: 12; Safety: 12	100 mg maraviroc (+ketoconazole 400 mg QD)	4160	4212	524	2.92	14.23
		Evaluated for: PK: 12; Safety: 12	100 mg maraviroc (+ placebo QD)	894	873	155	3.25	17.03

Source: Clinical Study Report A4001006; Tables 1.1, 2.1, 5.1.2 and 5.4.2.
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated
t=tlast, the last time with a quantifiable concentration

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters				
				AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001011 (Belgium)	To investigate the effects of rifampicin and efavirenz on the steady state pharmacokinetics of maraviroc, to determine the safety and toleration of maraviroc when co-administered with rifampicin or efavirenz and to investigate whether maraviroc dose adjustment can compensate for the effects of rifampicin and efavirenz.	Open, randomised, placebo-controlled, parallel group study. Subjects: 36 Sex: 36 M/0 F Mean Age (min/max): 31.1 (18/45) years						
		<u>GROUP 1</u> Evaluated for: PK: 12; Safety: 12	100 mg maraviroc BID (Day 7)	695	n/c	182	3.25	n/c
		Evaluated for: PK: 12; Safety: 12	100 mg maraviroc BID + Rifampicin 600 mg QD (Day 21)	256	n/c	60.9	2.21	n/c
		Evaluated for: PK: 12; Safety: 12	200 mg maraviroc BID + Rifampicin 600 mg QD (Day 28)	723	n/c	176	2.33	14.1
		<u>GROUP 2</u> Evaluated for: PK: 12; Safety: 12	100 mg maraviroc BID (Day 7)	543	n/c	140.3	3.25	n/c
		Evaluated for: PK: 12; Safety: 12	100 mg maraviroc BID + Efavirenz 600 mg QD (Day 21)	300	n/c	68.1	2.92	n/c
		Evaluated for: PK: 12; Safety: 12	200 mg maraviroc BID + Efavirenz 600 mg QD (Day 28)	624	n/c	163	2.58	13.4
		<u>GROUP 3</u> Evaluated for: PK: 12; Safety: 12	100 mg maraviroc BID (Day 7)	550	n/c	138	2.92	n/c

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters				
				AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001011 continued		Evaluated for: PK: 12; Safety: 12	100 mg maraviroc BID (Day 21)	624	n/c	153	2.58	n/c
		Evaluated for: PK: 12; Safety: 12	100 mg maraviroc BID (Day 28)	580	n/c	138	3.38	12.9

Source: Clinical Study Report A4001011; Tables 1.1, 2.1, 5.1.1, 5.1.2 and 5.1.3
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated
AUC(0-t) is actually AUCtau

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters				
				AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001012 (Belgium)	To investigate the effect of steady state maraviroc on the pharmacokinetics of a single oral dose of midazolam and to investigate the safety and toleration of maraviroc and midazolam when co-administered.	Randomised, double blind, placebo-controlled, two-period crossover study Subjects: 12 Sex: 6 M/6 F Mean Age (min/max): 31.1 (23/444) years						
		Evaluated for: PK: 12; Safety: 12	300 mg (3x100 mg tablets) maraviroc BID + 7.5 mg midazolam	120	122	46.9	1.00	5.34
		Evaluated for: PK: 12; Safety: 12	Placebo tablets + 7.5 mg midazolam	102	104	38.7	0.79	5.25

Source: Clinical Study Report A4001012; Tables 1.1, 2.1. 5.1.1 and 5.1.2.
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated
t=tlast, the last time with a quantifiable concentration

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001013 (Belgium)	To investigate the effects of ritonavir, saquinavir plus ritonavir and lopinavir plus ritonavir on the steady state pharmacokinetics of maraviroc, to explore whether maraviroc dose adjustment can compensate for the effects of ritonavir, saquinavir plus ritonavir and lopinavir plus ritonavir on the steady state pharmacokinetics of maraviroc and to investigate the safety and toleration of maraviroc when co-administered with ritonavir, saquinavir plus ritonavir and lopinavir plus ritonavir.	Open label, randomised, placebo-controlled, four treatment, four group, parallel group study Subjects: 32 Sex: 20 M/12 F Mean Age (min/max): 30.8 (19/44) years <u>GROUP 1</u> Evaluated for: PK: 8; Safety: 8	100 mg maraviroc BID	547	n/c	129	3.00	n/c
		Evaluated for: PK: 8; Safety: 8	100 mg maraviroc BID + ritonavir 100 mg BID	1277	n/c	228	2.80	n/c
		Evaluated for: PK: 8; Safety: 8	50 mg maraviroc BID + ritonavir 100 mg BID	439	n/c	67.7	2.50	n/c
		<u>GROUP 2</u> Evaluated for: PK: 8; Safety: 8	100 mg maraviroc BID	663		154	3.30	n/c
		Evaluated for: PK: 8; Safety: 8	100 mg maraviroc BID + saquinavir 1000 mg BID + ritonavir 100 mg BID	4920	n/c	900	2.60	n/c
		Evaluated for: PK: 8; Safety: 8	25 mg maraviroc BID + saquinavir 1000 mg BID + ritonavir 100 mg BID	839	n/c	133	2.10	n/c
		<u>GROUP 3</u> Evaluated for: PK: 8; Safety: 8	100 mg maraviroc BID	499	n/c	121	4.00	n/c

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters				
				AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001013 continued		Evaluated for: PK: 8; Safety: 8	100 mg maraviroc BID + lopinavir 400 mg BID + ritonavir 100 mg BID	1704	n/c	268	2.90	n/c
		Evaluated for: PK: 8; Safety: 8	50 mg maraviroc BID + lopinavir 400 mg BID + ritonavir 100 mg BID	695	n/c	88.5	2.40	n/c
		GROUP 4 Evaluated for: PK: 8; Safety: 8	100 mg maraviroc BID	597	n/c	138	2.40	n/c
		Evaluated for: PK: 8; Safety: 8	100 mg maraviroc BID + placebo	533	n/c	191	2.00	n/c
		Evaluated for: PK: 8; Safety: 8	100 mg maraviroc BID + placebo	526	n/c	194	1.80	n/c

Source: Clinical Study Report A4001013; Tables 1.1, 2.1. 5.1.1, 5.1.2, 5.1.3 and 5.1.4.
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated
AUC(0-t) is actually AUCtau

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters				
				AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001017 (U.K.)	To investigate the effect of antiretroviral combinations on the pharmacokinetics of a single oral dose of maraviroc 300 mg. To assess the safety and toleration of maraviroc when administered in combination with four selected antiretroviral therapies.	Open, single period, single centre study Subjects: 37 Sex: 37 M/0 F Mean Age (min/max): 38.1 (28/52) years						
		COHORT 1 Evaluated for: PK: 8; Safety: 8	300 mg maraviroc + efavirenz 600 mg QD + Zidovudine/Lamivudine* (lamivudine 150 mg + zidovudine 300 mg)	1060	n/c	389	2.13	n/c
		COHORT 2 Evaluated for: PK: 8; Safety: 8	300 mg maraviroc + efavirenz 600 mg QD + didanosine 250 mg enteric coated QD + tenofovir 300 mg QD.	1093	n/c	447	1.88	n/c
		COHORT 3 Evaluated for: PK: 8; Safety: 8	300 mg maraviroc + Nevirapine 200 mg BID + lamivudine 150mg BID, + tenofovir 300 mg QD.	2273	n/c	900	2.00	n/c
		COHORT 4 Evaluated for: PK: 5; Safety: 5	300 mg maraviroc + Lopinavir/Ritonavir* (lopinavir +ritonavir) 400mg BID +stavudine 40 mg BID + lamivudine 150 mg BID	5987	n/c	1050	2.20	n/c

Source: Clinical Study Report A4001017; Tables 1.1, 2.1. and 5.1.
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated
AUC(0-t) is actually AUCtau

* ：新薬承認情報提供時に置き換えた

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001018 (U.S.A)	To investigate the effect of Trimethoprim/Sulfamethoxazole* on the steady-state pharmacokinetics of maraviroc and assess the safety and toleration of maraviroc when administered in combination with Trimethoprim/Sulfamethoxazole*.	Open label, randomised, placebo-controlled, two-period crossover study. Subjects: 16 Sex: 8 M/8 F Mean Age (min/max): 24.1 (19/43) years						
		Evaluated for: PK: 15; Safety: 15	300mg maraviroc + Trimethoprim/Sulfamethoxazole* 960 mg (800/160 mg)	3388	n/c	848	3.08	n/c
		Evaluated for: PK: 13; Safety: 13	300 mg maraviroc + placebo	3060	n/c	705	2.77	n/c

Source: Clinical Study Report A4001018; Tables 1.1, 2.1 and 5.1.
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated
AUC(0-t) is actually AUC0-12

* ：新薬承認情報提供時に置き換えた

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters				
				AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001020 (U.K.)	To investigate the effect of steady state maraviroc on the steady state pharmacokinetics of Zidovudine/Lamivudine* and assess the safety and toleration of maraviroc when administered in combination with Zidovudine/Lamivudine*.	Double-blind, third party open, randomised, placebo-controlled, two-period crossover study Subjects: 12 Sex: 8 M/4 F Mean Age (min/max): 31.4 (21/45) years						
		Evaluated for: PK: 12; Safety: 12	300 mg maraviroc BID + Zidovudine/Lamivudine* (lamivudine 150 mg + zidovudine 300 mg)	5491	n/c	1305	1.09	n/c
		Evaluated for: PK: 11; Safety: 11	Placebo + Zidovudine/Lamivudine* (lamivudine 150 mg + zidovudine 300 mg)	4852	n/c	1125	1.05	n/c

Source: Clinical Study Report A4001020; Tables 1.1, 2.1 and 5.1.
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated
AUC(0-t) is actually AUC_{0-12}

* ：新薬承認情報提供時に置き換えた

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001021 (U.K.)	To investigate the effect of 1) efavirenz and Lopinavir/ Ritonavir*on the steady state pharmacokinetics of maraviroc 300 mg BID; 2) efavirenz and boosted saquinavir on the steady state pharmacokinetics of maraviroc 100mg BID; 3) efavirenz with Lopinavir/ Ritonavir* and saquinavir on the steady state pharmacokinetics maraviroc 100 mg BID; 4) Lopinavir/Ritonavir*on the steady state pharmacokinetics of maraviroc 300 mg BID; 5) boosted saquinavir on the steady state pharmacokinetics of maraviroc 100 mg BID 6) saquinavir and Lopinavir/ Ritonavir*on the steady state pharmacokinetics of maraviroc 100 mg BID and investigate the safety and toleration of maraviroc when administered with efavirenz plus either Lopinavir/Ritonavir* or boosted saquinavir and when co-administered with both Lopinavir/Ritonavir* and saquinavir.	Open, randomised, placebo-controlled, 2-way crossover study Subjects: 36 Sex: 33 M/3 F Mean Age (min/max): 27.4 (18/44) years <u>COHORT 1</u> Period 1 Evaluated for: PK: 11; Safety: 11	300 mg maravirocBID + Lopinavir/Ritonavir* BID (Days 1-21)	10030	n/c	1810	2.36	n/c
			plus efavirenz 600 mg QD (Days 8-21)	6198	n/c	1068	2.15	n/c
		Period 2 Evaluated for: PK: 11; Safety: 11	300 mg maravirocBID + placebo BID (Days 1-21))	2499	n/c	914	2.00	n/c
			plus placebo QD (Days 8-21	2448	n/c	854	2.00	n/c
		<u>COHORT 2</u> Period 1 Evaluated for: PK: 11; Safety: 11	100 mg maraviroc BID + boosted saquinavir BID (Days 1-21)	4852	n/c	888	2.18	n/c
			plus efavirenz 600 mg QD (Days 8-21)	2714	n/c	437	2.15	n/c
		Period 2 Evaluated for: PK: 11; Safety: 11	100 mg maravirocBID + placebo BID (Days 1-21)	486	n/c	187	1.50	n/c
			plus placebo QD (Days 8-21)	543	n/c	194	1.85	n/c

* ：新薬承認情報提供時に置き換えた

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001021 continued		COHORT 3						
		Period 1 Evaluated for: PK: 6; Safety: 6	100 mg maraviroc BID + saquinavir 1000 mg BID +Lopinavir/Ritonavir* BID (Days 1-21)	2946	n/c	413	1.67	n/c
			plus efavirenz 600 mg QD (Days 8-21)	n/c	n/c	n/c	n/c	n/c
		Period 2 Evaluated for: PK: 6; Safety: 6	100 mg maraviroc BID + placebo BID (Days 1-21)	451	n/c	119	1.75	n/c
			plus placebo QD (Days 8-21)	n/c	n/c	n/c	n/c	n/c

Source: Clinical Study Report A4001021; Tables 13.1.1, 13.2.1, 13.5.1.1.1, 13.5.1.2.1 and 13.5.1.3.1
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated
AUC(0-t) is actually AUC_{0-12}

* ：新薬承認情報提供時に置き換えた

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001022 (Singapore)	To investigate the effect of tenofovir on the pharmacokinetics of multiple oral doses of maraviroc (300mg BID) and investigate the safety and toleration of maraviroc (300mg BID), when administered with tenofovir.	Open, randomised, placebo-controlled, two-way crossover study Subjects: 12 Sex: 10 M/2 F Mean Age (min/max): 31.8 (22/44) years						
		Evaluated for: PK: 12; Safety: 12	300 mg maraviroc BID + tenofovir 300 mg	3613	n/c	1245	2.00	n/c
		Evaluated for: PK: 11; Safety: 11	300 mg maraviroc BID + placebo	3536	n/c	1214	1.86	n/c

Source: Clinical Study Report A4001022; Tables 13.1.1, 13.2.1, and 13.5.1.
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated
AUC(0-t) is actually AUC_{0-12}

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters				
				AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001025 (Singapore)	To investigate the effects of atazanavir (alone and boosted with ritonavir) on the pharmacokinetics of multiple oral doses of maraviroc and to investigate the safety and toleration of mraviroc when administered with atazanavir (alone and boosted with ritonavir).	Open, randomised, placebo-controlled, two-period crossover study Subjects: 12 Sex: 12 M/0 F Mean Age (min/max): 28.7 (21/43) years						
		Evaluated for: PK: 12; Safety: 12	300 mg maraviroc BID + atazanavir 400 mg	9966	n/c	1914	2.50	n/c
		Evaluated for: PK: 12; Safety: 12	300 mg maraviroc BID + placebo	2790	n/c	915	2.00	n/c
		Evaluated for: PK: 12; Safety: 12	300 mg maraviroc BID + atazanavir 400 mg + ritonavir 100 mg	12755	n/c	2441	2.00	n/c
		Evaluated for: PK: 12; Safety: 12	300 mg maraviroc BID + placebo	2614	n/c	914	1.92	n/c

Source: Clinical Study Report A4001025; Tables 13.1.1, 13.2.1, 13.5.1.1 and 13.5.1.2
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated
AUC(0-t) is actually AUC_{0-12}

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001042 (Belgium)	To investigate the effects of tipranavir administered in combination with with ritonavir, (boosted tipranavir) on the pharmacokinetics of multiple oral doses of maraviroc (150mg BID) and to investigate the safety and toleration of maraviroc in the presence of boosted tipranavir.	open, randomized, 2 way crossover study Subjects: 12 Sex: 6 M/6 F Mean Age (min/max): 32.7 (22/43) years						
		Evaluated for: PK: 12; Safety: 12	150 mg maraviroc BID + tipranavir 500 mg + ritonavir 100 mg	1282	n/c	298	1.46	n/c
		Evaluated for: PK: 12; Safety: 12	150 mg maraviroc BID + placebo	1260	n/c	347	2.58	n/c

Source: Clinical Study Report A4001042; Tables 13.1.1, 13.2.1, and 13.5.1.1
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated
AUC(0-t) is actually AUC_{0-12}

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001046 (U.K.)	To investigate the range of maraviroc exposures, safety and toleration, following a single dose of 150mg maraviroc in HIV positive subjects receiving antiretroviral therapy containing boosted saquinavir	Open, single period, single centre study. Subjects: 8 Sex: 7 M/1 F Mean Age (min/max): 45.9 (38/56) years Evaluated for: PK: 8; Safety: 8	150 mg maraviroc	4145	4588	756	1.6	18.4

Source: Clinical Study Report A4001046; Tables 13.1.1, 13.2.1, and 13.5.1
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated
t=tlast, the last time with a quantifiable concentration

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001016 (Singapore)	To assess the effect of single doses of maraviroc on the QTc interval and to evaluate its safety and toleration in healthy subjects.	Randomised, single dose, placebo and active controlled five way crossover study Subjects: 61 Sex: 30 M/31 F Mean Age (min/max): 29.9 (19/44) years						
		Evaluated for: PK: 60; Safety: 61	100 mg maraviroc	396	n/c	111	2.80	n/c
		Evaluated for: PK: 59; Safety: 59	300 mg maraviroc	1840	n/c	464	2.60	n/c
		Evaluated for: PK: 58; Safety: 58	900 mg maraviroc	5259	n/c	1148	2.20	n/c

Source: Clinical Study Report A4001016; Tables 1.1, 2.1, 5.1.1, 5.1.2 and 5.1.3.
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters				
				AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001033 (Belgium)	To investigate the effect of maraviroc on the cardiovascular function of healthy male subjects	Part 1 an open, randomized, two-period (period 1 and 2) crossover assessment of a single sublingual spray of 0.4 mg GTN v no-treatment (GTN placebo). Part 2: double blind, randomized, placebo-controlled, two period (periods 3 and 4) crossover assessment of a single oral dose of maraviroc 900mg v placebo (maraviroc placebo). Subjects: 16 Sex: 16 M/0 F Mean Age (min/max): 30.2 (19/45) years Evaluated for: PK: 0; Safety: 16	900 mg maraviroc	n/c	n/c	n/c	n/c	n/c

Source: Clinical Study Report A4001016; Tables 13.1.1 and 13.2.1
No pharmacokinetic parameters were calculated for this study.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Mean Pharmacokinetic Parameters					
			Treatment	AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001007 (Germany, Netherlands, U.K.)	To demonstrate that short-term maraviroc monotherapy decreased plasma viral load in HIV infected subjects 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 IC50/90 and assess the safety and tolerability of maraviroc in HIV infected subjects.	Randomised, double blind, placebo-controlled, multicentre study Subjects: 45 Sex: 45 M/0 F Mean Age (min/max): 34.2 (23/48) years Evaluated for: PK: 9; Safety: 9	25 mg maraviroc QD	44.1	n/c	6.87	4.25	n/c
		Evaluated for: PK: 8; Safety: 8	50 mg maraviroc BID	142	n/c	27.7	3.83	n/c
		Evaluated for: PK: 8; Safety: 8	100 mg maraviroc BID	454	n/c	104	10.5	n/c
		Evaluated for: PK: 8; Safety: 8	300 mg maraviroc BID	2552	n/c	618	33.6	n/c

Source: Clinical Study Report A4001007; Tables 1.1, 2.1, and 5.1.2
AUC(0-t), AUC(0-8) and Cmax are expressed as geometric means; Tmax and t½ are expressed as arithmetic means.
M=Male, F=female, PK=Pharmacokinetics and n/c=not calculated
For A4001007, AUC(0-t) is actually AUC_{0-12}

Section 2.7.2 Table A1 Summary of Human Pharmacokinetic Studies

Protocol No. (Country)	Study Objective(s)	Study Design, Subject Demographics, Number Evaluated	Treatment	Mean Pharmacokinetic Parameters AUC(0-t) (ng·h/mL)	AUC(0-8) (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	t½ (h)
A4001015 (Germany, U.K, U.S.A)	To assess the effect of food and the effect of once daily (QD) compared to twice daily (BID) dosing on the anti-viral effect and the pharmacokinetic-pharmacodynamic relationships in HIV-1 infected subjects on short-term maraviroc monotherapy, and to assess the safety and tolerability of maraviroc.	Randomised, double-blind, placebo-controlled, multicentre, five treatment, parallel group study. Subjects: 37 Sex: 35 M/2 F Mean Age (min/max): 38.0 (27/53) years Evaluated for: PK: 9; Safety: 9	100 mg QD (1x 100 mg tablet);	571	n/c	161	3.25	n/c
		Evaluated for: PK: 8; Safety: 8	150 mg BID (1x 100 mg tablet and 1 x 50 mg tablet), fasted	933	n/c	273	3.00	n/c
		Evaluated for: PK: 8: Safety: 8	150 mg BID (1x 100 mg tablet and 1 x 50 mg tablet) (fed)	474	n/c	110	2.25	n/c
		Evaluated for: PK: 8; Safety: 8	300 mg QD (3 x 100 mg tablets); fasted	2264	n/c	484	3.25	n/c

Source: Clinical Study Report A4001015; Tables 1.1, 2.1 and 5.1.

AUC(0-t), AUC(0-∞) and Cmax are expressed as geometric means ; Tmax and t½ are expressed as arithmetic means.

M=Male F=Female PK=Pharmacokinetics n/c=not calculated.

For A4001015, AUC(0-t) is actually AUC_{tau} which is 0-12 for BID regimens and 0-24 for QD regimens.

