CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-128

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 22128	Submission Date(s): Dec 19, 2006
Brand Name	Selzentry
Generic Name	Maraviroc
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OCP Division	Division 4
ORM division	DAVP
Applicant	Pfizer Inc.
Relevant IND(s)	IND 65229
Submission Type	Priority
Formulation; Strength(s)	150 mg and 300 mg film-coated tablets
Indication	Treatment for treatment-experienced patients infected with CCR5-tropic HIV-1, in combination with other antiretroviral agents

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1. EXECUTIVE SUMMARY

Maraviroc, in combination with other antiretroviral agents, is proposed for treatment-experienced adult patients infected with CCR5-tropic HIV-1. A viral tropism assay should be used to select individuals infected with viral strain(s) that use the CCR5 co-receptor to enter cells and exclude patients infected with viral strain(s) that use the CXCR4 co-receptor. CCR5 antagonists should be effective in patients with CCR5 tropic HIV, but not in patients with CXCR4 tropic or mixed/dual CCR5/CXCR4 tropic HIV. Tropism determination aids the selection of patients most likely to respond to a CCR5 antagonist.

The consideration for approval of this NDA is based on safety and efficacy data from two double-blind, placebo-controlled trials of 24 weeks duration in treatment-experienced patients. The study results indicate a 300 mg dose equivalent of maraviroc (dose adjusted for drug-drug interaction), given once or twice daily, when dosed in combination with optimized background therapy (OBT) in treatment-experienced patients infected with CCR5 tropic HIV-1, leads to a greater decline in viral load than OBT alone (placebo). The mean reduction in HIV-1 RNA from baseline to Week 24 with maraviroc plus OBT is at least 1.8 log10 copies/mL, compared to approximately 1.0 log10 copies/mL with OBT alone. There was no indication of a clinically meaningful difference between maraviroc QD and BID across the whole population studied, based on the primary and key secondary efficacy endpoints measured following 24 weeks of therapy. However, patients with lower CD4 count, higher viral loads and fewer potentially active drugs in their OBT, seem to receive greater benefit from maraviroc BID. Based on Phase I studies and evaluation of other CCR5 antagonists, specific safety concerns during review of this NDA were QTc prolongation, hepatotoxicity, infections or malignancies. The safety and efficacy studies demonstrated an acceptable safety and tolerability profile. Therefore, the proposed dose is 300 mg BID or dose equivalent based on drug-drug interaction.

1.1 Recommendation

The Clinical Pharmacology information provided by the applicant is acceptable. The additional outstanding issues that need to be addressed are listed in the Phase IV Commitments section.

A concentration controlled trial evaluating safety and efficacy of an optimized dosing strategy for patients with maraviroc Cmin <50-75 ng/mL is not recommended at this time. The need for such a study will be evaluated after review of the 48 week efficacy and safety data. The week 48 data might help to further understand long term exposure-response relationship and to determine the threshold Cmin, if any.

1.2 Phase IV Commitments

- Conduct a study to evaluate the effect of renal impairment on the pharmacokinetics of maraviroc
  a) at a dose of 150 mg when combined with a boosted protease inhibitor in subjects with mild and moderate renal impairment

b) at a dose of 300 mg alone in subjects with severe renal impairment and subjects with end-stage renal disease who require dialysis.

Protocol submission: December 30, 2007
Final report submission: December 30, 2008

- Conduct a study to evaluate the potential for maraviroc metabolite(s) to inhibit CYP2D6 enzymes. Debrisoquine urinary ratio data suggest maraviroc or its metabolite(s) may inhibit CYP2D6 at dose of 600 mg.

  Protocol submission: December 30, 2007
  Final report submission: June 30, 2008

- Conduct a study to evaluate the potential of maraviroc to inhibit P-gp.

  Protocol submission: December 30, 2007
  Final report submission: June 30, 2008

- Conduct a study to evaluate the potential of maraviroc to induce CYP1A2.

  Protocol submission: December 30, 2007
  Final report submission: June 30, 2008

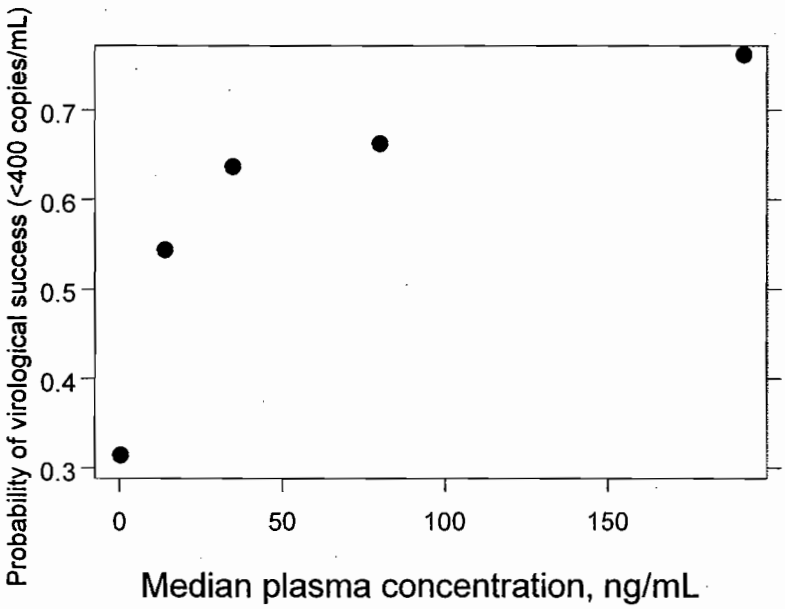
1.3 Summary of Important Clinical Pharmacology Findings