2.7.3 SUMMARY OF CLINICAL EFFICACY

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AIDS	acquired immune deficiency syndrome
ANOVA	analysis of variance
AUC	area under the plasma concentration-time curve
BID	twice daily treatment regimen
CCR5	CC Chemokine Receptor 5
CD	cluster of differentiation
CI	confidence interval
CXCR4	CX Chemokine Receptor 4
DSMB	data safety monitoring board
FAS	full analysis set of patients
GSS	genotypic susceptibility score
HAART	highly active antiretroviral therapy
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus subtype 1
IC_{50}	the molar concentration at which in vitro viral replication was inhibited by 50%
IC_{90}	the molar concentration at which in vitro viral replication was inhibited by 90%
LOCF	last observation carried forward
LOQ	limit of quantification
MVC	maraviroc
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
OBT	optimised background therapy
OSS	overall susceptibility score
PBL	peripheral blood lymphocytes
PI	protease inhibitor
PK/PD	pharmacokinetic-pharmacodynamic
PSGT	Phenosense. GT assay for determination of virus susceptibility to antiretroviral agents (PIs, NRTIs and NNRTIs)
PSS	phenotypic susceptibility score
QD	once daily treatment regimen
RNA	ribonucleic acid
RT-PCR	reverse transcriptase polymerase chain reaction
TAD	time averaged difference

2.7.3. SUMMARY OF CLINICAL EFFICACY

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 expose the bridging sheet and form 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 (Chan DC, 1998)]. The chemokine receptors most commonly utilised by HIV-1 in vivo are CC chemokine receptor 5 (CCR5) and/or CX chemokine receptor 4 (CXCR4) (Choe H, 1996, Deng H, 1996, Dragic T, 1996, Feng Y, 1996). The ability of gp120 to bind to either one or both receptors defines the tropism of the virus and HIV-1 strains are categorised as R5 (CCR5-tropic), X4 (CXCR4-tropic) or R5/X4 (strains using both CCR5 and CXCR4; also referred to as 'dual-tropic') (Berger EA, 1998). A patient plasma sample may also contain a heterogeneous population of viruses with different tropism termed 'mixed tropism'. CCR5 antagonists only inhibit strains which are obligate users of CCR5, while X4 and R5/X4 strains ("CXCR4-using") can infect cells in the presence or absence of a CCR5-specific antagonist.

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 an excellent safety and tolerability profile. The results of longer-term Phase 3 studies, A4001027 and A4001028, have shown that a 300 mg dose equivalent of maraviroc, given once (QD) or twice daily (BID), when dosed in combination with optimised background therapy (OBT) in heavily treatment-experienced patients, leads to a clinically significant greater decline in viral load than OBT alone, 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.

The proposed indication for maraviroc is "<Maraviroc> in combination with other antiretroviral agents, is indicated for treatment-experienced adult patients infected with CCR5-tropic HIV-1."

The maraviroc doses studied in this patient population were the equivalent of 300 mg QD or 300 mg BID. This document summarises the efficacy results from the two Phase 3 registrational studies in the target patient population 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 compared with placebo in combination with OBT (OBT alone):

Provided a superior reduction in HIV-1 RNA level from baseline to Week 24;

Resulted in a greater 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;

Resulted in a greater increase in absolute CD4 and CD8 cell counts from baseline to Week 24.

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

The superior 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 harm.

The following sections of this document provide a summary of all the studies designed to provide efficacy data during the maraviroc Phase 2/3 clinical development programme in treatment-experienced HIV-1 infected patients. The safety data for these studies are presented in detail in Module 2 7.4 Summary of Clinical Safety. Additional information may be found in the individual clinical study reports, which are cross-referenced accordingly throughout the document.

2.7.3.1. Background and Overview of Clinical Efficacy

2.7.3.1.1. Introduction

Two Phase 2a dose selection monotherapy studies (A4001007 and A4001015) were conducted. The first Phase 2a Study A4001007 originally included maraviroc doses of 25 mg QD and 100 mg BID. The rationale for selecting these doses were based on the fact that for standard antiretroviral agents that target the virus directly, there is a direct relationship between antiviral effects, as measured by a decrease in plasma HIV-1 RNA level, and plasma drug concentrations, so dose ranges that were likely to be clinically effective could be selected based on the in vitro molar concentrations, which resulted in 50% (IC_{50}) and 90 % (IC_{90}) inhibition of viral replication. However, an argument can be made that for maraviroc, saturation of the CCR5 receptor could be a better predictor of efficacy. In the Phase 1 multiple dose escalation study (A4001002: A double-blind, randomised, parallel group, placebo-controlled single and multiple escalating oral dose study to investigate the safety, toleration and pharmacokinetics of maraviroc [UK-427,857] in healthy male subjects; Module 5.3.3.1 Healthy Subject Pharmacokinetic and Initial Tolerability Study Reports) it was demonstrated that although 100 mg BID was the minimum dose of maraviroc required to maintain a plasma concentration above the in vitro antiviral IC_{90} for 24 hours, a single 25 mg dose resulted in a high degree of CCR5 receptor saturation for more than 24 hours despite the plasma concentration falling rapidly to well below the antiviral IC_{90}. These doses were therefore selected to

investigate the pharmacokinetic-pharmacodynamic relationship of maraviroc and to determine whether pharmacokinetic parameters, or saturation of the CCR5 receptor, correlated better with antiviral effects in vivo.

Following completion of the first phase of the study, a pre-planned interim analysis was performed and maraviroc 50 mg and 300 mg BID doses were added to more fully explain the dose response relationship. Dosing regimens included in the second Phase 2a Study A4001015 (100 mg QD, 150 mg BID and 300 mg QD) were selected to provide an adequate dose response range for both QD and BID regimens when the results were combined with Study A4001007. The rationale for including both QD and BID dosing regimens were to evaluate whether the observed antiviral effects were independent of dosing regimen for the same total daily dose. In addition, a dose of 150mg BID in combination with a high fat meal was added to investigate whether the effect of food on maraviroc pharmacokinetics that was observed in the Phase 1 Study A4001004, which reduced the C_{max} and AUC of maraviroc 100 mg by 68 and 52% respectively (described in detail in Module 2.7.1 Summary of Biopharmaceutics and Analytical Methods), affected efficacy.

Data from these studies demonstrated that all doses of maraviroc ≥200 mg total daily dose (including 300 mg given QD or BID) resulted in similar mean viral load reductions of >1 $\log_{10}$ copies/mL from baseline at Day 11. In addition, a dose of 150 mg BID given with or without food resulted in similar mean viral load reductions (A4001007 and A4001015 clinical study reports, Module 5.3.4.2 Patient PD and PK/PD Study Reports). A summary of the results of these dose ranging studies is provided in Section 2.7.3.1.2 below.

As maraviroc is a CYP3A4/P-gp substrate, exposure is increased in the presence of potent CYP3A4/P-gp inhibitors, such as PIs, which are commonly used in combination regimens for the treatment of HIV-1 and therefore likely to be included as part of a patient's OBT in the Phase 2b/3 studies. The extent of these interactions was quantified in the Phase 1 drug-drug interaction programme (described in detail in Module 2.7.2. Summary of Clinical Pharmacology Studies). As expected, CYP3A4/P-gp inhibitors, including ketoconazole, saquinavir, lopinavir/ritonavir, atazanavir and ritonavir caused significant increases in the systemic exposure of maraviroc with mean increases in C_{max} and AUC_t ranging from 1-5 fold and 3-10 fold, respectively. A halving of the maraviroc dose appeared to correct for the increase in C_{max}, although AUC_t was not fully corrected. Given these data it was decided to implement a 0.5-fold dose adjustment for maraviroc in the presence of PIs. Although this adjustment was not predicted to adjust for the increases in AUC_t (which correlates best with viral load reduction in monotherapy) in all instances, it was intended to adequately adjust for increases in C_{max}, which is the pharmacokinetic parameter believed to best correlate with maraviroc-related dose-limiting adverse events (e.g., postural hypotension). It was thought that this strategy would optimise efficacy, whilst minimising both the side effects and the complexity of dose adjustments.

The efficacy of maraviroc for the target treatment indication was evaluated in two, double-blind, placebo-controlled Phase 3 registrational studies, A4001027 and A4001028, including more than 1000 treatment-experienced patients infected with CCR5 tropic HIV-1 who were failing their current regimen and either heavily treatment-experienced and/or infected with multi-class resistant HIV-1. These two studies were identical in design and conducted in overlapping geographic locations. The primary objective of these studies was to confirm 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. What follows in this document are the results of a planned interim Week 24 analysis of these studies.

There is a complex association between HIV-1 co-receptor tropism, transmission and pathogenesis which is not yet fully understood (Moore JP, 2004, Philpott, 2003). Generally, strains that are transmitted and establish new infections in a host are R5 (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 strains is a marker for disease progression rather than the cause is not known (Moore JP, 2004). It also remains to be determined whether the emergence of CXCR4-using strains during treatment with a CCR5 antagonist is associated with the same clinical outcome as when they emerge during the natural course of HIV-1 infection.

Study A4001029 was therefore designed to determine the safety of maraviroc in treatment-experienced patients infected with non-CCR5 tropic (dual/mixed tropic and 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. The primary and secondary efficacy results from Study A4001029 are presented in this submission as supportive data. Table 1 provides a summary of studies that are presented in this submission to support the efficacy and dose selection of maraviroc for use in heavily treatment-experienced patients infected with CCR5 tropic HIV-1. The design of these studies and the results of the analyses are described in detail in this summary document.

Table 1. Summary of Studies Providing Support for the Dose Selection and Efficacy of Maraviroc in this Submission

Study/Treatments (Randomisation)	Study Design	Main Outcome
Phase 2a Dose Ranging Studies		
A4001007 *Cohort 1*: Maraviroc 25 QD: 100 mg BID: Placebo. (1:1:1) *Cohort 2*: Maraviroc 50 mg BID: 300 mg BID: Placebo. (1:1:0.5)	A randomised, double-blind, placebo-controlled study of maraviroc in asymptomatic patients infected with CCR5 tropic HIV-1 to investigate pharmacodynamics, pharmacokinetics, safety and toleration. Patients received study drug as monotherapy for 10 days.	All doses of maraviroc produced a viral load decrease statistically significantly superior to placebo at the 10% significance level. Doses of 100 mg and 300 mg BID produced a large and similar decrease in viral load, took longer to return to baseline values than other doses and resulted in trough plasma concentrations above the mean antiviral IC_{90} of primary isolates.
A4001015 Maraviroc 150 mg BID (fed & fasted): 100 mg and 300 mg QD (fasted): Placebo (fed & fasted). (4:4:4:4:1:1)	A randomised, double-blind, placebo-controlled, parallel group investigation into the effects of food and dose regimen (QD versus BID) on the anti-viral and pharmacokinetic/pharmacodynamic effects of 10-day monotherapy with maraviroc in asymptomatic patients infected with CCR5 tropic HIV-1.	Viral load decrease was similar for 150 mg fed and fasted treatment groups and for 300 mg QD group. Therefore, doses =150 mg may be given with food without significant effect on efficacy and a daily dose of 300 mg produced similar efficacy given as QD or 150 mg BID.
Phase 3 Registrational Studies		
A4001027 **Maraviroc[a] 300 mg QD: 300 mg BID: Placebo. (2:2:1)**	**A multicentre, randomised, double-blind, placebo-controlled trial of maraviroc in combination with OBT versus OBT alone for the treatment of antiretroviral-experienced patients infected with CCR5 tropic HIV-1. The study was conducted in North America and endpoints formally evaluated at 24 weeks. The study is ongoing to 48 weeks.**	**Mean change from baseline to Week 24 in HIV-1 RNA demonstrated statistical superiority of both maraviroc QD and BID over placebo. All secondary endpoints were consistent with the primary endpoint and supported superior efficacy of maraviroc over placebo.**
A4001028 **Maraviroc[a] 300 mg QD: 300 mg BID: Placebo. (2:2:1)**	**A multicentre, randomised, double-blind, placebo-controlled trial of maraviroc in combination with OBT versus OBT alone for the treatment of antiretroviral-experienced patients infected with CCR5 tropic HIV-1. The study was conducted in Europe, Australia and North America[b] and endpoints formally evaluated at 24 weeks. The study is ongoing to 48 weeks.**	**Mean change from baseline to Week 24 in HIV-1 RNA demonstrated statistical superiority of both maraviroc QD and BID over placebo. All secondary endpoints were consistent with the primary endpoint and supported superior efficacy of maraviroc over placebo.**
Phase 2b Supportive Studies		
A4001029 Maraviroc[a] 300 mg QD: 300 mg BID: Placebo. (1:1:1)	A multicentre, randomised, double-blind, placebo controlled trial of maraviroc in combination with OBT versus OBT alone for the treatment of antiretroviral-experienced patients infected with non-CCR5 tropic (CCR5/CXCR4, CXCR4-using or non-phenotypable) HIV-1. The study was global and endpoints formally evaluated at 24 and 48 weeks.	All treatment groups produced a similar decrease in viral load; neither dose of maraviroc demonstrated non-inferiority nor was statistically superior to placebo. Unadjusted for multiple comparisons, the increase in CD4 cell count was statistically significantly higher for maraviroc BID compared with placebo. The increase in CD8 cell count was statistically significantly higher for both doses for maraviroc compared to placebo.

Source: Clinical study reports; Module 5.3.4.2. Patient PD and PK/PD Study Reports (Studies A4001007 and A4001015), .Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication (Studies A4001027, A4001028 and A4001029).

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

[b] A4001028 was originally designed to be conducted in Europe and Australia. Due to difficulties in recruitment the study was opened up to patients from Investigator sites in the USA.

OBT = Optimised Background Therapy.

2.7.3.1.2. Summary of Early Phase 2a Dose Ranging Studies

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. The objectives of Study A4001007 were to demonstrate that short-term maraviroc monotherapy decreased plasma viral load in HIV 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. Full details of these studies are found in the A4001007 and A4001015 clinical study reports (Module 5.3.4.2 Patient PD and PK/PD Study Reports).

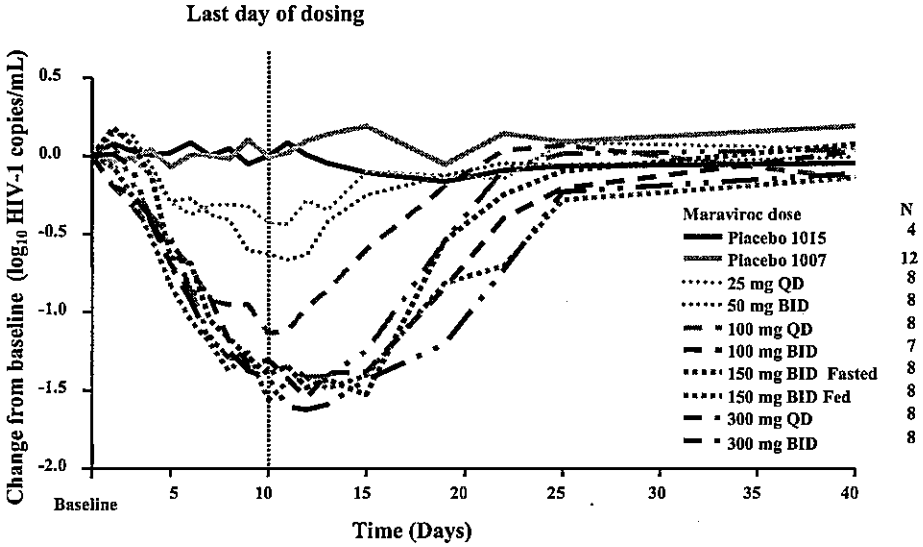
For both Phase 2a studies, patients were asymptomatic and infected with a confirmed CCR5 tropic virus as determined by the Monogram Biosciences recombinant virus assay (Section 2.7.3.1.5.2). Patients found to harbour mixed/dual tropic virus, CXCR4-using virus, or non-phenotypable virus at screening were excluded from the study.

CCR5 receptor occupancy was carried out by a centralised laboratory (Esoterix Inc., Austin, USA) using an experimental MIP-1⇓ internalization assay. Receptor occupancy was reported as the percentage of cell-surface-expressed CCR5 receptors on peripheral blood lymphocytes (PBLs) that could not be down-regulated when PBL-enriched plasma from patients was incubated ex vivo with recombinant MIP-1⇓. Cell-surface CCR5 expression was measured by flow cytometry using a fluorescently-labelled CCR5-specific monoclonal antibody (2d7). Percentage receptor occupancy was calculated using expression data obtained for PBL aliquots incubated (i) with chemokine in the presence of 1 ∝M maraviroc; and (ii) in the absence of additional maraviroc.

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. In addition, a post-hoc combined analysis of mean maximal (nadir) reduction in plasma viral load was conducted. The study design and patient populations were similar for both studies and therefore combined results are presented. 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/∝L, respectively (Fatkenheuer G, 2005).

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 1).

Figure 1. 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. The mean viral load change from baseline at Day 11 and nadir for Studies A4001007 and A4001015 are presented in Table 2.

Table 2. Mean Change from Baseline in HIV-1 RNA at Day 11 and Nadir (Combined Studies A4001007 and A4001015)

Dose	No. of Patients		Median Time to Nadir (Days)	Mean (Range) Change in HIV-1 RNA (log_{10} copies/mL)		Patients with >1.0 log_{10} Reduction in HIV-1 RNA	
	Randomised	Treated for 10 Days		Day 11	Nadir	Day 11	Nadir
25 mg QD	9	8[a]	10	-0.43[e] (-1.08, 0.02)	-0.59 (-1.10, 0.02)	1	1
50 mg BID	8	8	13	-0.66 (-1.37, 0.40)	-0.86 (-1.37, -0.14)	4	5
100 mg QD	9	8[b]	10	-1.13 (-1.70, -0.43)	-1.25 (-1.70, -0.61)	5	6
100 mg BID	8	7[c]	12	-1.42 (-1.84, -1.04)	-1.68 (-2.10, -1.37)	7	7
150 mg BID	8	8	12	-1.45 (-1.71, -0.90)	-1.77 (-2.16, -1.43)	7	8
150 mg BID (fed)	8	8	15	-1.34 (-1.79, -0.51)	-1.74 (-2.09, -1.13)	7	8
300 mg QD	8	8	12	-1.35 (-1.62, -0.95)	-1.60 (-2.08, -1.14)	7	8
300 mg BID	8	8	11	-1.60[f] (-2.42, -0.78)	-1.84 (-2.42, -1.49)	7	8
Placebo (A4001007)	12	12	8[g]	0.02 (-0.45, 0.56)	-0.32[g] (-0.63, 0.11)	0	0
Placebo (A4001015)	4[d]	4		0.09 (-0.20, 0.27)		0	

Source: Fatkenheuer G et al 2005 (Fatkenheuer G, 2005).
[a] One patient withdrew consent.
[b] One patient discontinued treatment because of a headache of moderate severity (not considered to be treatment related) before dosing on Day 3.
[c] One patient in the group treated with 100 mg BID had dual/mixed-tropic virus at baseline and was excluded from the efficacy analysis. Inclusion of this patient in the analysis resulted in a mean change in HIV-1 RNA from baseline to Day 11 of -1.20 log_{10} copies/mL (range -1.84 to 0.33).
[d] Two fed and two fasted.
[e] P=0.056 compared with placebo, Williams step down test.
[f] P<0.01 compared with placebo, Williams step down test.
[g] These values apply to both placebo groups.
QD = Once daily dosing; BID = Twice daily dosing; CI = Confidence interval.

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 (Table 3).

Table 3. Determination of the Effect of Food and Dosing Regimen on the Efficacy of Maraviroc (Study A4001015)

Treatment Group Comparison	Difference[a]	90% CI of Difference
Maraviroc 150 mg BID (Fasted) vs. Maraviroc 150 mg BID (Fed)	-0.103	-0.390, 0.185
Maraviroc 150 mg BID (Fasted) vs. Maraviroc 300 mg QD (Fasted)	-0.099	-0.387, 0.188

Source: A4001015 Clinical Study Report (Module 5.3.4.2 Patient PD and PK/PD Study Reports).
[a] Viral Load (Log_{10}) at baseline minus viral load (log_{10}) at Day 11.

Mean CD4 cell count increases between Day 1 and Day 11 in the maraviroc treatment groups were variable and ranged from +5 cells/∝L (150 mg BID fasted), to +150 cells/∝L

(50 mg BID). In the A4001007 and A4001015 placebo groups mean CD4 cell count decreased by 2 cells/∝L and 31 cells/∝L, 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. This prolonged occupancy of CCR5 by maraviroc may be responsible for the delay in viral rebound, however, no association between CCR5 receptor occupancy and viral load reduction was observed.

Sixty-two patients enrolled into these Phase 2a studies harboured 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 (PID 1[redacted]1302 and PID 1[redacted]1305 from 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 harbouring CXCR4-using virus prior to treatment (PID 1[redacted]1112 from 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 programme.

Dose selection for the Phase 2b/3 studies was based on viral load reduction data from Studies A4001007 and A4001015, pharmacokinetic/pharmacodynamic modelling, 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. Early dose selection processes are summarised in Section 2.7.3.5 and Module 2.7.2 Summary of Clinical Pharmacology Studies. 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} (discussed in Section 2.7.2.3.2 Module 2.7.2 Summary of Clinical Pharmacology). 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.

2.7.3.1.3. Maraviroc Phase 2b/3 Clinical Development Programme

More than approximately 2000 HIV-1 infected patients have been randomised and have received blinded study drug in the Phase 2b/3 development programme, which commenced in November 2004. This clinical programme includes long-term studies of maraviroc in combination with other antiretroviral drugs in both treatment naïve patients (infected with CCR5 tropic HIV-1) and treatment experienced patients (infected with CCR5-tropic and non CCR5-tropic HIV-1) (Table 4).

Table 4. Maraviroc Phase 2b/3 Programme 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, NA	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 Phase 3 registrational trials (A4001027 and A4001028), which provide the efficacy data for this submission in treatment-experienced patients infected with CCR5 tropic HIV-1 and Study A4001029, which provides supporting safety data for the use of maraviroc in patients infected with dual/mixed-tropic, CXCR4-tropic or non-phenotypable HIV-1. For the purposes of this summary document, efficacy data is presented at the 24-week study endpoint for all patients.

To ensure the safety of study participants a Data Safety Monitoring Committee (DSMB) was formed to oversee all the studies in the maraviroc Phase 2b/3 clinical development programme. The 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, with the same recommendation. 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 of this study 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 clinical 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 (percentage 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. The efficacy results of the maraviroc QD treatment arm compared with the two remaining blinded treatment arms from this interim analysis are presented in Table 5.

Table 5. Summary of Efficacy Endpoint Analysis at Week 16 Interim Analysis (Study A4001026)

Efficacy Endpoint	Maraviroc 300 mg QD (N=68)	Blinded Maraviroc 300 mg BID / Efavirenz 600 mg QD (N=137)
Mean (95% CI) TAD $\log_{10}$ HIV-1 RNA level (copies/mL)	-2.206 (-2.435, -1.976)	-2.419 (-2.546, -2.293)
Number (%) Patients with HIV-1 RNA level <400 copies/mL	53 (77.9)	120 (87.6)
Number (%) Patients with HIV-1 RNA level <50 copies/mL	45 (66.2)	97 (70.8)

Source: A4001026 Week 16 Interim Analysis Study Report.
QD = Once daily dosing; BID = Twice daily dosing; TAD = Time Averaged Difference; CI = Confidence Interval.
Date of data cut off for interim analysis = 23 November 2005.

There was a larger mean decrease in TAD in HIV-1 RNA level and a greater percentage of patients achieved an HIV-1 RNA level <400 and <50 copies/mL in the blinded maraviroc 300 mg BID / efavirenz 600 mg QD treatment group compared with the maraviroc 300 mg QD treatment group.

In addition, analyses of efficacy based upon screening HIV-1 RNA (<100,000 copies/mL and =100,000 copies/mL) and baseline CD4 cell count (<200 cells/∝L and =200 cells/∝L) were performed (Table 6). Compared with subjects in the blinded maraviroc BID/efavirenz treatment group, lower response rates were observed in the maraviroc QD treatment group for subjects with baseline CD4 cell count <200 cell/∝L as well as subjects with screening HIV-1 RNA level of =100,000 copies/mL. Response rates for subjects with baseline CD4 cell count =200 cells/∝L or screening HIV-1 RNA <100,000 copies/mL were comparable between the maraviroc QD and the blinded maraviroc BID/efavirenz treatment groups.

Table 6. Percentage of Patients with HIV-1 RNA <400 copies/mL at Week 16 Based on Screening HIV-1 RNA and Baseline CD4 Cell Count (Study A4001026)

	Patients with <400 copies/mL at Week 16, n/N (%)	
	Maraviroc QD	Blinded Maraviroc BID/Efavirenz QD
Screening HIV-1 RNA (copies/mL)		
<100,000	30/34 (88.24)	63/71 (88.73)
=100,000	23/34 (67.65)	57/66 (86.36)
Baseline CD4 cell count (cells/μL)		
<200	19/27 (70.37)	33/36 (91.67)
≥200	34/41 (82.93)	87/101 (86.14)

Source: A4001026 Week 16 Interim Analysis Report.
QD = Once daily dosing; BID = Twice daily dosing.

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 in this submission. The safety data for these patients are presented in Module 2.7.4 Summary of Clinical Safety and in the abbreviated clinical study report in Module 5.3.5.4 Other Study Reports.

2.7.3.1.4. Design of Phase 2b/3 Clinical Studies Providing Efficacy for this Submission

2.7.3.1.4.1. Objectives

Studies A4001027 and A4001028 were identical (apart from geographical location) Phase 3 registrational studies designed to investigate the efficacy of maraviroc in heavily treatment-experienced patients infected with CCR5 tropic HIV-1, which is the target indication population for this application. Sample sizes were later changed as explained in Section 2.7.3.1.4.5. Study A4001029 was a designed as a Phase 2b safety study in patients infected with dual/mixed-tropic, CXCR4-tropic or non-phenotypable virus. The efficacy results from this study are presented in this submission as supportive data.

The primary objective for the Phase 2b/3 clinical 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 safety data for these studies are presented in Module 2.7.4 Summary of Clinical Safety.

2.7.3.1.4.2. Selection of Patient Population

The two Phase 3 registrational studies included in this submission investigated heavily treatment-experienced patients infected with CCR5 tropic HIV-1, who were failing their current antiretroviral therapy or were not on therapy. Patients had at least 6 months of prior treatment with at least 1 agent (2 agents for PIs) from 3 of the 4 antiretroviral drug classes or documented resistance to three of the four antiretroviral drug classes and plasma HIV-1 RNA =5000 copies/mL.

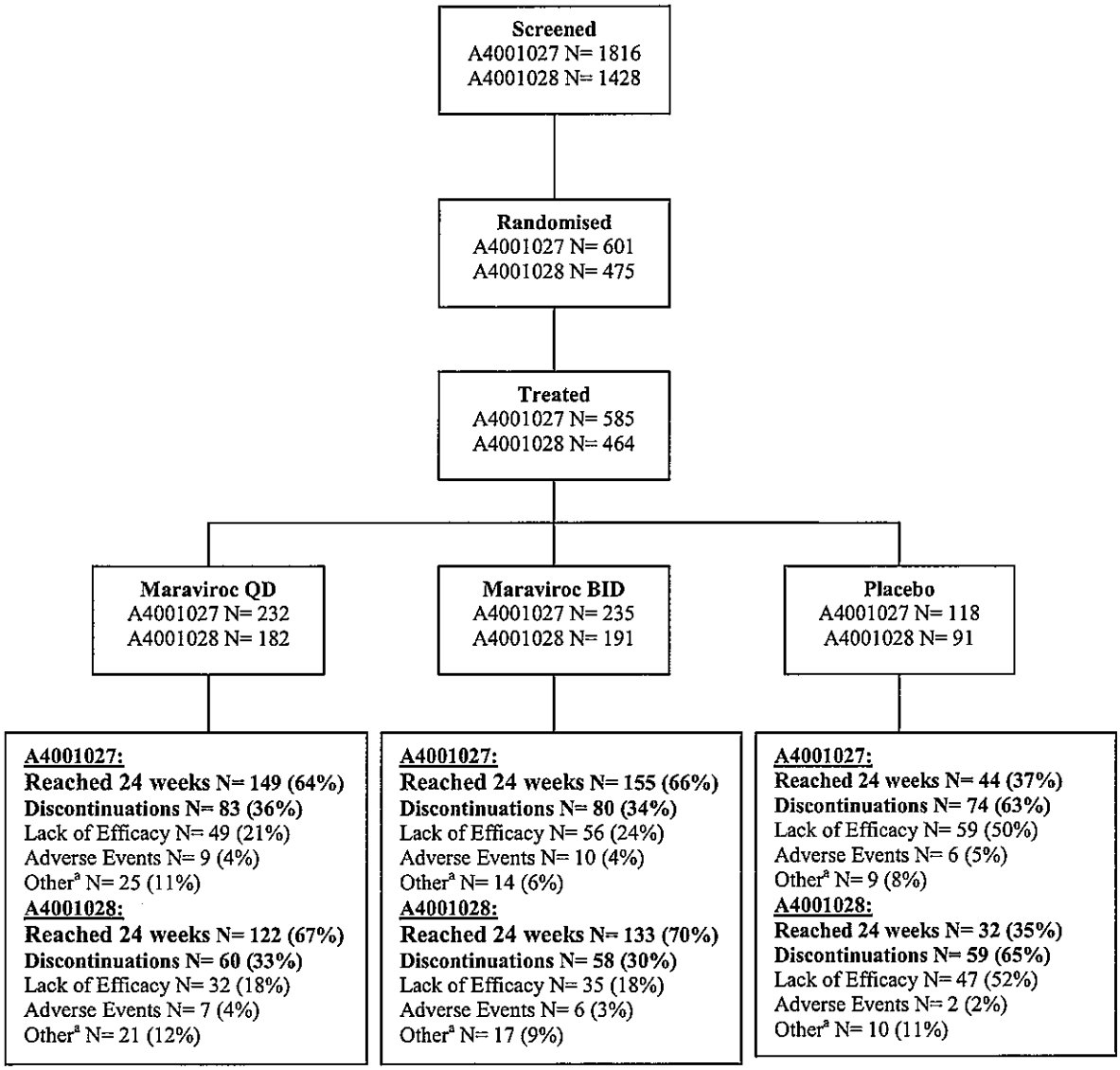
The Phase 2b safety Study A4001029 included patients infected with non-CCR5 tropic (dual/mixed tropic, CXCR4-tropic or non-phenotypable) virus who had an HIV-1 RNA =5000 copies/mL and with genotypic or phenotypic resistance to two of the four antiretroviral drug classes, or =3 months of antiretroviral 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, Section 2.7.3.1.5.2). 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 randomisation 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 and to confirm eligibility.

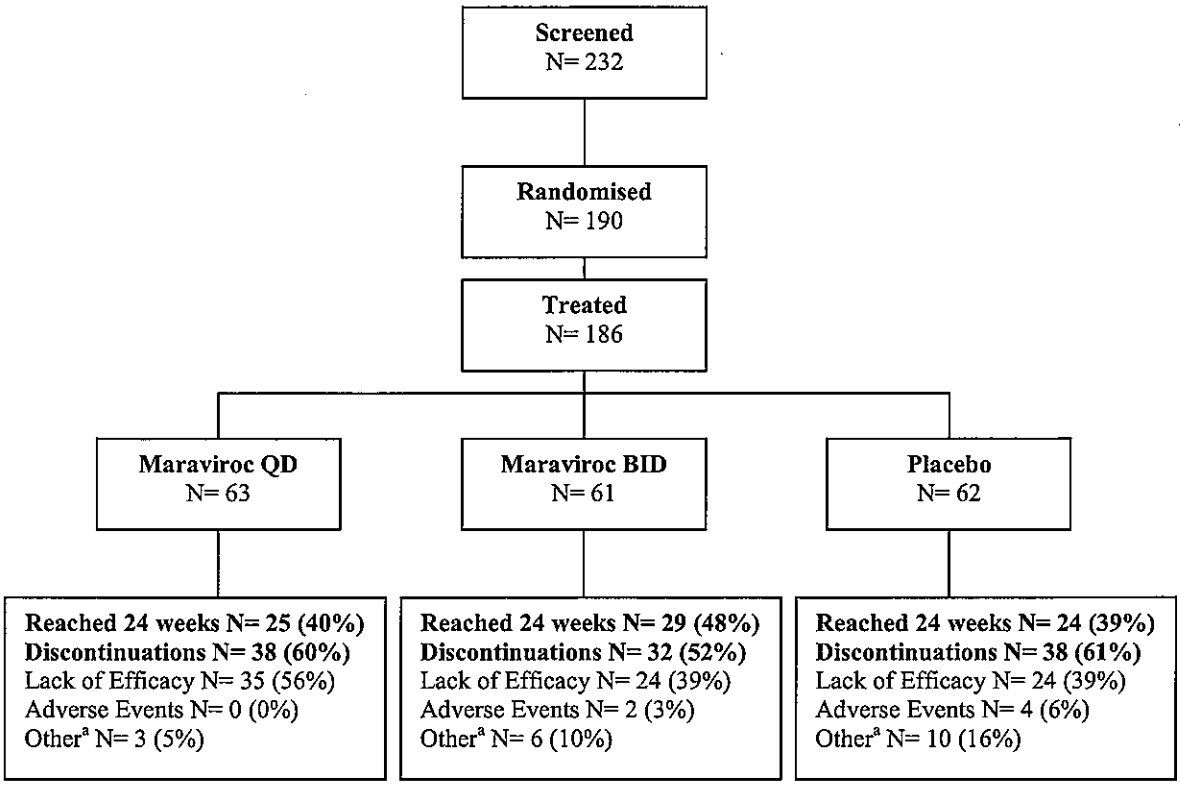
Figure 2 and Figure 3 below present the process of patient recruitment into the maraviroc Phase 2b/3 clinical studies and the derivation of the populations evaluated for efficacy. The most common reason for screen failure in Studies A4001027 and A4001028 was presence of a dual/mixed or CXCR4 tropism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

Figure 2. Derivation of Efficacy Population for Studies A4001027 and A4001028



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

Figure 3. Derivation of Efficacy Population for Study A4001029

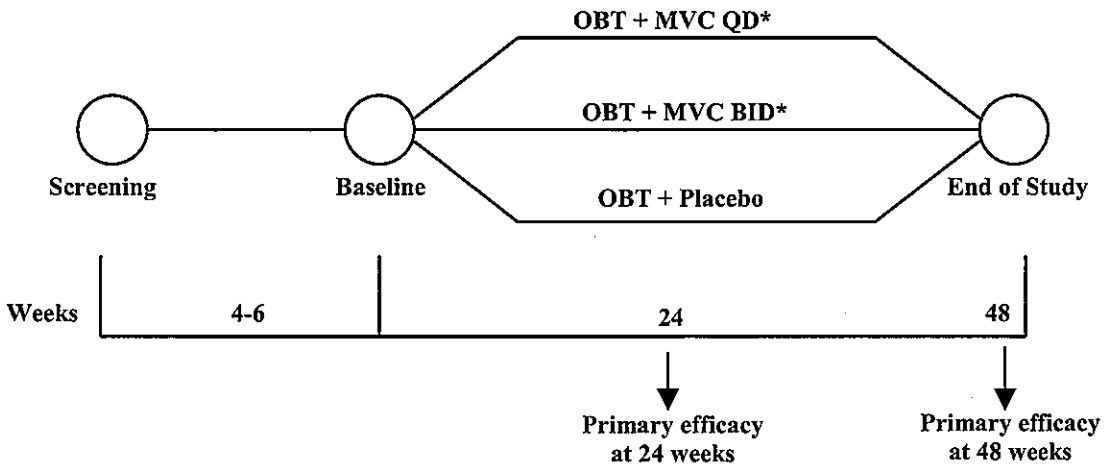


[a] 'Other' may include subject died and subject defaulted.

2.7.3.1.4.3. Study Design

The two identical registrational Phase 3 studies (A4001027 and A4001028) were multicentre, double-blind, randomised, placebo-controlled studies conducted in overlapping geographical locations (A4001027 in North America and A4001028 in Europe, Australia and the USA). 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 programme is presented in the schematic diagram below (Figure 4):

Figure 4. 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 randomisation and starting study drug. The delay before randomisation was necessary to determine the tropism assignment of the patients' virus and to perform genotypic and phenotypic susceptibility (using the Phenosense. GT [PSGT] assays, details provided in Section 2.7.3.1.5.3), which were available 3-5 weeks after receipt of the samples. Additional tests carried out at screening included measurement of orthostatic blood pressure, screening for the presence of hepatitis B and C antibodies and/or antigen, CD4/CD8 cell counts and plasma HIV-1 RNA level. Upon receipt of the results of these analyses, 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 randomisation visit. Plasma HIV-1 RNA level was repeated at this timepoint (randomisation visit). The Sponsor's medical team reviewed each OBT selection, in order to identify any potential safety concerns for a given combination. Plasma HIV-1 RNA level, CD4/CD8 cell count and viral tropism assignment were repeated at baseline. 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. Assessments carried out at baseline were repeated at these visits, including viral tropism assignment in patients with detectable virus.

2.7.3.1.4.4. Blinding and Randomisation of Study Drug

For Studies A4001027, A4001028 and A4001029 maraviroc was administered in a double-blind manner with a matching placebo tablet. The Sponsor was unblinded for the Week 24 analysis, but the patients and Investigators remain blinded until the study completion at the end of 48 weeks.

For Studies A4001027 and A4001028 patients were randomised to receive maraviroc QD, maraviroc BID or placebo all in combination with OBT in a 2:2:1 ratio. Patients were stratified at the time of randomisation by the use of enfuvirtide in the OBT and by screening plasma HIV-1 RNA level (<100,000 or =100,000 copies/mL) to ensure balance across treatment groups of these factors. For Study A4001029 patients were randomised to receive maraviroc QD, maraviroc BID or placebo all in combination with OBT in a 1:1:1 ratio. For all three studies, randomisation was according to a computer generated pseudo-random code using the method of permutated blocks, balanced within each randomisation strata (screening HIV-1 RNA =100,000 copies/mL and using enfuvirtide, screening HIV-1 RNA =100,000 copies/mL and not using enfuvirtide etc). Randomisation numbers were assigned by a central/web telephone computer-based system via a telephone call, which was made on the day of randomisation.

2.7.3.1.4.5. Sample size

Phase 3 Registrational Studies A4001027 and A4001028

A total of 1000 patients were to be randomised into the two pivotal Phase 3 studies to provide adequate numbers to demonstrate safety and efficacy. Initial plans were to recruit 500 patients into each study. However, difficulties in recruitment into Study A4001028 meant that differences in the recruitment rate between the studies were increasing over time. This was felt to be problematic for data analysis as prolonged recruitment may have an impact on study variability, as patients recruited later may differ from those recruited earlier due to the access to newly approved drugs and expanded access programmes. Therefore, after discussion with the US Food and Drug Administration (FDA), the decision was made to include US investigational sites into A4001028, which was initially restricted to European countries and Australia, and to adjust the sample size for these two studies.

For A4001027, a total of 600 patients were required to be randomised in a 2:2:1 ratio (240 on maraviroc QD, 240 on maraviroc BID and 120 on placebo). For Study A4001028, a total of 400 patients were required to be randomised in a 2:2:1 ratio (160 on maraviroc QD, 160 on maraviroc BID and 80 on placebo). For both studies, under the assumption of a standard deviation of 0.8, with a 2-sided significance level of 0.025 (Bonferroni adjustment for multiple comparisons) there was still >95% power to detect a difference of 0.5 in change from baseline in $\log_{10}$ HIV RNA levels between each maraviroc treatment arm and placebo.

Phase 2b Supportive Study A4001029

A total of approximately 192 patients were required to be randomised in a 1:1:1 ratio (64 subjects each on maraviroc QD; maraviroc BID; and placebo). The primary endpoint population was all patients whose virus was classified as dual/mixed-tropic using the Trofile™ HIV Entry Tropism assay (Section 2.7.3.1.5.2). With the assumption that 79% of patients would be infected with dual/mixed tropic virus, 9% with CXCR4-using virus and 12% with non-phenotypable virus, a total of approximately 192 patients would have to be randomised to ensure that 150 patients infected with dual/mixed-tropic HIV-1 were randomised.

Under the assumption of a standard deviation of 0.8 with a 2-sided significance level of 0.025 (Bonferroni adjustment for multiple comparisons), there was 80% power to detect a difference of 0.5 in change from baseline in $\log_{10}$ HIV RNA between each maraviroc treatment arm and placebo. With 50 patients infected with dual/mixed-tropic HIV-1 per treatment group, assuming a standard deviation of 0.8, a true benefit of each maraviroc dose over placebo of 0.25 $\log_{10}$ copies/mL, a 1-sided significance level of 0.0125 (Bonferroni adjustment for multiple comparisons) and a non-inferiority margin of 0.25 $\log_{10}$ copies/mL (i.e., the upper bound of the 1-sided confidence interval was below 0.25), there was 80% power to demonstrate non-inferiority between each maraviroc dose and placebo.

2.7.3.1.4.6. Dosing regimen

Blinded Therapy

In Studies A4001027, A4001028 and A4001029 patients were randomised to receive maraviroc 300 mg QD dose equivalent, maraviroc 300 mg BID dose equivalent or placebo all in combination with OBT. Maraviroc is a substrate for CYP3A4/P-gp and therefore, the dose was adjusted to maraviroc 150 mg QD or BID in those patients receiving a PI (except for tipranavir/ritonavir) and/or delavirdine in their OBT due to the increased exposure of maraviroc observed in the presence of these co-administered antiretroviral agents due to enzyme inhibition (details are provided in Module 2.7.2 Summary of Clinical Pharmacology Studies).

Maraviroc and placebo were administered as oral tablets for all studies. Table 7 presents the double-blinded treatments administered to each treatment group for these studies in treatment-experienced patients.