Maraviroc is the first agent of a new pharmacological class of antiretroviral agents known as CCR5 antagonists, which act on a human cellular target to prevent infection of the cell by HIV-1. Maraviroc has demonstrated activity in vitro against a wide range of CCR5 tropic clinical isolates, including those resistant to any of the four existing drug classes of antiretroviral medicinal products. The two Phase 3 studies, A4001027 and A4001028, have demonstrated that a 300 mg dose equivalent of maraviroc, given once or twice daily, in combination with optimized background therapy (OBT) in treatment-experienced patients infected with CCR5 tropic HIV-1, leads to a greater and clinically relevant decline in viral load than OBT alone (placebo). There was no indication of a clinically meaningful difference between maraviroc QD and BID across the whole population studied, based on the primary and key secondary efficacy endpoints measured following 24 weeks of therapy. However, patients with lower CD4 count, higher viral loads and fewer potentially active drugs in their OBT, seem to receive greater benefit from maraviroc BID. The exposure-response analysis also supports the use of maraviroc BID. The proposed dose is 300 mg BID or dose equivalent based on drug-drug interaction.

The clinical pharmacology of maraviroc has been characterized in healthy and HIV-1 infected subjects, as well as *in vitro* studies. These studies show maraviroc demonstrates the following clinical pharmacology and biopharmaceutical characteristics:

- Exposure-response analysis shows that the antiviral efficacy was increased with increased maraviroc concentrations. Patients with Cmin >50-75 ng/mL have a better chance of virologic success. In addition to Cmin, the probability of success is also influenced by other patient specific factors such as baseline CD4+ count, baseline viral load and overall sensitivity score (OSS).

Figure S1. Cmin-response relationship. The mean response is plotted against the median Cmin for each quartile. The placebo response is plotted at Cmin=0.



- Toxicity (ALT/AST elevation, hypotension) in the Phase 2b/3 studies was not dose/concentration dependent within maraviroc therapeutic concentration range.

- In a thorough QT study, the change in QTc after administration of moxifloxacin minus the baseline QTc after placebo as a function of time was found to be unusual. The change was near maximal at 1 hour and remained unusually elevated at 12 hours. This unusual result means that assay sensitivity has not been demonstrated in this study; i.e., it is unclear that had product administration prolonged the QTc, it could have been detected. At the time of this review, the IRT-QT team was uncertain whether administration of maraviroc prolongs the QTc above the threshold established in the ICH E14 guideline. Please refer to IRT-QT review for further details.

- Postural hypotension was observed in Phase I studies. The observed incidence of postural hypotension across Phase 1/2a studies was analyzed. The results indicated that the incidence of postural hypotension increased above that of placebo at unit doses of ≥600 mg maraviroc. However, events of postural hypotension are rare at 300 mg QD and BID (the doses used in the phase 2b/3 registrational studies). The study also indicated that Cmax is an important predictor for postural hypotension. In a Phase 1 study to investigate the haemodynamic effects of oral maraviroc, there was no apparent relationship between % change from baseline in ICG (Impedance Cardiography Technology) parameters or change from baseline in supine blood pressure and pulse rate compared with maraviroc plasma concentration. However, 3/16 subjects experienced postural hypotension in the maraviroc treatment group (900 mg single dose) as compared to 0/3 subjects in the placebo group. In

conclusion, 300 mg or adjusted dose for comparable Cmax to 300 mg maraviroc in the case of drug-drug interaction, does not pose a risk of postural hypotension.

- The following tables present maraviroc pharmacokinetic parameters in healthy subjects and HIV-1 infected patients.

Table S1. Summary of Multiple-Dose Pharmacokinetic Parameters in Healthy Subjects(A4001002)

Maraviroc Dose	Day[a] (n)	Mean Pharmacokinetic Parameters					Aet µg (% of dose)
		AUCtau[b,c] (ng·h/mL)	Cmax[c] (ng/mL)	Tmax[d] (h)	t½[d] (h)	CLR[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

Table S2. Summary of Pharmacokinetic Parameters for HIV-1 Infected Subjects (A4001007, A4001015) on 300 mg doses.

Treatment	Day (n)	Mean Pharmacokinetic Parameter Value (range)					Accumulation Ratio[c]
		AUC_{12}[a] (ng.h/mL)	AUC_{24}[a] (ng.h/mL)	C_{max}[a] (ng/mL)	T_{max}[b] (h)	$t_{½}$[b] (h)	
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
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

- Maraviroc is a substrate of P-gp. The absolute bioavailability of maraviroc increases with dose, probably due to the saturation of P-gp with increased maraviroc concentrations in the gut, which results in more than a dose proportional increase in maraviroc exposure. The absolute bioavailability of a 100 mg dose is 23% and is predicted to be 33% at 300 mg based on population PK analysis. Maraviroc PK are approximately linear following intravenous (IV) administration.
- Maraviroc accumulation was approximately 20% for BID dosing and 9% for QD dosing and steady state is observed within 7 days.
- Coadministration of a 300mg tablet with a high fat breakfast reduced maraviroc C_{max} and AUC by 33% in healthy volunteers. However, there was little effect of food on antiviral activity in a 10-day maraviroc monotherapy study. Therefore, there were no food restrictions in the Phase 3 studies. In Phase 3 studies, almost 50% of subjects on 150mg BID took their dose within the food time window (food taken within 4 hours prior and 1 hour post last dose record) in 76 to 100% of their recorded occasions. For 300 mg BID group, approximately 57% of the subjects took their dose within the food time window in more than 50% of their recorded occasions. For BID patients in studies A4001027 and A4001028, the efficacy data (success endpoints at week 24 with viral load <50 and <400 copies/mL) were combined with the PK fed quartiles to test for any changes in efficacy with fed status. The success percentages show that there are no differences between the quartiles, so fed status does not appear to have an effect on efficacy at 24 weeks.
- Maraviroc is approximately 76% bound to human plasma proteins, and shows moderate affinity for albumin and alpha-1 acid glycoprotein. The volume of distribution of maraviroc is approximately 194L following intravenous administration.
- A mass balance study indicates approximately 20% of the radiolabel was recovered in the urine and 76% was recovered in the feces over 168 hours. Maraviroc was the major component present in urine (mean: 8% of dose) and feces (mean: 26% of dose). The remainder was excreted as metabolites. Unchanged maraviroc was the major circulating component in plasma, accounting for a mean of 42% of the circulating radioactivity. The major metabolites observed in plasma were UK-408,027

(22%), an amine analogue (11%) and UK-463,977 (5%). UK-408,027 and UK-463,977 have been evaluated in vitro and show no antiviral activity.

- The pharmacokinetics of maraviroc have not been evaluated in subjects with impaired renal function (Phase 4 commitment). Renal clearance accounts for about 25% of the total clearance when 300 mg maraviroc is administered alone. However, data from several drug-drug interaction studies indicated when maraviroc is coadministered with CYP3A inhibitors, total maraviroc clearance is reduced while maraviroc renal clearance increases by 13 - 44% as compared to maraviroc administered alone; thus the percent of maraviroc clearance due to the renal route increases with coadministration of CYP3A inhibitors.
- A single dose study in subjects with mild or moderate hepatic impairment is ongoing. Since maraviroc is metabolized by the liver, concentrations are likely to be increased in these subjects.
- Population pharmacokinetic analysis of pooled Phase 1/2a data indicated HIV status (i.e. whether a subject was infected with HIV-1 or not) age, gender and weight do not affect maraviroc pharmacokinetic parameters. Exposure was 26.5% higher in Asians (N=95). However, a study designed to evaluate PK differences between Caucasians and Singaporeans showed no difference between these two populations. No subjects over the age of 65 years were enrolled.
- Maraviroc is a CYP3A substrate as well as a P-gp substrate. Therefore, co-administration of maraviroc and drugs that induce CYP3A and/or P-gp may decrease maraviroc plasma concentrations and reduce its therapeutic effect. Conversely, co-administration of maraviroc and drugs that inhibit CYP3A and/or P-gp may increase maraviroc plasma concentrations and increase or prolong its therapeutic and adverse effects.
- The effect of CYP3A inhibitors and inducers on maraviroc concentrations is an important issue because maraviroc will often be administered with CYP3A inhibitors and/or inducers. The majority of the subjects in clinical trials A4001027 and A4001028 received a CYP3A inhibitor, and some subjects received a CYP3A inducer. The applicant proposes to reduce maraviroc doses to half (150 mg BID) when coadministered with a CYP3A inhibitor ± inducer (except tipranavir/ritonavir), and double maraviroc doses (600 mg BID) when coadministered with a CYP3A inducer (without an inhibitor, excluding the inducers nevirapine and rifabutin). These dose adjustments are acceptable. However, we clarify in the label that maraviroc dose is reduced when maraviroc is coadministered with potent CYP3A inhibitors, but not mild or moderate inhibitors. We are concerned that reduction of maraviroc to 150 mg BID when a moderate or mild CYP3A inhibitor is administered (without other CYP3A inhibitor) may result in maraviroc concentrations lower than those observed in the clinical trials.
- Maraviroc is unlikely to affect the pharmacokinetics of drugs that are primarily metabolized by cytochrome P450 enzymes because it does not inhibit the major cytochrome P450 enzymes at clinically relevant concentrations in vitro (IC50 > 30 μM) and has no clinically significant effect on a sensitive probe CYP3A substrate, midazolam. Maraviroc had no effect on the debrisoquine metabolic ratio (MR) at 300 mg BID or less in vivo. However, there was 234% increase in debrisoquine MR on treatment compared to baseline with maraviroc 600 mg QD, suggesting potential inhibition of CYP2D6 at higher doses. It is not clear if maraviroc metabolite(s) inhibits

CYP2D6, which could be significant when maraviroc is coadministered with CYP3A inducer at 600 mg BID (Phase 4 commitment).