Table 7. Daily Blinded Study Treatments Administered (Studies A4001027, A4001028 and A4001029)

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

Source: A4001027, A4001028 and A4001029 Clinical Study Reports (Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication).
[a] Patients whose OBT included a PI (except tipranavir/ritonavir) and/or delavirdine received maraviroc 150 mg QD or 150 mg BID.
OBT = Optimised background therapy; QD = Once daily dosing; BID = Twice daily dosing; PI = Protease inhibitor.
NB: The protocol recommended that patients with efavirenz in their OBT should also receive a boosting PI.

Choice of Optimised Background Therapy (OBT).

Investigators chose OBT with 3-6 approved antiretroviral agents, excluding 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.

According to the protocols for the Phase 2b/3 studies, experimental antiretroviral agents available through pre-approval access programmes 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.

2.7.3.1.4.7. Efficacy Endpoints at Week 24 Analysis Timepoint

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 percentage of subjects with an HIV-1 RNA <400 copies/mL at Week 24;

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

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

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

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

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

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

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

Additional Endpoints:

To assess HIV-1 tropism at baseline and at the time of failure;

To assess the association between baseline resistance and virological response;

To compare the safety and tolerability of each of the two maraviroc regimens versus the placebo regimen.

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.

2.7.3.1.4.8. 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.

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 labelled "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.

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 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.

2.7.3.1.5. Methods of Analysis to Support Study Endpoints and Resistance Testing

This section provides a brief summary of the methods used to assess virologic and immunologic endpoints, viral tropism assignment, determination of resistance mutations and virus susceptibility and pharmacogenomic testing in the maraviroc Phase 2b/3 clinical development programme. For each of these methods of analysis, excluding viral load and CD4/CD8 cell count measurements, which were determined using standard methods, and the Monogram Biosciences Phenosense. GT (PSGT) assay, a more detailed methodology report is included in Module 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies.

2.7.3.1.5.1. Virologic and Immunologic Endpoints

2.7.3.1.5.1.1. Viral Load (Plasma HIV-1 RNA Level)

Viral load determinations were carried out by a centralised laboratory (Covance). Plasma HIV-1 RNA levels were determined using RT-PCR (Roche Amplicor HIV–1 MONITOR Test v1.5) with a lower limit of detection of 400 copies/mL as standard. For samples with a

reading of <400 copies/mL an ultrasensitive assay with a lower limit of detection of 50 copies/mL was performed. Any HIV-1 RNA value <50 copies/mL (the lower limit of quantification [LOQ] from the ultrasensitive assay) was treated as a value of 49. Baseline values were calculated as the mean of 3 pre-dose values (screening, randomisation and baseline), but the screening value was used to determine study eligibility.

2.7.3.1.5.1.2. CD4/CD8 Cell Count

CD4 and CD8 cell counts were carried out by a central laboratory (Covance), on samples taken at timepoints pre-specified in the study protocol, using standard flow cytometry techniques.

2.7.3.1.5.2. 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 5.

Figure 5. Schematic Diagram Showing the Principle of the Assay used to Determine Viral Tropism

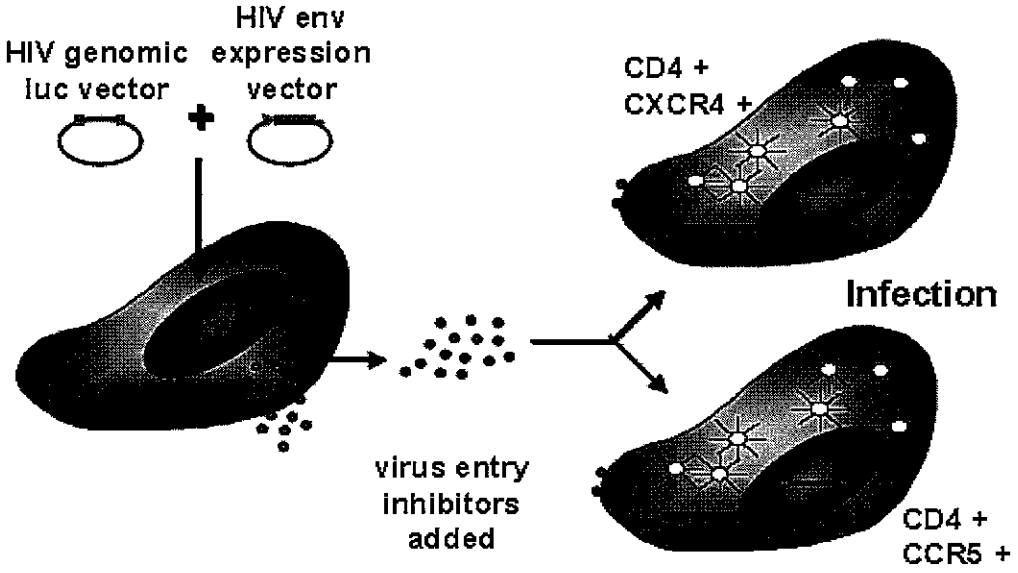


Figure Legend: The assay uses an ***HIV envelope expression vector*** that carries the entire HIV envelope encoding sequence amplified from the sample to be tested. When a plasma sample is analysed, an HIV expression vector library is created, which is composed of a large pool of sequences representing 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 categorised in vitro as CCR5-tropic, CXCR4-tropic or dual-tropic. However, a single patient may harbour 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 8 below:

Table 8. Validation of the PhenoSense™ HIV Entry Tropism Assay (Monogram Biosciences)

Parameter	Overview	Key Performance Finding
Accuracy	Comparison to other methods using characterised 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 copies/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. The methodology and results are detailed in Microbiology Review Of Resistance/Tropism in the Maraviroc Clinical Programme Module 5.3.5.4 Other Studies.

2.7.3.1.5.3. Resistance Mutations and Virus Susceptibility Scores at Baseline

2.7.3.1.5.3.1. 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 in Section 2.7.3.1.5.3.3. 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.

2.7.3.1.5.3.2. 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 in Section 2.7.3.1.5.3.3.

2.7.3.1.5.3.3. Calculation of Genotypic, Phenotypic and Overall Susceptibility Scores

In order to estimate the activity of OBT in each patient, the susceptibility testing from Sections 2.7.3.1.5.3.1 and 2.7.3.1.5.3.2 above were used to calculate the GSS, PSS and OSS.

Table 9 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 ≤500copies/mL.

Table 9. 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.

2.7.3.1.5.3.4. 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. The detailed methodology and results of these exploratory analyses are presented in the Special Review of Resistance in the Maraviroc Clinical Programme (Module 5.3.5.3 Reports of analyses of data from more than one study).

2.7.3.1.5.4. Pharmacogenomic Testing

2.7.3.1.5.4.1. Assessment of CCR5 . 32 Genotype

With appropriate regulatory permission and patient informed consent, blood samples for genetic analysis were collected prior to treatment with either maraviroc or placebo. Patient's DNA samples were analysed in the Sponsor's laboratories to establish CCR5 . 32 status and additional CCR5 locus polymorphisms. The results of these exploratory analyses are presented in the Pharmacogenomics Special Review Report for the maraviroc clinical programme (Module 5.3.5.3 Reports of analyses of data from more than one study), which contains summary reports of pharmacogenomic analyses from more than one study.

2.7.3.1.5.4.2. Analysis of Promotor Haplotype

Combinations of ten of the selected promoter polymorphisms (SNPs) specify ten CCR5 promoter region haplotype alleles, designated P1 through to P10 (Martin MP, 1998). Haplotypes P1 and P4 occur with highest frequency in various populations and were used as the basis to classify individual haplotype pairs (P1 and P4, P1 and other allele, P4 and other allele, neither P1 or P4). In addition to CCR5 . 32 status and additional CCR5 locus polymorphisms, pharmacogenomic studies incorporated analysis of clinical endpoints by classification of likely promoter haplotype as assigned by EM algorithm.

2.7.3.2. Summary of Results of Individual Studies

This section provides a summary of primary and secondary efficacy results from the studies included in this application to support the efficacy of maraviroc. Studies are classified as Phase 3 registrational studies and a Phase 2b supportive study. The pre-defined combined meta-analysis from the two Phase 3 registrational studies is presented in Section 2.7.3.3. Any subgroups analyses and analyses in special populations are presented in Section 2.7.3.4.

2.7.3.2.1. Phase 3 Registrational Studies A4001027 and A4001028

Two multicentre, randomised, double-blind, placebo-controlled registrational Phase 3 superiority studies were conducted to support this application. The study design was identical for both studies and the patient populations were similar between studies and between treatment groups. The results of both studies showed similar effects on the primary and secondary endpoints, therefore these two studies are described together in this section of the document.

Objectives: The primary objective of these studies was to confirm the hypothesis that maraviroc in combination with OBT provided an additional reduction in plasma HIV-1 RNA compared with placebo in combination with OBT, as measured by the difference between each of the two maraviroc regimens versus placebo in the mean change from baseline in plasma HIV-1 RNA at 24 and 48 weeks.

Methods of Study: Patients (N= 585 from A4001027 and N= 464 from A4001028) received a maraviroc 300 mg QD or 300 mg BID dose equivalent or placebo (all in combination with open-label OBT) in a double-blind manner, according to the schedule outlined in Section 2.7.3.1.4.6. No food restrictions were recommended for these studies. The majority of these patients were receiving at least one PI (excluding tipranavir/ritonavir) and/or delavirdine in their OBT and therefore received a dose adjustment to 150 mg maraviroc.

Patient Demographics and Evaluation Groups: The inclusion/exclusion criteria were identical for the two Phase 3 registrational Studies A4001027 and A4001028. As expected, therefore, the baseline characteristics were similar for each study. Table 10 below presents the demographics and baseline characteristics for all treatment groups included in these 2 studies. The study population for both studies (A4001027 and A4001028) predominantly consisted of white males and the range of age, gender and racial groups was similar for all treatment groups. Overall, this was an advanced and heavily pre-treated HIV infected patient population, with a median CD4 count of < 200 cells/∝L, a mean duration of HIV diagnosis of approximately 14 years and more than two-thirds with two or fewer active drugs available to construct a treatment regimen.

Table 10. 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/∝L	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 Sensitivity 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 Sensitivity 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 Sensitivity 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)
. 32 Genotype (W/W, W/D)	200/17	207/13	101/11	157/15	166/15	75/5

Source: A4001027 and A4001028 Clinical Study Reports.
[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.

The numbers of patients discontinuing from treatment was greater in the placebo treatment group compared with both maraviroc treatment groups for both studies (Table 11). 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. 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.

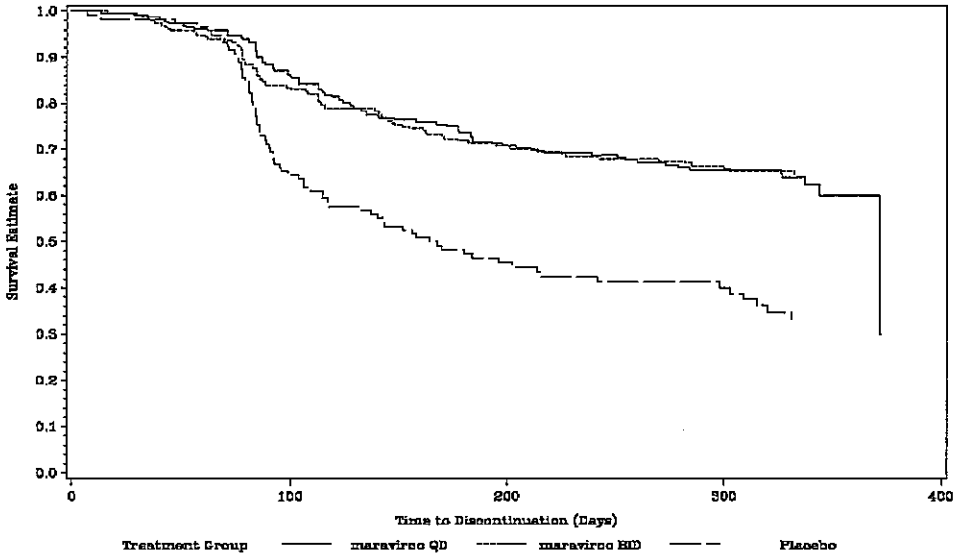
Table 11. Patient Evaluation Groups - Studies A4001027 and A4001028

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)

Source: A4001027 and A4001028 Clinical Study Reports.
[a] Full analysis set.
QD = Once daily dosing; BID = Twice daily dosing.

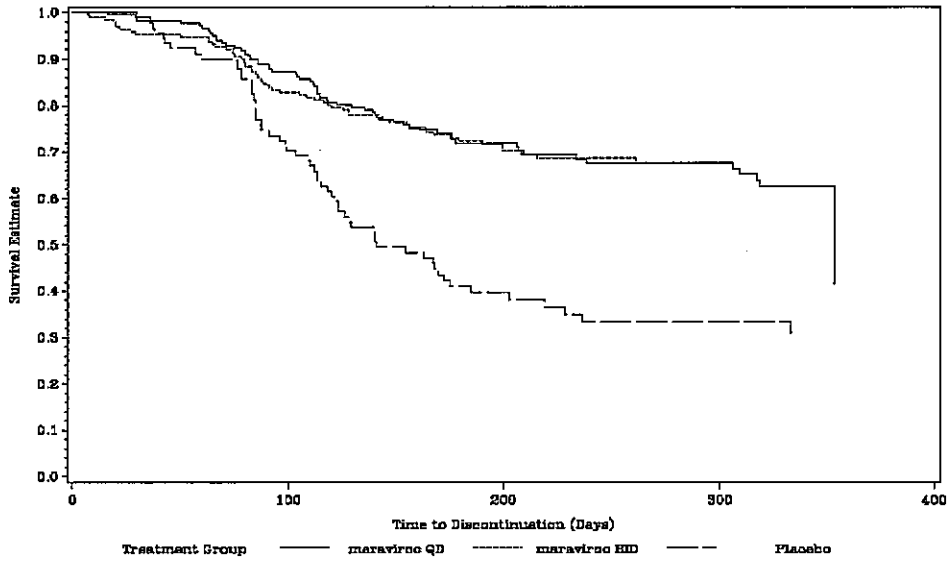
Time to discontinuation in both studies was longer in the maraviroc treatment groups compared with the placebo treatment groups. There did not appear to be a difference between the maraviroc treatment groups. Kaplan Meier plots of time to discontinuation by treatment group for both studies, based on the "Full Analysis Set – As Treated" population, are presented below (Figure 6 and Figure 7).

Figure 6. Kaplan Meier Plot of Time to Discontinuation Study A4001027



Source: A4001027 Clinical Study Report Figure 14.11.1.
The apparent steep drop at the end of the maraviroc QD curve is due to 1 patient discontinuing at Day 372 when only 2 patients had reached this timepoint.

Figure 7. Kaplan Meier Plot of Time to Discontinuation Study A400128



Source: A4001028 Clinical Study Report Figure 14.11.1.
The apparent steep drop at the end of the maraviroc QD curve is due to 1 patient discontinuing at Day 353 when only 3 patients had reached this timepoint.

Primary Efficacy Results: In Study A4001027 there was a greater mean decrease in HIV-1 RNA from baseline to Week 24 in both maraviroc treatment groups compared with placebo (-1.818 and -1.952 versus -1.030 $\log_{10}$ copies/mL for maraviroc QD, BID and placebo respectively). Study A4001028 provided similar results for the primary endpoint (-1.950 and -1.971 versus -0.929 $\log_{10}$ copies/mL for maraviroc QD, BID and placebo respectively).

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.

For both studies, the results of the "Full Analysis Set – As Randomised", "Per Protocol – As Randomised" and "Per Protocol – As Treated" population were consistent with the results for the "Full Analysis Set – As Treated" population presented above (these analyses are presented in the A4001027 and A4001028 Clinical Study Reports Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication).

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 2.7.3.1.4.7), 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 12 below.

Table 12. 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 HIV-1 RNA (log_{10} copies/mL)			Study A4001028 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

Source: A4001027 and A4001028 Clinical Study Reports, Appendix Table A 10.3.6.
[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, demonstrating that maraviroc QD and BID were superior compared with placebo.

Secondary Endpoints: A similar pattern of results was observed for the secondary endpoints analysed in Studies A4001027 and A4001028. 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 13). The results for all secondary endpoint analyses demonstrated superiority for both maraviroc groups compared with placebo as the confidence intervals were completely to the left side and completely excluded zero.

Table 13. 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)	118 (61.8)	21 (23.1)
<50 copies/mL, n (%)	98 (42.2)	114 (48.5)	29 (24.6)	84 (46.2)	79 (41.4)	19 (20.9)
=0.5 log_{10} Viral Load Decrease, n (%)	151 (65.1)	161 (68.5)	46(39.0)	121 (66.5)	134 (70.2)	29 (31.9)
=1.0 log_{10} Viral Load Decrease, n (%)	15 (68.5)	166 (70.6)	55 (46.6)	128 (70.3)	137 (71.7)	32 (35.2)

Source: A4001027 and A4001028 Clinical Study Reports.
QD = Once daily dosing; BID = Twice daily dosing.

For both studies, there was a significantly greater mean increase in CD4 and CD8 cell counts from baseline in both maraviroc treatment groups compared with placebo (Table 14 and Table 15). In addition, for both studies at Week 24, there was an increase from baseline in

CD4% (CD4 cell count as a percentage of the total lymphocyte count) of similar size in all the treatment groups and a small decrease in CD8% (CD8 cell count as a percentage of the total lymphocyte count) from baseline in the maraviroc treatment groups and a larger decrease in the placebo treatment group.

Table 14. Summary of Mean Changes from Baseline to Week 24 in CD4 Cell Count (Studies A4001027 and A4001028)

Treatment Group	Study A4001027 CD4 Cell Count (cells/∝L)			Study A4001028 CD4 Cell Count (cells/∝L)		
	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

Source: A4001027 and A4001028 Clinical Study Reports, Table 13.4.6.11.
[a] Compared with placebo.
QD = Once daily dosing; BID = Twice daily dosing; CI = Confidence interval; N/C = Not calculated; se = Standard error.

Table 15. Summary of Mean Changes from Baseline to Week 24 in CD8 Cell Count (Studies A4001027 and A4001028)

Treatment Group	Study A4001027 CD8 Cell Count (cells/∝L)			Study A4001028 CD8 Cell Count (cells/∝L)		
	N	Adjusted Mean (se)	Difference[a] (95% CI)	N	Adjusted Mean (se)	Difference[a] (95% CI)
Maraviroc QD	227	283.5 (30.2)	284.2 (182.5, 385.9)	180	340.7 (41.6)	218.6 (78.6, 358.5)
Maraviroc BID	233	302.3 (29.7)	303.1 (201.9, 404.2)	185	255.4 (40.9)	133.2 (-6.0, 272.5)
Placebo	116	-0.74 (42.2)	N/C	90	122.2 (58.2)	N/C

Source: A4001027 and A4001028 Clinical Study Reports, Table 13.4.6.12.
[a] Compared with placebo.
QD = Once daily dosing; BID = Twice daily dosing; CI = Confidence interval; N/C = Not calculated; se = Standard error.

Conclusion: Statistical analysis of the primary endpoint, mean change from baseline to Week 24 in viral load, demonstrated that both doses of maraviroc were superior compared with placebo for both Phase 3 registrational studies. No difference in efficacy outcome was observed between the two studies.

This outcome was repeated for each of the pre-defined secondary analyses, which included virologic and immunologic endpoints. These studies were not designed to compare the QD and BID doses of maraviroc directly, however, both studies demonstrated similar results between maraviroc doses and in the overall combined analysis within each study there was no indication of a clinically relevant difference between them. A combined analysis of both studies is presented below which further explores the comparative efficacy of maraviroc QD and BID.

Detailed analyses for Studies A4001027 and A4001028 are presented within the Clinical Study Reports, which are included in Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication.

2.7.3.2.2. Phase 2b Supportive Study A4001029

2.7.3.2.2.1. A4001029 Analysis of Primary and Key Secondary Endpoints

Study A4001029 was a multicentre, double-blind, randomised, placebo-controlled Phase 2b study to investigate the safety and antiviral effects of two doses of maraviroc (QD and BID) in heavily treatment-experienced patients infected with non-CCR5 tropic (dual tropic, CXCR4-tropic or non-phenotypable) HIV-1. The safety data for this study is presented in Module 2.7.4 Summary of Clinical Safety.

Objectives: The primary objective of this study was to assess if maraviroc in combination with OBT provided an additional reduction in plasma HIV-1 RNA level compared with OBT alone at Week 24. Secondary objectives included the percentage of patients achieving an HIV-1 RNA level <400 and <50 copies/mL, percentage of patients achieving at least a 0.5 and 1.0 $\log_{10}$ reduction in HIV-1 RNA level from baseline, differences in the magnitude of change in CD4 and CD8 cell count from baseline and TAD in $\log_{10}$ HIV-1 RNA level.

Methods of Study: Patients (N=186) were treated with maraviroc 300 mg QD or 300 mg BID dose equivalents or placebo, each in combination with OBT. The majority of these patients were receiving at least one PI and/or delavirdine in their OBT and therefore received a dose adjustment to a maraviroc 150 mg unit dose. Of the patients treated in this study 167 were classified as infected with dual/mixed tropic HIV-1, which was the principal population analysed, 8 patients were infected with CXCR4-tropic virus only, 1 patient was infected with CCR5 tropic virus, and for 7 patients no tropism result was available.