- Maraviroc does not affect the pharmacokinetics of zidovudine and lamivudine, and is not affected by co-trimoxazole and tenofovir.
- The potential of maraviroc to inhibit P-gp was not studied (Phase 4 commitment).
- The potential of maraviroc to induce CYP1A2 was not studied (Phase 4 commitment).

Overall, the cumulative data regarding the clinical pharmacology of maraviroc support the proposed use of this drug for treatment-experienced patients infected with CCR5-tropic HIV-1, in combination with other antiretroviral agents

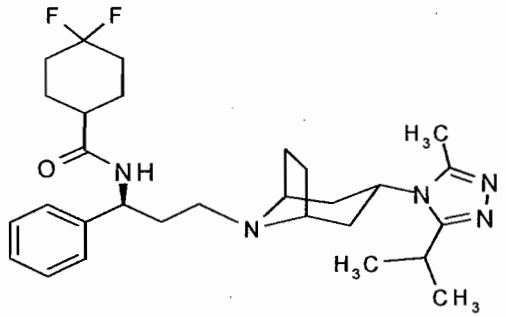
2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The structure and physical properties of maraviroc are shown below:

Structural formula:



Chemical Name: 4,4-difluoro-*N*-{(1*S*)-3-[*exo*-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclohexanecarboxamide

Molecular Weight: 513.67

pH-solubility profile: highly soluble across the physiological pH range (pH 1.0 to 7.5)

PKa: 3.3 and 7.9

Log P (partition coefficient): 2.1

Apparent Permeability: limited permeability and polarized transport across the cell monolayer (Caco-2 cells).

The quantitative composition of the to-be-marketed maraviroc tablets are shown in the following table:

Component	Grade	Function	150 mg Unit Formula (mg/ tablet)	300 mg Unit Formula (mg/ tablet)
Maraviroc	Pfizer	Active ingredient	150.00	300.00
Microcrystalline Cellulose	USP	[redacted]		
Dibasic Calcium Phosphate Anhydrous	USP			
Sodium Starch Glycolate	USP			
Magnesium Stearate	NF			
Opadry® II Blue (85G20583) [d]	Pharm			
[redacted]				
Total Weight			624.00	1248.00

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?
As shown in Figure Q1, the first step in the process of HIV-1 entry into the host cell is the specific binding of viral envelope glycoprotein, gp120, to CD4 of the host cell (the primary receptor for HIV-1). It was found that a human chemokine receptor is an essential co-receptor for HIV-1 infection. The binding of gp120 to CD4 causes a conformational change in gp120 that exposes the bridging sheet and forms a co-receptor binding site. 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. The chemokine receptors most commonly utilized by HIV-1 in vivo are CC chemokine receptor 5 (CCR5) and/or CX chemokine receptor 4 (CXCR4). A schematic model of the HIV-1 entry process is shown in Figure 1. The ability of gp120 to bind to either one or both receptors defines the tropism of the virus. HIV-1 strains are therefore categorized as R5 (CCR5-tropic), X4 (CXCR4-tropic) or R5X4 (strains using both CCR5 and CXCR4; also referred to as 'dual-tropic'). A patient may harbor a mixture of viruses with different co-receptor usage.