Patient Demographics and Evaluation Groups: The study population was predominantly white male. The range of age, gender and racial mix was similar for all treatment groups (Table 16). This was an extremely advanced patient population, with a median CD4 cell count of <50 cells/∝L 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 16. 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/∝L)			
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 . 32 Genotype			
WT/WT	44	54	46
WT/. 32	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)

Source: A4001029 Clinical Study Report.
[a] Baseline values were calculated as the average of three pre-dose assessments taken at screening, randomisation 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.

Primary Efficacy Results: The following Table 17 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 of each maraviroc dose versus placebo.

Table 17. 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

Source: A4001029 Clinical Study Report, Table 13.4.6.1.2.
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.

Secondary 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 18).

Table 18. 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)

Source: A4001029 Clinical Study Report.
[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 19 presents the change in CD4 and CD8 cell counts from baseline to Week 24 for all treatment groups.

Table 19. Statistical Analysis of Change from Baseline to Week 24 in CD4 and CD8 Cell Count[a] (Study A4001029)

Treatment Group	CD4 Cell Count (cells/∝L)			CD8 Cell Count (cells/∝L)		
	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

Source: A4001029 Clinical Study Report.
[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.

There was an increase in CD4% of similar size in all treatment groups (mean increase: 2.04, 2.75 and 3.48% for maraviroc QD, BID and placebo respectively) and a small CD8% decrease in the maraviroc groups but a larger decrease in the placebo group (Mean decrease: -0.22, -0.32 and -2.59% for maraviroc QD, BID and placebo respectively).

There was a larger mean decrease in viral load from baseline to Week 24 for patients with an OSS =2 in all treatment groups. This is consistent with the fact that patients with more active drugs in antiretroviral drug regimen in general have a better virologic response. There was a trend towards a larger viral load decrease in both maraviroc treatment groups than placebo for patients with an OSS of 0-1 (mean change in HIV-1 RNA from baseline -0.793 and -0.537 versus -0.288 $\log_{10}$ copies/mL for maraviroc QD, BID and placebo respectively). This pattern was repeated for secondary efficacy endpoints, most notably for change in CD4 cell count in patients with an OSS of 0-1 (mean change in CD4 cell count from baseline +54 and +44 versus -7 cells/∝L for maraviroc QD, BID and placebo respectively).

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.

Conclusion: The primary reason for conducting this study was to determine whether it was safe to add maraviroc to OBT in patients with documented dual/mixed tropic HIV-1. Of particular concern was the possibility that 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 non-inferiority assumptions made of a small benefit for maraviroc (0.25 $\log_{10}$ superiority to placebo). There was no evidence of virologic harm and there was a trend

towards a larger viral load change in both the maraviroc treatment groups compared with placebo for patients with an OSS of 0-1.

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.

The adverse event profile for both maraviroc treatment groups was similar to that of the placebo treatment group. There were no clinically significant safety concerns highlighted by the results of this study. The results are presented in detail in Module 2.7.4 Summary of Clinical Safety.

Detailed analyses for Study A4001029 are presented within the Clinical Study Report, which is included in Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication.

2.7.3.2.2.2. Analysis of Viral Tropism and CD4 Data at Week 24 and Time of Failure

A post hoc analysis to investigate changes in viral tropism assignment in patients receiving maraviroc in study A4001029 and the effect on clinical outcome was performed. The full results of this analysis are presented in a separate report (Post Hoc Analysis Report: Protocol A4001029, Module 5.3.4.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication).

2.7.3.2.2.2.1. Changes in Viral Tropism Result During the Study

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 dual/mixed to CCR5 tropic, while 2 had a change in tropism result from dual/mixed to CXCR4 tropic. These patients were included in the analysis of the Full Analysis Set population but were excluded from the Per Protocol analysis population.

Of the patients who failed treatment and for whom a valid tropism test result was available, 31 of 75 patients (41%) had a different viral tropism result at failure (Table 20). 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 a CXCR4 tropism result at failure in the maraviroc arms, compared with 2 of out 22 (9%) patients in the placebo group, consistent with selective suppression by maraviroc of CCR5 tropic virus strains in these patients.

Table 20. Tropism Status at Failure for Patients with Dual/Mixed Status at Screening who Discontinued due to Treatment Failure

	Time of treatment failure Tropism Status					
Treatment arm	R5	X4	D/M	NR	BLQ	N
QD	1	12	19	0	1[a]	33
BD		12	9	0	0	21
Placebo	4	2	16	1	0	23
N	5	26	44	1	1	77

Data extracted from study A4001029 Table 13.4.10.1.3
[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

2.7.3.2.2.2.2. Increases in CD4 Cell Counts for Virologic Responders versus Failures

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 21).

Table 21. Mean Change (Range) in CD4 Cell Count (cells/∝L) from Baseline to Week 24

	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 randomisation 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.

2.7.3.2.2.2.3. Changes in CD4 Cell Count for Patients who had a CXCR4 Tropism Result at Time of Failure

Changes in CD4 cell count from baseline to the time of treatment failure were the same for patients on maraviroc who had a CXCR4 tropism result at failure and those whose tropism result remained dual/mixed (Table 22), confirming that a CXCR4 tropism result was not associated with an adverse CD4 cell count outcome in this patient population.

Table 22. 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

			Change from baseline		
Treatment arm	**Tropism BL to TOF**	**N**	**Mean**	**Median**	**Range**
MVC 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
MVC 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	-104	-104	-118 to -89
	D/M to other[b]	1	+29	+29	N/A

Data extracted from A4001029 CSR Tables A10.11.2 and A10.12.1.
[a] BLQ
[b] Non phenotypable/no result
BL = baseline (Day 1 pre-dose); TOF = protocol defined treatment failure; D/M = Dual/mixed tropism result/ X4 = CXCR4 tropism result; R5 = CCR5 tropism result; N/A = Not available.

2.7.3.3. Comparison and Analyses of Results across 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, double-blind, placebo-controlled registrational studies, which were conducted in overlapping geographic areas; A4001027 from North America and A4001028 from Europe, Australia and the USA. These studies were designed to reflect a heavily treatment-experienced HIV-1 population who were failing their current antiretroviral therapy or were infected with multi-drug resistant virus. These Phase 3 studies were designed and carried out in accordance with the FDA Guidance for Industry document (Antiretroviral Drugs Using Plasma HIV RNA measurements – Clinical Considerations for Accelerated and Traditional Approval, October 2002).

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. Maraviroc was not expected to, and did not, demonstrate superior virological efficacy over placebo in this patient population. It did not demonstrate non-inferiority to placebo. It did, however, demonstrate no harm in this patient population; there were no differences in efficacy parameters from placebo and the adverse event profile was similar to placebo for both doses of maraviroc. The efficacy

results of this study have not been combined with the Phase 3 registrational studies and therefore do not appear in this section of the document.

This section describes the primary and secondary efficacy endpoints of a pre-defined interim analysis conducted at Week 24 and presents the combined results of the two Phase 3 registrational studies. Subgroup analyses conducted on this combined data set are presented in Section 2.7.3.4.

2.7.3.3.1. Study Populations

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. In addition, the median resistance mutations associated with PIs, NNRTIs, NRTIs and enfuvirtide were similar between treatment groups (Table 23).

Table 23. 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/∝L)[a,b]	195.7	189.2	187.2
PI Resistance Mutations at Screening,	N= 412[c]	N= 425[c]	N=206[c]
Median (Range)	10 (0, 18)	10 (0, 17)	10 (0, 17)
NNRTI Resistance Mutations at	N= 412[c]	N= 425[c]	N=206[c]
Screening, Median (Range)	1 (0, 5)	1 (0, 5)	1 (0, 5)
NRTI Resistance Mutations at	N= 412[c]	N= 425[c]	N=206[c]
Screening, Median (Range)	6 (0, 11)	6 (0, 11)	6 (0, 13)
Patients with Enfuvirtide Mutations at	N=411[c]	N= 424[c]	N= 209[c]
Screening, n (%)	78 (19.0)	90 (21.2)	45 (21.5)

Source: A4001027 and A4001028 Clinical Study Report Tables 13.2.1.1, 13.4.3.1.1, 13.4.4.1 and Table 15.9.1 Summary of Clinical Efficacy.

[a] Mean of all pre-dose assessments (screening, randomisation (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.

As noted, 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 24).

Table 24. 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)

Source: Table 13.4.9.1.11 Summary of Clinical Efficacy.
[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.

2.7.3.3.2. Comparison of Efficacy Results of all Studies

Two independent, double-blind, placebo-controlled pivotal studies were conducted (A4001027 and A4001028). These two studies demonstrated similar clinically significant reductions in viral load from baseline to Week 24 for maraviroc QD and BID compared with placebo. The primary endpoint and selected secondary endpoints for these studies are presented in Table 25 below.

Table 25. Selected Efficacy Endpoints at Week 24 (Studies A4001027 and A400128)

	Study A4001027			Study A4001028		
	Maraviroc QD	Maraviroc BID	Placebo	Maraviroc QD	Maraviroc BID	Placebo
Mean (se). HIV-1 RNA[a] (copies/mL)	N= 232 -1.818 (0.092)	N= 235 -1.952 (0.091)	N= 118 -1.030 (0.129)	N= 182 -1.950 (0.105)	N= 191 -1.971 (0.103)	N= 91 -0.929 (0.147)
Patients <400 copies/mL, n (%)	N= 232 127 (54.7)	N= 235 142 (60.4)	N= 118 37 (31.4)	N= 182 101 (55.5)	N= 191 118 (61.8)	N= 91 21 (23.1)
Patients <50 copies/mL, n (%)	N= 232 98 (42.2)	N= 235 114 (48.5)	N= 118 29 (24.6)	N= 182 84 (46.2)	N= 191 79 (41.4)	N= 91 19 (20.9)
Patients >1 $\log_{10}$ Reduction in HIV-1 RNA, n (%)	N= 232 151 (65.1)	N= 235 161 (68.5)	N= 118 46 (39.0)	N= 182 121 (66.5)	N= 191 134 (70.2)	N= 91 29 (31.9)
Mean (se). CD4 Count[a] (cells/∝L)	N= 227 106.6 (7.3)	N= 233 111.1 (7.2)	N= 116 52.1 (10.1)	N= 180 111.7 (7.8)	N= 185 101.9 (7.7)	N= 90 63.8 (10.9)
Mean (se). CD8 Count[a] (cells/∝L)	N= 227 283.5 (30.2)	N= 233 302.3 (29.8)	N= 116 -0.7 (42.2)	N= 180 340.7 (41.6)	N= 185 255.4 (40.9)	N= 90 122.2 (58.2)

Source: A4001027 and A4001028 Clinical Study Reports.
[a] Change from Baseline to Week 24.
QD = Once daily dosing; BID = Twice daily dosing; se = Standard error.

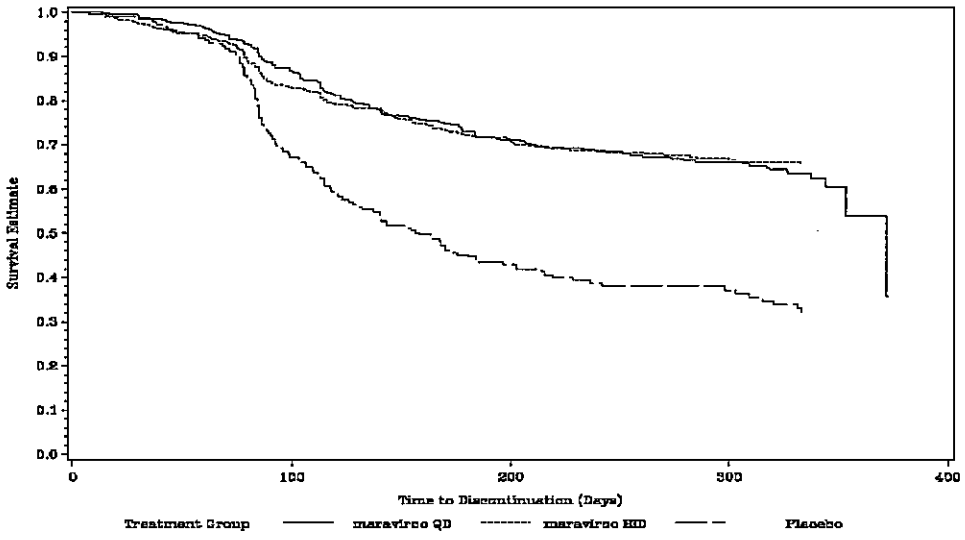
A pre-determined meta-analysis of these two registrational studies was conducted and the results are presented in the following sections of this document. Unless otherwise stated, analyses are presented for the 'as treated' population from the Full Analysis Set, as defined in Section 2.7.3.1.4.8. The baseline value used in the calculation of change from baseline is the average of the pre-dose measurements collected at the screening, randomisation and baseline visits.

The following sections present the results for the comparison between both doses of maraviroc and placebo. A comparison of maraviroc QD treatment versus BID treatment is discussed in Section 2.7.3.5.

2.7.3.3.2.1. Time to discontinuation and treatment failure

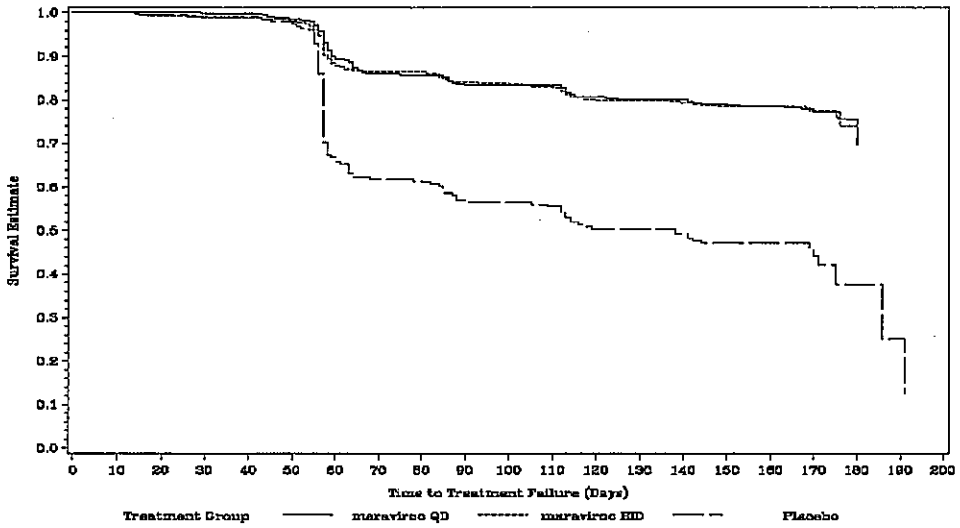
Both the time to discontinuation and the time to treatment failure were longer in the maraviroc QD and BID treatment groups compared with the placebo treatment group. There did not appear to be a difference between the maraviroc treatment groups. Kaplan Meier plots of time to discontinuation (to week 48 visit) and time to failure (to week 24 visit) presented by treatment group, based on the "Full Analysis Set – As Treated" population, are presented below (Figure 8 and Figure 9).

Figure 8. Kaplan Meier Plot of Time to Discontinuation (Combined Studies A4001027 and A4001028)



Source: Figure 14.11.1 Summary of Clinical Efficacy.
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.

Figure 9. Kaplan Meier Plot of Time to Treatment Failure (Combined Studies A4001027 and A4001028)

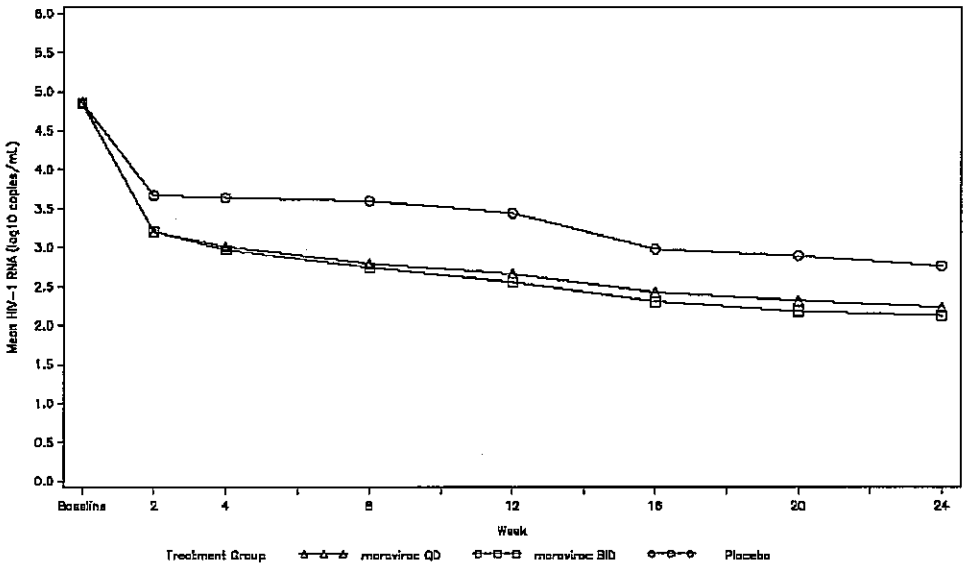


Source: Figure 14.11.3 Summary of Clinical Efficacy.

2.7.3.3.2.2. Primary Endpoint Analysis

There was a significantly greater reduction in viral load from baseline for both doses of maraviroc compared with placebo at each study visit. Figure 10 presents the mean HIV-1 RNA level by visit, considering only patients still receiving study drug at each visit, in the combined A4001027/A4001028 analysis.

Figure 10. Line Plot of Mean HIV-1 RNA Level (log_{10} copies/mL) by Visit (Combined Studies A4001027 and A4001028)



Source: Figure 14.1.1 Summary of Clinical Efficacy.
Only those patients still in study are included at each timepoint.

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: -1.875, -1.963 compared with -0.981 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 26 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 26. Statistical Analysis of Change from Baseline to Week 24 in log_{10} HIV-1 RNA (Combined Studies A4001027 and A4001028)

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

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

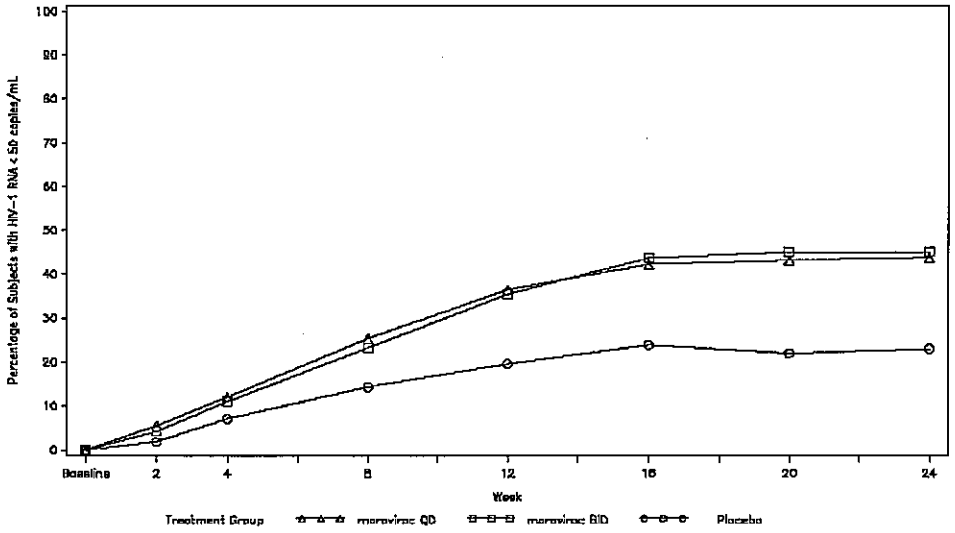
As in the individual studies, the 2-sided 97.5% confidence intervals were completely to the left side of zero, excluding zero, indicating the superiority of maraviroc QD and maraviroc BID over placebo. In addition, the upper bound of the 97.5% confidence intervals was to the left of 0.5 $\log_{10}$ copies/mL.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

2.7.3.3.2.3. Secondary Endpoint Analysis

2.7.3.3.2.3.1. 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)



Source: Figure 14.4.1 Summary of Clinical Efficacy.
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 27 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 27. Statistical Analysis of Proportion of Patients with HIV-1 RNA Level <50 copies/mL at Week 24 (Logistic Regression) (Combined Studies A4001027 and A4001028)

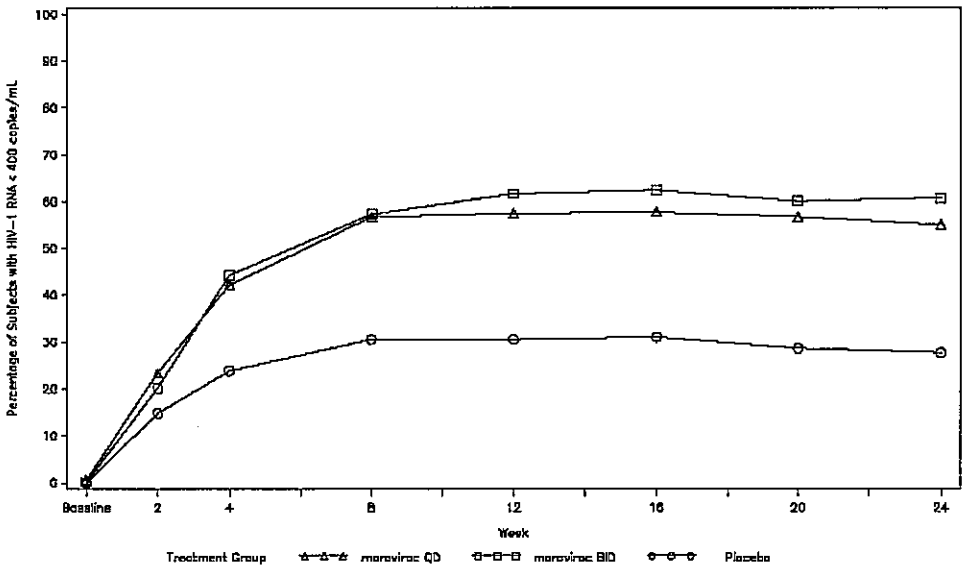
Treatment Group	N	Positive Response (%)	Odds Ratio	Treatment Comparison Maraviroc-Placebo 95% CI for Odds Ratio	P-Value
Maraviroc QD	414	44.0	2.87	1.95, 4.22	<0.0001
Maraviroc BID	426	45.3	3.02	2.05, 4.44	<0.0001
Placebo	209	23.0	N/C	N/C	N/C

Source: Table 13.4.6.5.1 Summary of Clinical Efficacy.
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.