Figure Q1. A model for HIV-1 entry

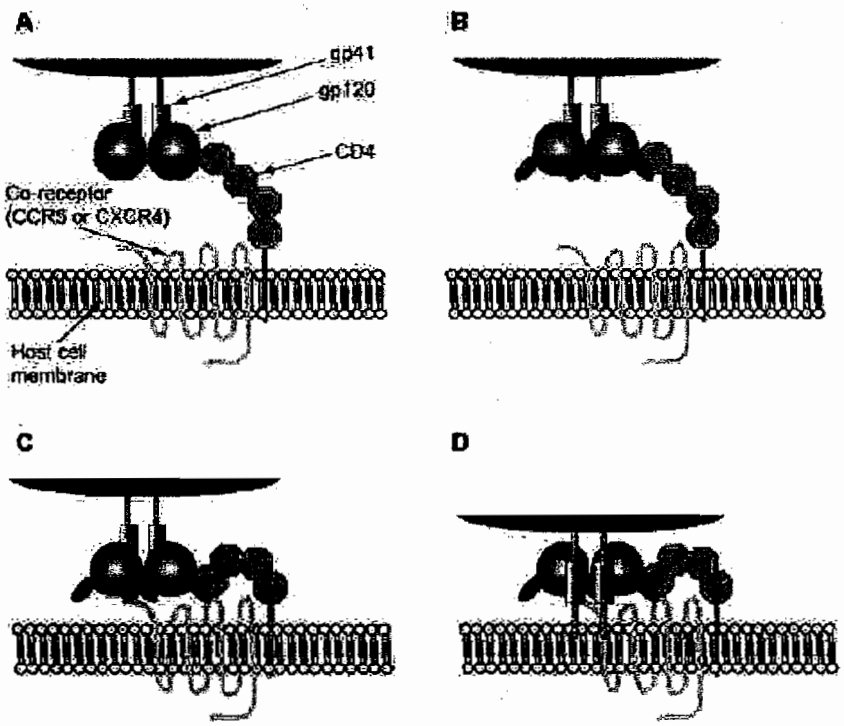


Figure legend. A model for HIV-1 entry. HIV-1 gp120 binds to CD4 (A). This induces conformational changes in gp120 and exposure of the co-receptor binding site (B), which is a complex domain that includes the V3 loop and is collectively termed the 'bridging sheet'. Exposure of the co-receptor binding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

Maraviroc is a CCR5 antagonist, which only inhibits strains that are obligate users of CCR5. Maraviroc binds to human CCR5 with a KD of 0.86 nM and has a dissociation half-life of approximately 16 hours at room temperature. By binding to a pocket within the transmembrane region of CCR5, maraviroc alters the three dimensional structure of CCR5 such that the viral envelope glycoprotein, gp120, is unable to recognize and bind to the co-receptor. Maraviroc blocks the soluble form of gp120 binding to CCR5 with an IC50 of 11 nM and inhibits gp120/CCR5-mediated membrane fusion with an IC50 of 0.22 nM.

Viral tropism was determined throughout the maraviroc program using a phenotypic assay. Samples in which only CCR5-tropic virus is detected in the assay are classified as 'R5-tropic'; samples in which only CXCR4-tropic virus is detected are classified as 'X4-tropic' and samples in which both CCR5-tropic and CXCR4-tropic virus is detected are classified as dual/mixed tropic.

The tropism assay was required to select individuals infected with viral strain(s) that use CCR5 co-receptor to enter cells and excluded subjects infected with viral strain(s) that use CXCR4 co-receptor. The tropism assay used by the applicant, Phenosense™ HIV Entry Tropism assay, has a turn-around time of 14-21 days at the Virologic Clinical Reference laboratory. The assay requires at least 1000 copies/mL of HIV RNA. The Sensitivity to amplify is 100% (21/21) of the samples with viral load > 5000 copies/mL, 97% (59/61) of the samples with viral load ≥ 2000 copies/mL, 94% (90/96) of the samples with viral load 500- 2000 copies/mL. The assay has a sensitivity of 100% for CXCR-4-tropic or dual/mixed HIV at a 10% mixture, and 83% at a 5% mixture. The tropism assay fails to work in 3-7% of the patients, which may be due to failure to amplify one virus strain.

Maraviroc is indicated for treatment-experienced patients infected with CCR5-tropic HIV-1, in combination with other antiretroviral agents

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The recommended dose of maraviroc differs based on concomitant medications due to drug interactions [see Table Q1]. Maraviroc can be taken with or without food. Maraviroc must be given in combination with other antiretroviral medications.

Table Q1 Recommended Dosing Regimen

Concomitant Medications	CELSENTRI Dose
CYP3A4 inhibitors (with or without a CYP3A4 inducer)including: • protease inhibitors (except tipranavir/ritonavir) • delavirdine • ketoconazole, itraconazole, clarithromycin, • Other strong CYP3A inhibitors (e.g., nefazadone, telithromycin)	150mg twice daily
Other concomitant medications, including tipranavir/ritonavir, nevirapine, all NRTIs and enfuvirtide	300mg twice daily
CYP3A4 inducers (without a CYP3A4 inhibitor) including: • efavirenz • rifampin • carbamazepine, phenobarbital, and phenytoin	600mg twice daily

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The pharmacokinetics/pharmacodynamics, dose response, safety and tolerability of maraviroc were initially evaluated in two randomized, 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 IC50/90. Subjects were randomized to receive maraviroc 25mg QD, 50mg BID, 100mg BID, 300mg BID or matching placebo for 10 days. 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. Subjects were randomized to receive maraviroc 150mg BID fasted, 150 mg BID fed, 100mg QD fasted or 300mg QD fasted or matching placebo for 10 days.

Dose selection for the Phase 2b/3 studies was based on viral load reduction data from Studies A4001007 and A4001015, pharmacokinetic/pharmacodynamic modeling, clinical study simulations, pharmacokinetics, drug-drug interaction studies, pre-clinical serial passage resistance studies and a safety database of over 400 subjects dosed for up to 4 weeks.

Two multicenter, randomized, double-blind, placebo-controlled registrational Phase 2b/3 superiority studies (A4001027 and A4001028) 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 primary objective of these studies was to confirm the hypothesis that maraviroc in combination with Optimized Background Therapy (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 (300 mg BID dose equivalent (n=419) and 300 mg QD dose equivalent (n=408)) versus placebo (n=207) in the mean change from baseline in plasma HIV-1 RNA at 24 and 48 weeks. These studies used 150 mg QD and 150 mg BID of maraviroc when administered with PIs (except tipranavir/ritonavir) or delavirdine (CYP3A4/P-gp inhibitors) or 300 mg QD and 300 mg BID when administered in the absence of PIs/delavirdine. More than 75% of the patients in each group received an optimized regimen contained a PI (other than tipranavir/ritonavir) and/or delavirdine.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Viral load and CD4 cell count are accepted markers for efficacy in trials with antiretroviral agents. The primary efficacy endpoint in studies A4001027 and A4001028 was 'change from baseline to 48 weeks in HIV-1 RNA measured on a logarithmic scale'. An interim analysis was conducted at 24 weeks for accelerated approval. Secondary endpoints included the percentage of patients with fewer than 50 or 400 copies of HIV-1 RNA per

milliliter of plasma, time to loss of virologic response, change in CD4 and CD8 counts and changes in genotype, phenotype and/or tropism in treatment failures.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

Yes, appropriate moieties were quantified in all the clinical pharmacology studies. Maraviroc was quantified using a sensitive and validated HPLC/MS/MS method. It was not necessary to measure concentrations of maraviroc metabolites, except for in the mass balance study, since in vitro data indicate the principal metabolites did not have any pharmacological activity predicted to be biologically relevant.

2.2.4 Exposure-response

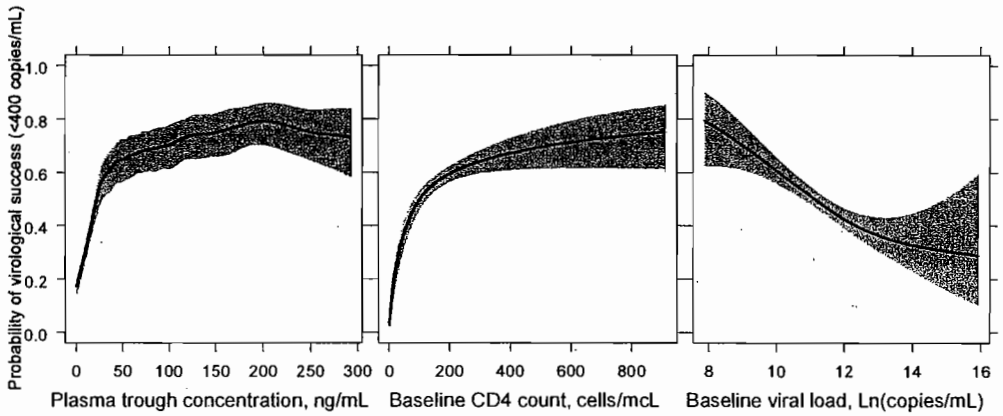
2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The data from two placebo controlled phase 2b/3 studies (1027 and 1028) of maraviroc and optimized background therapy (OBT) in treatment experienced patients infected with CCR5-tropic HIV-1 were used in exposure-response analysis. These trials used 150 mg QD and 150 mg BID of maraviroc when administered with PIs (except tipranavir/ritonavir) or delavirdine (CYP3A4/P-gp inhibitors) or 300 mg QD and 300 mg BID when administered in the absence of PIs/delavirdine. The effect of maraviroc exposure and several other predictors on the viral load was analyzed as a binary variable (success) using both logistic regression and generalized additive models (GAM). Several binary endpoints indicating virologic success, such as protocol defined failure[1] at week 24, viral load <50 copies/mL at 24 weeks, and viral load <400 copies/mL at 24 weeks were investigated. A total of 970 subjects (775 maraviroc treated and 195 placebo treated) were included in the analyses. A total of 79 subjects were excluded due to unavailability of covariate information. Plasma trough concentrations (Cmin) were used as an exposure variable, because it is highly correlated with other PK variables. Baseline CD4+ count, baseline viral load, overall sensitivity score (OSS) and Cmin were the most important predictors of virologic success. The following discussion focuses on findings derived from analyses of the clinically relevant endpoint, viral load <400 copies/mL at 24 weeks.

[1] 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 log10 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 log10 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 log10 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.

Figure Q2 illustrates the relationship between the probability of virologic success (<400 copies/mL) and Cmin, baseline CD4+ count and baseline viral load. The baseline tropism, time since diagnosis, time since the first treatment, NRTIS, T20S (presence and sensitivity to T20), T20H (previous treatment with T20) and TIPpresent (presence of tipranavir) were also found to impact the virologic success. The probability of virologic success is higher at higher Cmin and/or higher baseline CD4+ count and/or lower baseline viral load. Probability of virological success was lower when Cmin was below 50 ng/mL

Figure Q2. Cmin (left panel), baseline CD4+ count (middle panel) and baseline viral load (right panel) are important predictors of the virologic success. The shaded area represents twice standard error region.