2.7.3.3.2.3.2. 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)



Source: Figure 14.3.1 Summary of Clinical Efficacy.
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 28 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 28. Statistical Analysis of Proportion of Patients with HIV-1 RNA Level <400 copies/mL at Week 24 (Logistic Regression) (Combined Studies A4001027 and A4001028)

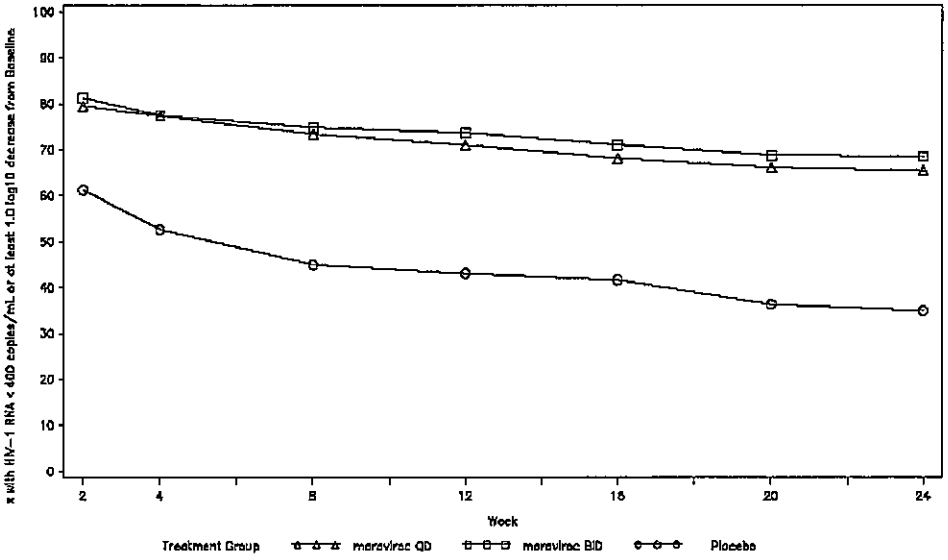
Treatment Group	N	Positive Response (%)	Odds Ratio	Treatment Comparison Maraviroc-Placebo 95% CI for Odds Ratio	P-Value
Maraviroc QD	414	55.1	3.48	2.41, 5.04	<0.0001
Maraviroc BID	426	61.0	4.49	3.10, 6.51	<0.0001
Placebo	209	27.8	N/C	N/C	N/C

Source: Table 13.4.6.3.1 Summary of Clinical Efficacy.
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.

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

There was a higher proportion of patients in the maraviroc QD and BID treatment groups who achieved at least a 1.0 $\log_{10}$ copies/mL reduction in HIV-1 RNA level from baseline or <400 copies/mL compared with placebo at each study visit (Figure 13).

Figure 13. Percentage of Patients with at Least a 1.0 log_{10} Reduction from Baseline in HIV-1 RNA or <400 copies/mL by Study Visit (Combined Studies A4001027 and A4001028)



Source: Figure 14.5 Summary of Clinical Efficacy.
Discontinuations and failures are included at all timepoints.

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 29 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 29. 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)

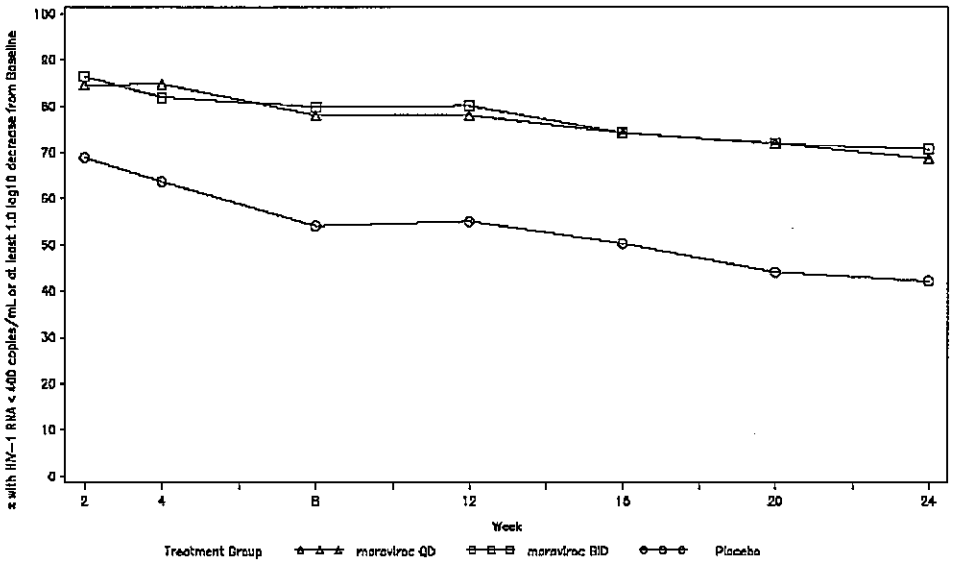
Treatment Group	N	Positive Response (%)	Odds Ratio	Treatment Comparison Maraviroc-Placebo 95% CI for Odds Ratio	P-Value
Maraviroc QD	414	65.7	3.63	2.55, 5.17	<0.0001
Maraviroc BID	426	69.2	4.25	2.98, 6.07	<0.0001
Placebo	209	35.9	N/C	N/C	N/C

Source: Table 13.4.6.7 Summary of Clinical Efficacy.
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.

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

There was a higher proportion of patients in the maraviroc QD and BID treatment groups who achieved at least a 0.5 log_{10} reduction in HIV-1 RNA level from baseline or <400 copies/mL compared with placebo at each study visit (Figure 14).

Figure 14. Percentage of Patients with at Least a 0.5 log_{10} Reduction from Baseline in HIV-1 RNA or <400 copies/mL by Study Visit (Combined Studies A4001027 and A4001028)



Source: Figure 14.6 Summary of Clinical Efficacy.
Discontinuations and failures are included at all timepoints.

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 30 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 30. 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

Source: Table 13.4.6.9 Summary of Clinical Efficacy.
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.

2.7.3.3.2.3.5. 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 31 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 31. Statistical Analysis for Time Averaged Difference (TAD) from Baseline to Week 24 in log_{10} HIV-1 RNA (Combined Studies A4001027 and A4001028)

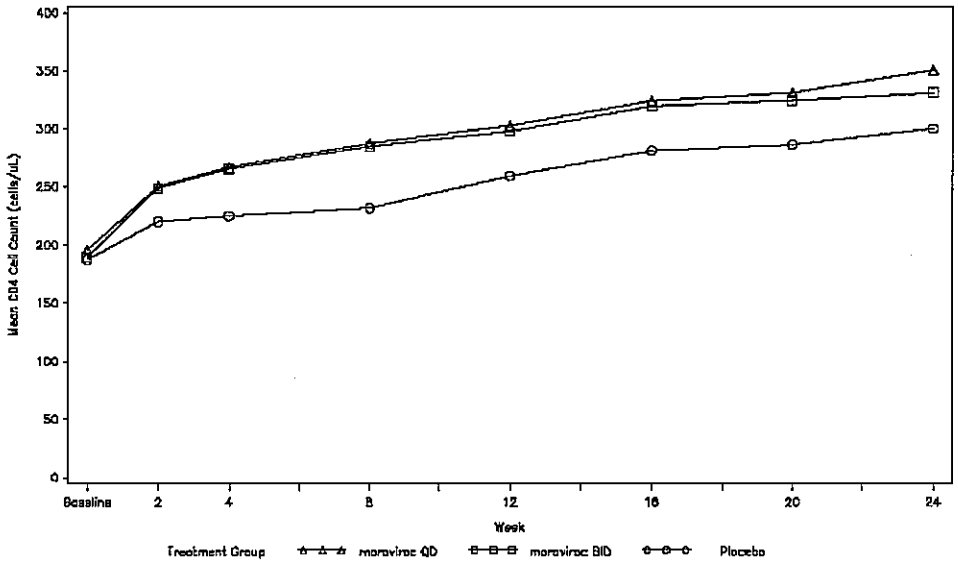
Treatment Group	N	Change from Baseline to Week 24 in TAD (log10 copies/mL)			Treatment Difference Maraviroc-Placebo	
		Raw Median	Raw Mean (se)	Adjusted Mean (se)	Estimate (se)	95% CI
Maraviroc QD	414	-2.105	-1.683 (0.059)	-1.686 (0.059)	-0.775 (0.101)	-0.973, -0.576
Maraviroc BID	426	-2.197	-1.748 (0.058)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

Source: Table 13.4.6.10 Summary of Clinical Efficacy.
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.

2.7.3.3.2.3.6. Change from Baseline to Week 24 in CD4 Cell Count

There was a greater increase in CD4 cell count from baseline for both maraviroc treatment groups compared with placebo at each study visit, considering only subjects still receiving study drug at each visit (Figure 15).

Figure 15. Line Plot of Mean CD4 Cell Count (cells/∝L) by Study Visit (Combined Studies A4001027 and A4001028)



Source: Figure 14.7 Summary of Clinical Efficacy.
Only those patients still in study are included at each timepoint.

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/∝L for maraviroc QD, BID and placebo respectively). Table 32 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 32. Statistical Analysis for Change in CD4 Cell Count from Baseline to Week 24 (Combined Studies A4001027 and A4001028)

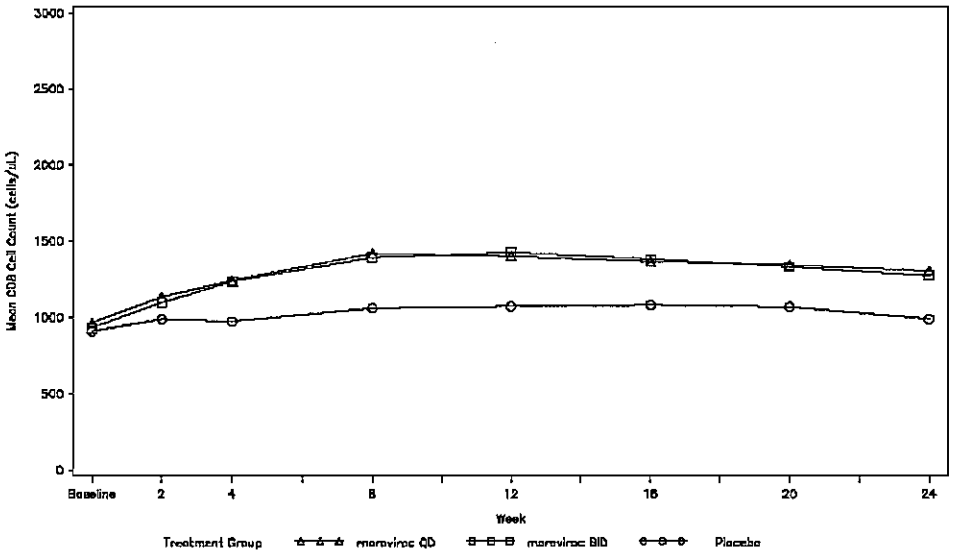
Treatment Group	N	Change from Baseline to Week 24 in CD4 Cell Count (cells/∝L)			Treatment Difference Maraviroc-Placebo	
		Raw Median	Raw Mean (se)	Adjusted Mean (se)	Estimate (se)	95% CI
Maraviroc QD	407	86.0	108.7 (6.0)	108.6 (5.3)	51.2 (9.2)	33.3, 69.2
Maraviroc BID	418	88.3	105.8 (4.9)	106.3 (5.3)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

Source: Table 13.4.6.11 Summary of Clinical Efficacy.
Last Observation Carried Forward (LOCF) was used to impute missing values.
CI = Confidence interval; N/C = Not calculated; se = Standard error.

2.7.3.3.2.3.7. Change from Baseline to Week 24 in CD8 Cell Count

There was a greater increase in CD8 cell count from baseline for both maraviroc treatment groups compared with placebo at each study visit, considering only subjects still receiving study drug at each visit (Figure 16).

Figure 16. Line Plot of Mean CD8 Cell Count (cells/∝L) by Study Visit (Combined Studies A4001027 and A4001028)



Source: Figure 14.9 Summary of Clinical Efficacy.
Only those patients still in study are included at each timepoint.

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/∝L for maraviroc QD, BID and placebo respectively). Table 33 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 33. 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/∝L)			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

Source: Table 13.4.6.12 Summary of Clinical Efficacy.
Last Observation Carried Forward (LOCF) was used to impute missing values.
CI = Confidence interval; N/C = Not calculated; se = Standard error.

2.7.3.4. Comparison of Results in Subpopulations

The results for the following subpopulation splits are presented for the combined Phase 3 registrational study meta-analysis.

2.7.3.4.1. Effects of Age

The majority of patients (98%) recruited into Studies A4001027 and A4001028 were <65 years old; there were very few patients =65 years. The primary endpoint, change in HIV-1 RNA from baseline to Week 24, was analysed by the following age brackets, <45 (N=434), 45-65 (N= 597) and =65 years (N= 18). Although there were very few patients aged =65 years, the results did not indicate an effect of age on response to therapy in any of the treatment groups.

2.7.3.4.2. Effects of Gender

The majority of patients (89%) participating in Studies A4001027 and A4001028 were male, which adequately represented the wider patient population from which the studies were recruited. An explanation of the global patient population that constitutes heavily treatment-experienced patients is provided in the Risk Management Plan.

Although there were very few females included in these studies the results did not indicate an effect of gender on reduction in HIV-1 RNA from baseline.

2.7.3.4.3. Effects of Race

The majority of patients participating in Studies A4001027 and A4001028 were white (83.9); 13.7% were black, 0.9% Asian and 1.4% were designated other (one patient was unspecified).

Regarding subgroup analysis by race, the summary of change from baseline in viral load at Week 24 by race (Table 34) indicated that the black placebo subgroup had an unusually high mean change from baseline (-1.515 $\log_{10}$ copies/mL) compared with the white placebo subgroup (-1.132 $\log_{10}$ copies/mL). This may be explained by the small number of patients in the black placebo subgroup, n=25, and also by the skewed nature of the data in the black

placebo treatment group towards higher decreases in viral load (10 of the 25 subjects in the placebo treatment group had a decrease in viral load >2.0 log_{10} copies/mL).

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

Race		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]
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)
Asian	N[b]	3	5	1
	Mean (SD)	-2.424 (0.458)	-2.729 (0.667)	0.101 (N/C)
	Median (Range)	-2.271 (-2.939,-2.062)	-2.972 (-3.485, -1.821)	0.101 (N/C)
Other	N[b]	4	7	3
	Mean (SD)	-2.690 (1.434)	-2.227 (1.316)	-0.261 (0.397)
	Median (Range)	-2.886 (-4.224, -0.763)	-2.842 (-3.389, -0.292)	-0.131 (-0.706, 0.055)

Source: Table 13.4.9.1.6 Summary of Clinical Efficacy.
[a] Number of patients in 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.
QD = Once daily dosing; BID = Twice daily dosing; N/C = Not calculated; SD = Standard deviation.

The mean change from baseline for the subgroup of black patients receiving maraviroc QD and BID was -1.799 log_{10} copies/mL and -1.704 log_{10} copies/mL, respectively, compared with -1.515 log_{10} copies/mL for placebo. The median change from baseline for black patients receiving maraviroc QD and BID, respectively, was -2.170 copies/mL and -1.858 log_{10} copies/mL compared with -0.801 log_{10} copies/mL for placebo. The difference in the mean and median results for the placebo treatment group at Week 24 in this 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 median viral load change from baseline to Week 24 for white patients was -2.437 log_{10} copies/mL compared with -2.170 log_{10} copies/mL for black patients. For patients receiving maraviroc BID the median viral load change from baseline for white patients was -2.571 log_{10} copies/mL and -1.858 log_{10} copies/mL for black patients. The range of change from baseline across the 4 racial subgroups (white, black, Asian and other) was similar, but the numbers in the Asian and other subgroups were very small.

Discussion of these results is included in Section 2.5.4 Module 2.5 Clinical Overview.

2.7.3.4.4. Effects of Geographic Region/Country

Study A4001027 was conducted exclusively in North America (USA and Canada). Study A4001028 included several countries from Europe, Australia and North America. Across the two studies, a total of 659 patients from the USA were included. Analysis of change from baseline in HIV-1 RNA at Week 24 for subjects from the USA compared with those from outside the USA in both studies demonstrated a significant treatment benefit for subjects receiving maraviroc, irrespective of whether they were from the USA, or from other regions included in the study. In addition, there was no clinically important difference in viral load reduction for patients receiving maraviroc depending on whether they were from the USA or not.

2.7.3.4.5. Effect of Clade B versus Non-Clade B Virus

Virus subtype (clade) varies geographically. Although Clade B virus is not the most common subtype worldwide, it the predominant subtype found in North America and Western Europe by a large margin (McCutchan., 2006, Osmanov S, 2002). As the majority of patients recruited into Studies A4001027 and A4001028 were from North America and Western Europe, it is not surprising that 94% of those for whom virus subtype could be determined were infected with Clade B virus. Table 35 presents the change from baseline to Week 24 in HIV-1 RNA split by Clade.

Table 35. Summary of Change from Baseline to Week 24 in HIV-1 RNA Split by Virus Subtype (Clade B, non-Clade B or Undetermined) (Combined Studies A4001027 and A4001028)

Virus Subtype		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]
Clade B	N[b]	385	400	197
	Mean (SD)	-2.081 (1.277)	-2.154 (1.281)	-1.170 (1.294)
	Median (Range)	-2.388 (-4.492, 2.039)	-2.467 (-4.547, 1.317)	-0.629 (-4.148, 0.965)
Non-Clade B	N[b]	19	15	7
	Mean (SD)	-2.264 (1.301)	-2.305 (1.213)	-1.279 (1.469)
	Median (Range)	-2.268 (-4.231, 0.259)	-2.557 (-3.890, -0.218)	-0.346 (-3.398, 0.218)
Undetermined	N[b]	4	4	3
	Mean (SD)	-2.318 (0.486)	-1.999 (1.655)	-0.181 (0.459)
	Median (Range)	-2.240 (-2.974, -1.819)	-2.554 (-3.199, 0.313)	-0.361 (-0.521, 0.341)

Source: Table 13.4.9.1.15 Summary of Clinical Efficacy.
[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) values were used to impute missing values.
QD = Once daily dosing; BID = Twice daily dosing; SD = Standard deviation.

Although no firm conclusions can be drawn from these results, as the numbers of patients infected with non-Clade B virus were very small, there was no pattern of effect of virus subtype observed in mean or median reduction in HIV-1 RNA from baseline in any of the treatment groups.

2.7.3.4.6. Efficacy Analysis Split by Baseline CD4 Cell Count

Primary and selected secondary efficacy endpoints were analysed for the combined A4001027 and A4001028 results by CD4 cell count at baseline in order to assess any differences in the response to treatment, as lower CD4 cell counts are often associated with more advanced disease. Patients' CD4 cell counts were divided into strata of <50, 50-100, 101-200, 201-350 and >350 cells/∝L. The majority of patients recruited into both studies, irrespective of treatment group had baseline CD4 cell counts of 101-350 cells/∝L.

Table 36 presents the change in HIV-1 RNA from baseline to Week 24 split by baseline CD4 cell count.

Table 36. 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/∝L	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/∝L	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/∝L	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/∝L	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/∝L	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)

Source: Table 13.4.9.1.3 Summary of Clinical Efficacy.
[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.

For each CD4 cell count group the superiority of both doses of maraviroc over placebo remained apparent. Although the group of patients with baseline CD4 cell count of <50 cells/∝L had a less marked reduction in mean and median HIV-1 RNA from baseline compared with patients with higher CD4 cell counts, the mean reduction in viral load for this category was still >1.3 log_{10} HIV-1 RNA copies/mL for both maraviroc treatment groups compared with 0.632 for placebo. For patients with baseline CD4 cell counts >50 cells/∝L there did not appear to be an association between CD4 cell count and reduction in viral load from baseline; both doses of maraviroc achieved a mean and median reduction in viral load of >2.1 (range 2.181 to 2.520) and >2.4 (range 2.465 to 2.645) log_{10} copies/mL respectively,

compared with a mean and median reduction of >0.9 (range 0.943 to 1.439) and >0.3 (range 0.396 to 1.306) $\log_{10}$ copies/mL for placebo (Table 36).