The variability in Cmin is high, with a range of 0.1 to 560 ng/mL. Figure Q3 illustrates distribution of Cmin across all dose groups and proposed market doses in the phase 2b/3 studies. For the proposed market doses, the proportion of patients with Cmin <50 ng/mL was higher for 300 mg BID (no PIs (except tipranavir/ritonavir) or delavirdine) group than 150 mg BID (with PIs (except tipranavir/ritonavir) or delavirdine) group as shown in Table Q2.

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Figure Q3: Distribution of plasma trough concentrations across all dose groups (upper panel). The lower panel represents distribution across the proposed market doses.

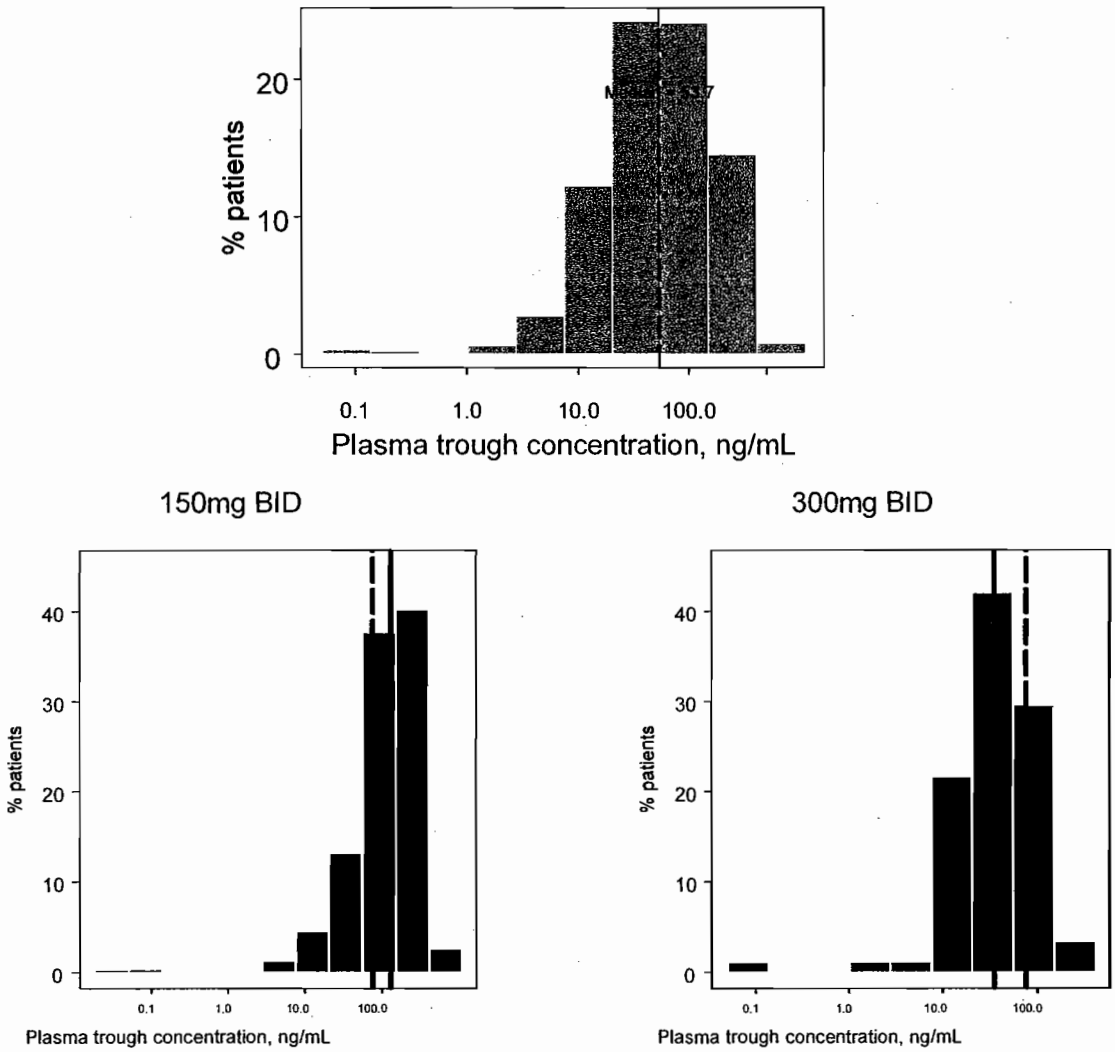
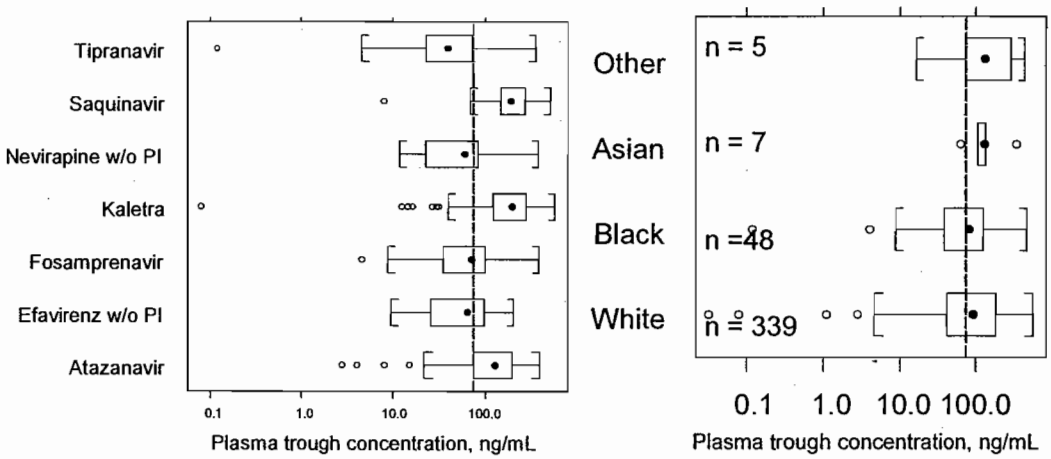