Table 37 presents the percentage of patients achieving an HIV-1 RNA <50 copies/mL at Week 24 by patients' CD4 cell count at baseline.

Table 37. 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/∝L)	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)

Source: Table 15.3.3 Summary of Clinical Efficacy.
[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/∝L 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/∝L 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/∝L, however, there were approximately twice as many patients achieving an HIV-1 RNA <50 copies/mL in the maraviroc BID group than maraviroc QD (20.0% versus 10.6%). However, maraviroc QD remained much higher than placebo (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 38).

Table 38. 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/∝L)	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)

Source: Table 15.2.3 Summary of Clinical Efficacy.
[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 39 presents the change in CD4 cell count from baseline to Week 24 split by CD4 cell count at baseline.

Table 39. 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/∝L)		Change in CD4 Cell Count (cells/∝L) 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)

Source: Table 15.4.1 Summary of Clinical Efficacy
[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.

2.7.3.4.7. Efficacy Analysis by Baseline Viral Load

HIV-1 RNA at screening (<100,000 and =100,000 copies/mL) was incorporated as a stratification factor into the randomisation 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 the same. 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.

Table 40 presents the change in HIV-1 RNA from baseline to Week 24 by screening HIV-1 RNA level.

Table 40. Summary of Change from Baseline to Week 24 in HIV-1 RNA by HIV-1 RNA Level at Screening (Combined Studies A4001027 and A4001028)

HIV-1 RNA Level at Screening		Change in HIV-1 RNA form Baseline (log_{10} copies/mL)		
		Maraviroc QD (N= 414)[a]	Maraviroc BID (N= 426)[a]	Placebo (N= 209)[a]
<100,000 copies/mL	N[b]	238	243	123
	Mean (SD)	-2.067 (1.095)	-2.129 (1.067)	-1.247 (1.286)
	Median (Range)	-2.385 (-3.597, 2.039)	-2.442 (-3.513, 0.780)	-0.688 (-3.428, 0.965)
=100,000 copies/mL	N[b]	170	176	84
	Mean (SD)	-2.127 (1.487)	-2.197 (1.526)	-1.032 (1.301)
	Median (Range)	-2.394 (-4.492, 0.822)	-2.797 (-4.547, 1.317)	-0.395 (-4.148, 0.619)

Source: Table 13.4.9.1.1 Summary of Clinical Efficacy.
[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.
QD = Once daily dosing; BID = Twice daily dosing; SD = Standard deviation.

The results were consistent for each of the maraviroc treatment groups regardless of HIV-1 RNA at screening. However, for the placebo treatment group there was a trend towards a slightly greater response in mean change in viral load from baseline in those patients with a screening HIV-1 RNA of <100,000 (-1.247 and -1.032 log_{10} copies/mL for <100,000 and =100,000 copies/mL respectively). The superiority of both maraviroc doses over placebo in terms of viral load response at Week 24 was consistent for subjects with <100,000 and =100,000 copies/mL at screening.

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 41 and Table 42). Both doses of maraviroc consistently demonstrated superiority over placebo for patients with low and high viral loads.

Table 41. 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)

Source: Table 13.4.9.3.1 Summary of Clinical Efficacy.
[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 41), 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%).

Table 42. 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)

Source: Table 13.4.9.2.1 Summary of Clinical Efficacy.
[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.

A similar result was observed for patients achieving an HIV-1 RNA of <400 copies/mL at Week 24 (Table 42), 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%).

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 43). 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/∝L 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/∝L for maraviroc QD, BID and placebo respectively for patients with

=100,000 HIV-1 RNA copies/mL (Table 43). There was no consistent pattern of effect for maraviroc QD versus BID dose groups.

Table 43. 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/∝L)		
		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)

Source: Table 13.4.9.4.1 Summary of Clinical Efficacy.
[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.

2.7.3.4.8. Effect of CCR5 . 32 Genotype

The primary endpoint was analysed for the combined A4001027 and A4001028 results by CCR5 . 32 genotype status of the patient. The majority of patients randomised into both studies were homozygous for the wild type allele whilst 7% were heterozygous for the CCR5 . 32 deletion (7%). The proportion of patients with the CCR5 . 32 deletion was approximately even between treatment groups.

Table 44 presents the change in HIV-1 RNA from baseline to Week 24 split by . 32 genotype status.

Table 44. Summary of Change in HIV-1 RNA from Baseline to Week 24 Split by . 32 Genotype (Combined Studies A4001027 and A4001028)

. 32 Genotype Status		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]
WT/WT	N[b]	351	368	174
	Mean (SD)	-2.090 (1.286)	-2.155 (1.279)	-1.171 (1.285)
	Median (Range)	-2.388(-4.492, 2.039)	-2.472 (-4.547, 1.137)	-0.639 (-3.665, 0.965)
Deletion/WT	N[b]	32	27	16
	Mean (SD)	-2.206 (1.032)	-2.491 (1.049)	-1.352 (1.594)
	Median (Range)	-2.267 (-4.295, 0.080	-2.738 (-3.956, -0.279)	-0.348 (-4.148, 0.111)
Missing	N[b]	25	24	17
	Mean (SD)	-1.973 (1.373)	-1.830 (1.452)	-0.868 (1.084)
	Median (Range)	-2.509 (-3.907, 0.224)	-2.101 (-4.504, 0.313)	-0.437 (-3.109, 0.341)

Source: Table 13.4.9.1.8 Summary of Clinical Efficacy.
[a] Number of patients in 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.
QD = Once daily dosing; BID = Twice daily dosing; SD = Standard deviation; WT = Wild type.

Although the numbers are small, patients heterozygous for the CCR5 . 32 deletion appeared to have a slightly greater response to therapy, irrespective of treatment arm, than patients without the deletion. The differences between genotype groups were found to be non-significant in the exploratory pharmacogenomic analysis (Pharmacogenomics Special Review Report for the maraviroc clinical programme Module 5.3.5.3 Reports of analyses of data from more than one study). The superiority of both doses of maraviroc over placebo in terms of viral load response at Week 24 remained for patients with and without the CCR5 . 32 deletion.

2.7.3.4.9. Effect of CCR5 Promoter Haplotype

The primary efficacy endpoint for the combined A4001027 and A4001028 results was analysed by likely CCR5 promoter haplotype. The proportion of patients in each classification were approximately even between treatment groups. There did not appear to be an association between reduction in HIV-1 RNA from baseline at Week 24 and CCR5 promoter haplotype for any treatment group and none was found in the exploratory pharmacogenomic analysis (Pharmacogenomics Special Review Report for the maraviroc clinical programme Module 5.3.5.3 Reports of analyses of data from more than one study). Both doses of maraviroc demonstrated superior efficacy over placebo.

2.7.3.4.10. Efficacy Analysis Split by Genotypic (GSS), Phenotypic (PSS) and Calculated Overall Susceptibility Score (OSS) at Screening

The primary and secondary efficacy endpoints were analysed for the combined A4001027 and A4001028 results by GSS, PSS and OSS 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. This section will provide the primary and selected secondary efficacy results for each calculated score in turn.

GSS, PSS and OSS were divided into scores of 0, 1, 2 and =3 (see Section 2.7.3.1.5.3.3 for details). 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 45 below.

Table 45. Summary of Genotypic (GSS), Phenotypic (PSS) and Overall Susceptibility Scores (OSS) at Screening (Combined Studies A4001027 and A4001028)

Susceptibility Scores		Maraviroc QD (N= 414)[a] n (%)	Maraviroc BID (N= 426)[a] n (%)	Placebo (N= 209)[a] 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

Source: Table 13.5.1 Summary of Clinical Efficacy.
[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.
QD = Once daily dosing; BID = Twice daily dosing.

2.7.3.4.10.1. Genotypic Susceptibility Score (GSS)

Table 46 presents the primary endpoint analysis, change in HIV-1 RNA from baseline to Week 24, split by GSS at baseline.

Table 46. 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)

Source: Table 15.1.2 Summary of Clinical Efficacy.
[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.

As expected, patients with a GSS of 0 had less of a response to treatment irrespective of treatment group. Patients with a GSS of 1, 2 or 3 had a greater response to treatment that appeared to be graded; the higher the GSS score the better the reduction in viral load from baseline. For each GSS, however, both doses of maraviroc continued to demonstrate superior efficacy over placebo. In subjects with a GSS of ≥ 3 (30%), the mean reduction in HIV-1 RNA from baseline through Week 24 was -2.642, -2.587, -2.296 $\log_{10}$ copies/mL for maraviroc QD, BID and placebo, respectively, suggesting a dilution of treatment effect due to susceptibility to multiple drugs in the regimen.

Table 47 and Table 48 present the results for the percentage of patients achieving <50 and <400 copies/mL at Week 24 by GSS.

Table 47. Percentage of Patients with an HIV-1 RNA <50 copies/mL at Week 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	N (%)	N	n (%)	N	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)

Source: Table 15.3.2 Summary of Clinical Efficacy.
[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 48. Percentage of Patients with an HIV-1 RNA <400 copies/mL at Week 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	N (%)	N	n (%)	N	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)

Source: Table 15.2.2 Summary of Clinical Efficacy.
[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 an 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.

2.7.3.4.10.2. Phenotypic Susceptibility Score (PSS)

The pattern of efficacy results by PSS was very similar to those of the primary and selected secondary efficacy endpoints by GSS at baseline, presented in Section 2.7.3.4.10.1 above. Table 49 presents the primary endpoint analysis, change in HIV-1 RNA from baseline to Week 24, by PSS at screening.

Table 49. Summary of Change in HIV-1 RNA from Baseline to Week 24 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)

Source: Table 15.1.1 Summary of Clinical Efficacy.
[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 50 and Table 51 present the results for the percentage of patients achieving <50 and <400 copies/mL at Week 24 by PSS.

Table 50. Percentage of Patients with an HIV-1 RNA <50 copies/mL at Week 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)

Source: Table 15.3.1 Summary of Clinical Efficacy.
[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 51. Percentage of Patients with an HIV-1 RNA <400 copies/mL at Week Split 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)

Source: Table 15.2.1 Summary of Clinical Efficacy.
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.

2.7.3.4.10.3. Overall Susceptibility Score (OSS)

Table 52 presents the primary endpoint analysis, change in HIV-1 RNA from baseline to Week 24, by calculated OSS at screening.

Table 52. 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)

Source: Table 13.4.9.1.7 Summary of Clinical Efficacy.
[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.

The calculated OSS demonstrated a similar pattern of results to the GSS and PSS analyses presented in the sections above. Table 53 and Table 54 present the results for the percentage of patients achieving an HIV-1 RNA <50 and <400 copies/mL at Week 24 by calculated OSS.

Table 53. Percentage of Patients with an HIV-1 RNA <50 copies/mL at Week 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)

Source: Table 13.4.9.3.3 Summary of Clinical Efficacy.
[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 54. Percentage of Patients with an HIV-1 RNA <400 copies/mL at Week 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)

Source: Table 13.4.9.2.3 Summary of Clinical Efficacy.
[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.

Again, 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.

2.7.3.4.11. Efficacy Analysis by Patients Who Received a Dose Adjustment of Maraviroc

The primary efficacy endpoint was analysed for the combined A4001027 and A4001028 results by whether patients were receiving a PI (except for tipranavir/ritonavir) and/or delavirdine in their OBT and therefore had their maraviroc dose adjusted to 150 mg QD or BID. This analysis was conducted to determine whether the dose adjustment implemented for these concomitant antiretroviral agents, which are known to inhibit CYP3A4, was adequate to provide comparable efficacy to patients not receiving the dose adjustment [i.e., in the absence of a PI (other than tipranavir/ritonavir) and/or delavirdine in their OBT].

Table 55 presents the change in HIV-1 RNA from baseline to Week 24 by whether patients were receiving a PI (except for tipranavir/ritonavir) and/or delavirdine in their OBT.

Table 55. Summary of Change in HIV-1 RNA from Baseline to Week 24 Split by Protease Inhibitor[a] and/or Delavirdine use in OBT (Combined Studies A4001027 and A4001028)

PI[a] and/or Delvavirdine in OBT		Change in HIV-1 RNA from Baseline (log_{10} copies/mL) Maraviroc QD (N= 414)[b]	Maraviroc BID (N= 426)[b]	Placebo (N= 209)[b]
Yes	N[c]	316	329	169
	Mean (SD)	-2.100 (1.301)	-2.169 (1.293)	-1.191 (1.288)
	Median (Range)	-2.419 (-4.428, 2.039)	-2.476 (-4.547, 1.317)	-0.649 (-4.148, 0.619)
No	N[c]	92	90	38
	Mean (SD)	-2.065 (1.174)	-2.118 (1.232)	-1.021 (1.326)
	Median (Range)	-2.327 (-4.492, 0.822)	-2.452 (-3.793, 0.780)	-0.463 (-3.650, 0.965)

Source: Table 13.4.9.1.11 Summary of Clinical Efficacy.
[a] Any protease inhibitor except for tipranavir/ritonavir.
[b] Number of patients in treatment group.
[c] 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.

The results demonstrate that there was no difference in reduction in viral load from baseline for patients receiving a PI (except for tipranavir/ritonavir) and/or delavirdine in their OBT compared with those who were not, for any of the treatment groups, and that 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.

2.7.3.4.12. Efficacy Analysis by Patients Who Received a Protease Inhibitor (PI) as Part of their OBT Regimen

The primary efficacy endpoint was analysed for the combined A4001027 and A4001028 results by whether patients were receiving a PI in their OBT, which included patients receiving tipranavir/ritonavir (Table 56).

Table 56. Summary of Change in HIV-1 RNA from Baseline to Week 24 Split by Protease Inhibitor use in OBT (Combined Studies A4001027 and A4001028)

PI 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]	373	385	193
	Mean (SD)	-2.102 (1.273)	-2.163 (1.279)	-1.174 (1.298)
	Median (Range)	-2.405 (-4.428, 2.039)	-2.476 (-4.547, 1.317)	-0.614 (-4.148, 0.965)
No	N[b]	35	34	14
	Mean (SD)	-1.988 (1.268)	-2.098 (1.294)	-0.959 (1.254)
	Median (Range)	-2.113 (-4.492, 0.822)	-2.454 (-3.793, 0.313)	-0.493 (-3.650, 0.381)

Source: Table 15.1.3 Summary of Clinical Efficacy.
[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.

These results demonstrate that there was no clinically important difference in reduction in viral load from baseline for patients receiving a PI in their OBT compared with those who were not, for any of the treatment groups, and that both doses of maraviroc continued to demonstrate superior efficacy over placebo.

2.7.3.4.13. Efficacy Analysis by Patients Who Received Tipranavir/ritonavir as Part of their OBT Regimen

The primary efficacy endpoint was analysed for the combined A4001027 and A4001028 results by whether patients were receiving tipranavir/ritonavir as part of their OBT. There were two reasons for this; tipranavir is a new PI with a different resistance profile and inclusion of tipranavir may therefore affect response to the OBT, secondly tipranavir only became available in the latter part of the studies and there was no stratification for its use. Table 57 presents the results of this analysis.

Table 57. Summary of Change in HIV-1 RNA from Baseline to Week 24 by Tipranavir/ritonavir use in OBT (Combined Studies A4001027 and A4001028)

Tipranavir 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]	65	62	29
	Mean (SD)	-2.137 (1.142)	-2.143 (1.243)	-0,985 (1.373)
	Median (Range)	-2.439 (-3.977, 0.505)	-2.518 (-4.273, 0.780)	0.404 (-3.428, 0.965)
No	N[b]	343	357	178
	Mean (SD)	-2.084 (1.296)	-2.160 (1.287)	-1.188 (1.282)
	Median (Range)	-2.382 (-4.492, 2.039)	-2.468 (-4.547, 1.137)	-0.661 (-4.148, 0.619)

Source: Table 15.1.4 Summary of Clinical Efficacy.
[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.

These results demonstrate that there was no clinically important difference in reduction in viral load from baseline for patients receiving tipranavir/ritonavir as part of their OBT compared with those who were not, for any of the treatment groups, and that both doses of maraviroc continued to demonstrate superior efficacy over placebo.

2.7.3.4.14. Efficacy Analysis by Enfuvirtide (T20) Use

Enfuvirtide use in OBT was used as a stratification factor incorporated into the randomisation of Studies A4001027 and A4001028 in order to ensure balance between treatment groups. Overall there were fewer patients recruited into both studies who did receive enfuvirtide as part of their OBT compared with those who did not receive enfuvirtide; 41% of the total number of patients in the combined analysis received enfuvirtide as part of their OBT.

Table 58 presents the change in HIV-1 RNA from baseline to Week 24 by enfuvirtide use in OBT.

Table 58. 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)

Source: Table 13.4.9.1.2 Summary of Clinical Efficacy.
[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.

The results were consistent within each treatment group regardless of enfuvirtide use. The superiority for both doses of maraviroc over placebo in terms of viral load response at Week 24 remained for patients with and without enfuvirtide use as a component of OBT. This pattern of results was also consistent for each of the key secondary endpoints assessed by enfuvirtide use as part of OBT.

2.7.3.4.15. Assessment of Virology Endpoints

2.7.3.4.15.1. Assessment of Viral Tropism in Phase 3 Studies in Patients Infected with CCR5 Tropic Virus

Viral tropism assignment 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) and the 315 patients who discontinued prior to Week 24. Therefore, assessment of tropism in patients still in study at Week 24 is not informative and is not presented in this summary document.

2.7.3.4.15.2. Changes in Tropism Assignment

One thousand and forty two patients with a CCR5 tropism result at screening were included in these studies. Seven patients were erroneously included in the studies as they did not have a CCR5 tropism result at screening: 4 patients had a dual/mixed tropism result, 1 patient had a CXCR4-tropism result, and for 2 patients tropism was recorded as non-reportable/ non-phenotypable.

2.7.3.4.15.2.1. Changes in tropism result between Screening and Baseline Visits

Of the 1042 patients with a CCR5 tropism result at screening, 79 (7.6%) patients had a different tropism result at baseline (Table 59); all of these were assigned as dual/mixed (A4001027 and A4001028 Tables 13.5.3). 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. Seven patients had a non-CCR5 tropism result at screening (1 CXCR4, 4 dual/mixed, and 2 non-reportable/ non-phenotypable). The 5 patients with a dual/mixed or CXCR4 tropism assignment had the same result at baseline. The number of patients with a dual/mixed or CXCR4 tropism result at baseline was similar across the three treatment groups (7.7, 7.5 and 8.3% in the maraviroc QD, BID and placebo treatment groups, respectively) (Table 59).

Table 59. Percentage of Patients Whose Virus Changed Tropism Assignment from CCR5 Tropic to CXCR4-using or Dual/Mixed Tropic Between Screening and Baseline (Combined Studies A4001027 and A4001028)

	MaravirocQD (N= 402)	Maraviroc BID (N=415)	Placebo (N= 206)
n (%)[b]	31 (7.7)	31 (7.5)	17 (8.3)
Difference[c]	14 (-0.5)	14(-0.8)	N/A
95% CI	-5.1, 4.0	-5.3, 3.7	N/A

Source: Table 13.5.6.1 Summary of Clinical Efficacy.
[a] Only patients with both screening and baseline tropism results were considered
[b] Number of patients whose virus has changed tropism assignment to CXCR4-using or dual/mixed tropic.
[c] Difference between maraviroc treatment and placebo.
QD = Once daily dosing; BID = Twice daily dosing; CI = Confidence interval.

2.7.3.4.15.2.1.1. Summary of Change from Baseline in Viral load at Week 24 by Tropism Status at Baseline

Table 60 demonstrates the change from baseline in HIV-1 RNA at week 24 by tropism result at baseline. The majority of patients enrolled into Studies A4001027 and A4001028 had exclusively CCR5-tropic virus detected at baseline. The change from baseline in viral load at Week 24 in this subset reflects that of the overall population (-2.168 and -2.254 $\log_{10}$ copies/mL, for maraviroc QD and BID respectively, compared to -1.149 $\log_{10}$ copies/mL for placebo). However, in patients with dual/mixed-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 (-1.510 and -1.450 $\log_{10}$ copies/mL respectively) and lower for the maraviroc BID group (-1.073 $\log_{10}$ copies/mL).

Two factors may have influenced this outcome. Firstly, there was a greater mean change from baseline in $\log_{10}$ HIV-1 RNA for the 17 patients on placebo with a dual/mixed tropism result (-1.450 $\log_{10}$ copies/mL) compared to the total placebo population of 207 (-1.160 $\log_{10}$ copies/mL) and that of the placebo subgroup with a CCR5 tropism result at baseline (-1.149 $\log_{10}$ copies/mL). 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 (-1.510 and -1.073 $\log_{10}$ copies/mL, for maraviroc QD and BID respectively, compared to -1.160 $\log_{10}$ copies/mL for placebo).

Secondly, the range of the viral load response for the dual/mixed subgroup is within that observed in the CCR5 subgroup, therefore this result is likely to be associated with the small numbers in the subgroup. However, in general, these results confirm the findings in study A4001029 in non-CCR5 tropic patients.

Table 60. 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)
CCR5	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)

Source: Table 15.1.5 Summary of Clinical Efficacy.
[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.
QD = Once daily dosing; BID = Twice daily dosing; SD = Standard deviation

2.7.3.4.15.2.2. Changes in Tropism Result at Time of Treatment Failure

Of the 204 patients with a CCR5 tropism result at baseline, and who experienced treatment failure, 67 (32.8%) had a change in tropism result to CXCR4 or dual/mixed at time of treatment failure (Table 61). All but 4 of these patients were in the maraviroc treatment arms.

Table 61. Percentage of Patients with a Change in Tropism Result from CCR5 to CXCR4 or Dual/Mixed Tropic Between Baseline and Time of Treatment Failure

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

Source: Table 13.5.7.2 Summary of Clinical Efficacy.
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 CCR5 to CXCR4 or dual/mixed.
[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 62. Of the 28 patients who had a dual/mixed tropism result at baseline and who failed treatment with maraviroc, only one patient had exclusively CCR5-tropic virus detected at

time of failure. In contrast of the 4 patients who had a dual/mixed tropism result at baseline and who failed treatment on placebo, 3 patients had exclusively CCR5-tropic virus detected at time of failure.

Table 62. Change in Tropism Result Between Baseline and Time of Treatment Failure

Treatment Group	Tropism at Baseline	Tropism at Time of Failure[a]			
		CCR5	CXCR4	Dual/mixed	NR/NP
Total Population, N=1045	CCR5	115 (11.0%)	15 (1.4%)	52 (5.0%)	20 (1.9%)
Failures, n=242	Dual/mixed	4 (0.4%)	8 (0.8%)	18 (1.7%)	3 (0.3%)
Maraviroc QD, N=412	CCR5	18 (4.3%)	8 (1.5%)	23 (5.6%)	7 (1.7%)
Failures, n=68	Dual/mixed	1 (0.2%)	1 (0.2%)	6 (1.5%)	1 (0.2%)
Maraviroc BID, N=424	CCR5	17 (4.0%)	7 (1.7%)	25 (5.9%)	8 (1.9%)
Failures, n=77	Dual/mixed	0	6 (1.4%)	11 (2.6%)	2 (0.5%)
Placebo, N=209	CCR5	80 (38.2%)	0	4 (1.9%)	5 (2.4%)
Failures, n=97	Dual/mixed	3 (1.4%)	1 (0.5%)	1 (0.5%)	0

Source: 13.5.4.2 Summary of Clinical Efficacy Tables.
[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) From A4001027 and A4001028 Tables 13.5.4.1.
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.

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

The mean changes from baseline in CD4 cell count for the overall population and by tropism result at time of failure for the three treatment groups are presented in Table 63. There was a higher mean change in CD4 cell count for patients who failed therapy with maraviroc, compared to placebo (+49.35 and +71.06 cells/∝L for maraviroc QD and BID, respectively, compared to +13.78 cells/∝L for patients receiving placebo).

Table 63. Summary of Change from Baseline in CD4 Cell Count at Week 24 (Using LOCF) by Tropism Status at Baseline and Failure

Tropism Status Baseline - Failure		Change in CD4 Cell Count from Baseline to Week 24 (cells/∝L) 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)

Source: Table 15.4.2 Summary of Clinical Efficacy.
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; R5 = CCR5 tropic virus; X4 = CXCR4-using virus; NR/NP = Non-reportable/non-phenotypable; BLQ = Viral load <500 copies/mL.

For those patients with a CCR5 tropism result at baseline, approximately twice as many patients who received maraviroc and failed therapy had a dual/mixed or CXCR4 tropism result at failure (n=63) compared to a CCR5-tropism result (n=35). The mean increase in CD4 cell count from baseline in patients who failed with a change in tropism to dual/mixed tropic or CXCR4, in both the maraviroc QD (37 cells/∝L) and BID (56 cells/∝L) groups was somewhat lower than that observed in the placebo group (n=4, 67.1 cells/∝L) but considerably greater than that seen in the total placebo group who failed (13.8 cells/∝L). In patients with a CCR5 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 dual/mixed or CXCR4-tropism result at failure who received maraviroc QD or BID (Table 63).

Increases of mean changes in CD4 cell counts for the maraviroc treatment groups were also seen for 30 patients with a non-CCR5 tropism result at baseline (dual/mixed, CXCR4 or non-phenotypable), and for 17 patients with a CCR5-tropism result at baseline but who had no tropism assignment at failure (Table 63).

The numbers of patients on the placebo arm with a non-CCR5 tropism result at failure were too low to draw any conclusions from the data (n=4, 5 and 8 respectively for CCR5 to dual/mixed/CXCR4, CCR5 to non-reportable/non-phenotyable/BLQ/missing and non-CCR5). However, all of the results were within the range of changes seen in the placebo group with a CCR5 tropism result at failure (Table 63).

Collectively these data are consistent with the data obtained from the post-hoc analysis performed on patients in Study A4001029 (Section 2.7.3.2.2.2).

2.7.3.4.15.3. Origin of CXCR4-Using Virus

Detailed virology studies were conducted on samples from selected patients from the Phase 2 and Phase 3 clinical programme, whose virus was assigned as CCR5-tropic at study entry and in whom CXCR4-using virus was detected whilst on therapy. 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'). The results of these analyses are summarised in The Microbiology Review of Mechanisms of Resistance/Shift in Tropism (Module 5.3.5.3 Reports of analyses of data from more than one study). The main findings of these studies are:

There was no difference in the origin of CXCR4-using virus that was detected on treatment in 16 patients who received maraviroc + OBT and four patients who received placebo + OBT (Studies A4001027 and A4001028)

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. In patients from the Phase 2a and Phase 2b studies who were subsequently followed in study off drug, this was reversed following cessation of therapy. These data are consistent with maraviroc's mechanism of action, as a CCR5 antagonist that selectively inhibits CCR5 tropic virus in a mixed population.

There was no evidence of a switch in co-receptor usage of a CCR5-tropic virus in any of the studies conducted.

2.7.3.4.15.4. Resistance to Maraviroc

Resistance to maraviroc was studied both in the pre-clinical and clinical phase of the program. The objective was to identify phenotypic and genotypic markers associated with maraviroc resistance. The design of these studies took into account the following:

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 it exerts its antiviral activity through binding to a host cell protein rather than a virus protein.

The viral envelope (gp120) is the relevant viral protein to study with respect to maraviroc resistance 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.

The design of the Phase 2b/3 clinical program meant that patients/investigators/sponsor were all blinded to treatment assignment until close to the point of file submission and hence all antiviral assays were conducted on blinded study samples.

The results of these studies are summarized in The Microbiology Review of Mechanisms of Resistance/Shift in Tropism (Module 5.3.5.3 Reports of analyses of data from more than one study). The main findings of the clinical phase of these analyses are:

Resistance to maraviroc is associated (in antiviral drug susceptibility assays) with dose response curves that have a plateau in maximal percentage inhibition (MPI) rather than a shift in IC_{50}. This is consistent with the use by the maraviroc-resistant viruses of both maraviroc-occupied and free CCR5 molecules to infect target cells.

Plateaus in MPI to maraviroc were identified as a phenotypic marker of maraviroc resistance in 5 patients (of 12 patients studied) who failed maraviroc therapy in Studies A4001027 or A4001028 with a CCR5-tropic virus. This was further substantiated by studying serial samples from two patients during the open label treatment phase.

Mutations in the V3 loop appeared to be associated with the plateaus in MPI. However, no signature mutations were identified (each patient had a different pattern of mutations).

Shifts in IC_{50} (without evidence of a plateau in MPI) were not identified as a common phenotypic marker of maraviroc resistance in patients failing therapy with a CCR5-tropic virus. A 3-fold to 5-fold shift in IC_{50} to maraviroc was identified in virus from one patient failing therapy with a CCR5-tropic virus.

Phenotypic markers of maraviroc resistance were not identified in 5 patients failing the 300mg QD maraviroc +zidovudine/lamivudine* arm of Study A4001026 with a CCR5-tropic virus. In contrast, the M184V lamivudine resistance mutation in reverse transcriptase was associated with treatment failure in 3 of these patients as well as the 3 patients who failed with a CXCR4-using virus.

There was no evidence of cross-resistance between enfuvirtide and maraviroc.

There was no evidence for maraviroc selecting for viruses that switch co-receptor usage. Given the fact that approximately one third of the patients who failed a maraviroc regimen in A4001027 and A4001028 did so with a CCR5-tropic virus (35 patients in total), and phenotypic markers of maraviroc resistance were only identified in 4 of 12 patients studied in

* ：新薬承認情報提供時に置換えた。

the resistance programme (during the blinded treatment phase) these data are consistent with there being a high barrier in vivo to resistance to maraviroc with continued CCR5 usage.

2.7.3.4.15.5. Changes in GSS/PSS/OSS from Screening to Time of Treatment Failure

Table 64 summarises the change in susceptibility scores at time of treatment failure. The majority of patients had either no change in their GSS, PSS and OSS or had a loss of susceptibility to 1 drug, with very few patients having an increase. The relatively small shift in the table is consistent with the fact that most patients had GSS, PSS and OSS values of ≤2 at screening (Section 2.7.3.1.5.3.3).

Table 64. Summary of Change in Susceptibility Scores from Screening to Time of Treatment Failure

Susceptibility scores	Change in susceptibility score								
	<-3	-3	-2	-1	0	1	2	3	>3
Genotype									
Maraviroc QD (N=69) n=57	0	0	3	18	36	0	0	0	0
Maraviroc BID (N=77) n=65	1	0	0	19	41	4	0	0	0
Placebo (N=97) n=87	1	0	2	26	54	2	1	1	0
Phenotype									
Maraviroc QD (N=69) n=57	0	5	6	18	25	3	0	0	0
Maraviroc BID (N=77) n=64	0	1	4	26	30	3	0	0	0
Placebo (N=97) n=85	1	3	7	28	43	3	0	0	0
Overall									
Maraviroc QD (N=69) n=57	0	2	9	16	27	3	0	0	0
Maraviroc BID (N=77) n=64	0	1	3	25	30	5	0	0	0
Placebo (N=97) n=85	1	0	9	27	44	4	0	0	0

Source: A4001027 and A4001028 Clinical Study Report Tables 13.5.2.1.
N = number of patients in the treatment group who have discontinued due to lack of efficacy.
n= number of patients contributing to the summary statistics, which were patients with valid values for baseline and on treatment.
QD = Once daily dosing' BID = Twice daily dosing.

2.7.3.5. Analysis of Clinical Information Relevant to Dosing Recommendations

The rationale for dose selection in the Phase 2b/3 treatment-experienced patient population was to maximise the benefit: risk ratio for maraviroc in these patients. The dose selection was based on viral load data from the Phase 2a monotherapy studies, data from Phase 2a, Phase 1/2a pharmacokinetic/ pharmacodynamic modelling, clinical trial simulations, drug-drug interaction studies, preclinical serial passage resistance studies and a safety database of over 400 subjects followed for up to 4 weeks.

Two monotherapy studies (A4001007 and A4001015) have been performed in treatment-naïve patients or patients who had not received antiretroviral treatment in the previous eight weeks. These studies investigated the anti-viral effects, pharmacokinetics, safety and tolerability of various doses and regimens of maraviroc administered for 10 days as monotherapy. The conclusions from these 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. Further discussion of these two monotherapy studies is provided in Module 2.7.2 Summary of Clinical Pharmacology Studies.

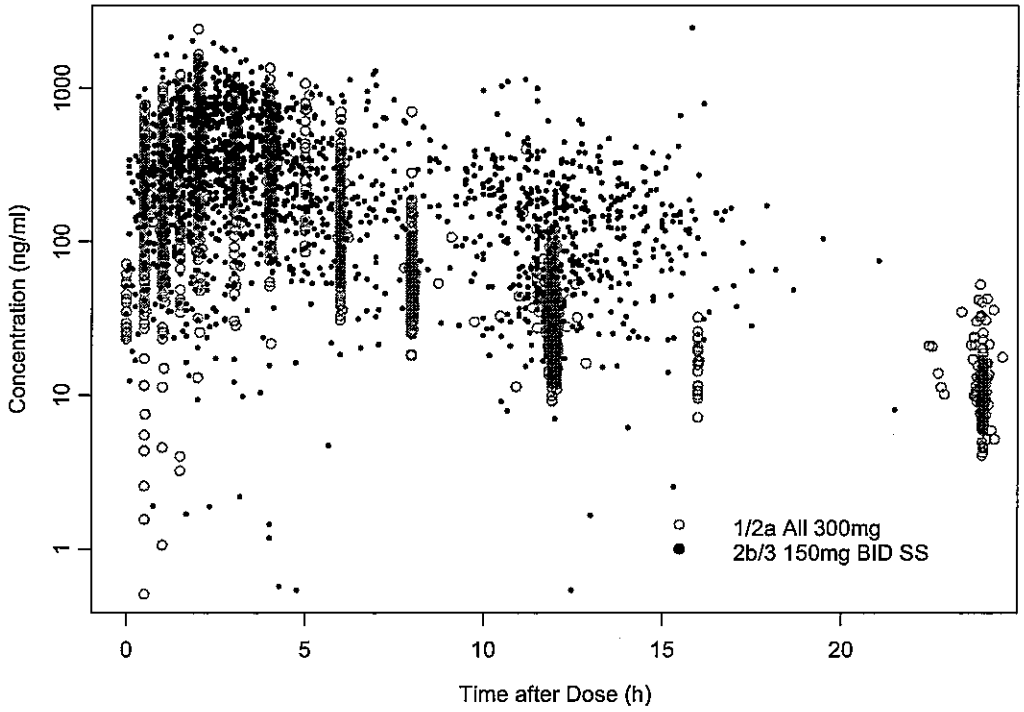
Evaluation of safety data from the Phase 1/2a studies identified postural hypotension as the dose limiting adverse event, occurring at a frequency greater than placebo at unit doses of >300 mg. These events were temporally related to Cmax. Based on these data, it was decided that dose adjustments to compensate for interactions with coadministered agents, should be based on maintaining a Cmax equivalent to 300 mg doses given alone. Controlling for the peak concentration, whilst potentially allowing total exposure to exceed that of 300mg alone, was deemed to give an optimal balance between safety and efficacy

Since maraviroc is a substrate for both CYP3A4 and P-gp, 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. The exception to this was saquinavir/ritonavir, which led to a 4-5 fold and 8-10 fold increase in Cmax and AUC respectively. 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 Cmax 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. 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.

Results from the population pharmacokinetic analysis of data from Study A4001029 and 500 patients from Studies A4001027 and A4001028 (Module 5.3.3.5 Preliminary Population Pharmacokinetic Analysis of Maraviroc in Pooled Phase 2b/3 Studies of Treatment Experienced Patients on Optimized Background Therapy) showed that the expectations of the pharmacokinetic behaviour of maraviroc were consistent with observations in Phase 2b/3 (Studies A4001027, A4001028 and A4001029). The dose adjustment strategy for CYP3A4 inhibitors appears appropriate, in that in patients receiving 150 mg maraviroc where samples for maraviroc concentrations were taken around Cmax (sampled in 150 mg BID arm) measured concentrations were similar to those seen with 300 mg doses in Phase 1 and 2a studies (Figure 17). .

Taken together, these data indicate that the maraviroc dose modification recommendations for the Phase 2b/3 clinical studies were successful in limiting Cmax so as not to significantly exceed that seen with 300 mg in the absence of interacting agents, while maintaining an average plasma exposure (Cav) that was at or above a that seen with 300 mg in the absence of interacting agents (median estimated increase in Cav over 300 mg reference of 1.56 fold for maraviroc QD and 1.73 for maraviroc BID).

Figure 17 150 mg BID Maraviroc Concentrations from Combined Phase 2b/3 Overlaid with all 300 mg Phase 1/2a Maraviroc Concentrations



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

Although the studies were not designed to compare the maraviroc QD and BID doses, an unplanned non-inferiority analysis was conducted based on the pooled maraviroc data from the two studies. The treatment difference between the maraviroc BID and maraviroc QD arms was -0.085 $\log_{10}$ copies/mL. The upper bound of the 95% confidence interval was less than 0.3 log10 copies/mL indicating non-inferiority of maraviroc QD compared to maraviroc BID (Table 65).

Table 65. Statistical Analysis of Change from Baseline to Week 24 in log10 HIV-1 RNA – Maraviroc QD versus Maraviroc BID (A4001027 and A4001028)

Treatment Group		Change from Baseline to Week 24 in HIV-1 RNA (log10 copies/mL)		Treatment difference Maraviroc BID-Maravirc QD	
	N	Median	Adjusted Mean (s.e.)	Estimate (s.e.)	97.5% CI
Maraviroc BID	426	-2.424	-1.960	-0.085 (0.0961)	-0.274, 0.104
Maraviroc QD	414	-2.274	-1.876	N/C	N/C

Source: Table 13.4.6.1.2 Summary of Clinical Efficacy.
CI = Confidence interval; s.e. = Standard error; N/C = Not calculated.

In addition, all secondary efficacy virologic endpoints were substantially greater for both maraviroc treatment groups than the placebo group; however, there was a slight trend in favour of the pooled maraviroc BID treatment groups for all of these endpoints (Table 66).

Table 66. Summary of Secondary Efficacy Endpoints at Week 24 (Combined Studies A4001027 and A4001028

	Maraviroc QD n (%)	Maraviroc BID n (%)	Placebo n (%)
N	414	426	209
Number of Subjects with:			
<400 copies/mL	228 (55.1)	259 (60.8)	58 (27.8)
<50 copies/mL	181 (43.7)	192 (45.1)	48 (23.0)
≥ 1.0 log10 viral load decrease	271 (65.5)	292 (68.5)	73 (34.9)
≥ 0.5 log10 viral load decrease	284 (68.6)	301 (70.7)	88 (42.1)

Source: Tables 13.4.3.3.1, 13.4.3.4.1, 13.4.3.5, 13.4.3.6 A4001027 and A4001028 Clinical Study Reports.
QD = Once daily dosing; BID = Twice daily dosing.

These findings should however be viewed in the light of a wide and overlapping range of maraviroc concentrations observed in the QD and BID maraviroc treatment arms.

2.7.3.6. Overall Conclusions

Maraviroc is first in a class of new antiretroviral agents that inhibit binding of HIV-1 to the CCR5 receptor, thereby blocking an essential initial step in viral replication. In the Phase 3 registrational studies, 1049 highly treatment-experienced patients were treated with at least one dose of active study drug or placebo. The purpose of these studies was to test the hypothesis that adding maraviroc, at a dose equivalent to either 300 mg QD or BID, to OBT would provide an additional reduction in plasma viral load compared with OBT alone, as measured by the difference between each of the 2 maraviroc treatment groups versus the placebo treatment group in the mean change from baseline in plasma viral load to Week 48. A planned interim analysis of this variable at Week 24, described in this document, has demonstrated superiority of both maraviroc QD and maraviroc BID over placebo. The estimate of the treatment difference for maraviroc QD was 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, indicating the superiority of maraviroc QD and maraviroc BID over placebo. The upper bound of the 95% confidence interval was less than 0.3 log10 copies/mL indicating non-inferiority of maraviroc QD compared to maraviroc BID.

In addition, all the secondary virologic endpoint results at Week 24 (subjects with viral load <400 and <50 copies/mL, 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 superior efficacy of both maraviroc treatment groups over placebo. Furthermore, the mean change in CD4 cell count (cells/μL) was substantially higher for the maraviroc treatment groups. 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 the placebo treatment group where an increase of 57.4 cells/μL was demonstrated.

Most patients who responded had no tropism assignment at Week 24, and many had no on-treatment tropism result as they had a viral load of <500 copies/mL at all visits from Week 4 onwards. Of the 1049 subjects in the study only a few were treatment failures due to insufficient clinical response and had a change in tropism result, although more of these subjects were in the maraviroc treatment groups compared with the placebo treatment group.

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 potentially active drugs in their OBT. In subjects with susceptibility scores of ≥3 at Week 24, the mean reduction in viral load from baseline demonstrated a smaller treatment benefit for maraviroc treated subjects compared with placebo, suggesting a dilution of treatment effect due to susceptibility to multiple drugs in the regimen.

Both maraviroc treatment groups met the primary endpoint criteria demonstrating superiority in comparison to placebo. Although the studies were not specifically designed to compare the maraviroc QD and maraviroc BID treatment groups, there was no indication of a clinically meaningful difference across the whole population studied between them, based on the primary and key secondary efficacy endpoints measured following 24 weeks of therapy. However certain patient groups, notably those with very low CD4 counts, higher viral loads and no active drugs seem to receive greater benefit from maraviroc BID. With respect to the first two subgroups, this trend appears to be consistent with the more apparent finding from the interim analysis of Study 1026, which demonstrated that treatment-naïve patients with higher viral loads and lower CD4 counts had a greater response rate in the 2 ongoing arms of that trial (maraviroc BID, efavirenz) relative to the discontinued maraviroc QD arm. .

2.7.3.7. References

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2.7.3.8. Appendix