Table Q2. Distribution of concentrations for 150 and 300 mg BID.

Dose group	Number of patients	Concentration range	% patients <25 ng/mL	% patients <50 ng/mL	% patients <75 ng/mL	% patients <100 ng/mL
150 mg BID	311	0.03-561.7	7.7	17.3	28.3	42.4
300 mg BID	88	0.12-204.7	33.0	65.91	77.3	89.8

An attempt was made to understand the factors leading to lower Cmin. The box plots in Figure Q4 illustrate that the distribution of Cmin in Phase 2b/3 studies is not affected by concomitant drugs (after dose adjustment based on coadministered drugs) and race groups. Other covariates were also investigated and were not found to be explanatory of the lower Cmin.

Figure Q4: Concomitant drugs (left panel)[2] and race (right panel) do not explain lower Cmin levels (BID regimen).



The proposed BID dosing results in high maraviroc pharmacokinetic variability. To understand the intrinsic source of variability (inter-patient vs within patient variability) in Cmin, data from naïve patients were analyzed (A4001015 study). In this study, Cmin measurements were available from day 6 to day 10. A random effect approach was used to estimate inter-patient and within patient variability. The inter-patient variability (%CV=50%) was greater than within patient variability (%CV=33%). The inter-occasion variability in the phase III trials was found to be higher (~45%) than the above monotherapy trial. However, phase III estimates of variability are usually less reliable due to difficulties in proper documentation in the phase III trials. However, the phase III values may represent a situation closer to a typical clinical setting exhibiting difficulty in assessing exact plasma levels.

Since Cmin is a major predictor of the virologic success, a threshold-based simulation was conducted to understand the advantage of doubling the dose for patients with 'below threshold' concentrations. The Cmin-virologic success relationship was employed to investigate the advantage of increasing maraviroc doses in patients with Cmin lower than a certain threshold Cmin. Five different threshold Cmins, 10, 25, 50, 75 and 100 ng/mL, were studied. Data from the proposed market doses (150 and 300 mg BID) were used for the simulations. A factor of 2 was applied to the original values, if the Cmin was below the defined threshold. If the Cmin was above the defined threshold, the original value was retained. Figure Q5 illustrates the predicted virologic success for threshold-based simulations.

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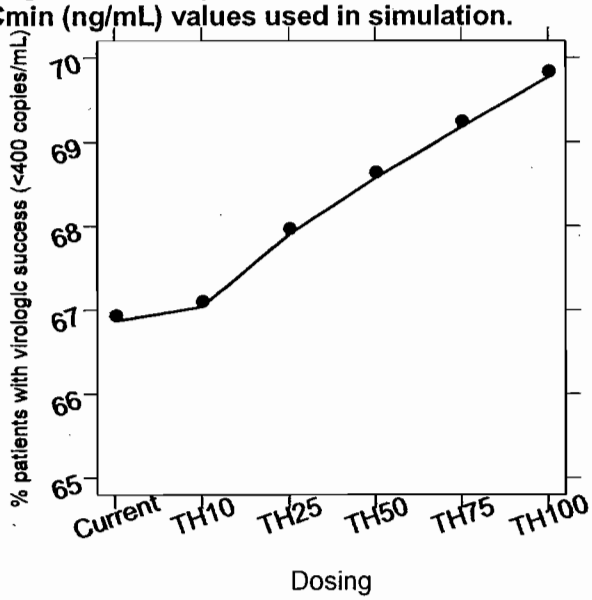
[2] For drug interaction plot, the multiple drugs in patients' OBT were not taken into account. The aim was to highlight if any concomitant medication might stand out as a predictor of lower concentrations

Figure Q5. The probability of virologic success can be increased up to 69% (vs. original 67%) by doubling the dose in patients with Cmin <75 ng/mL. THxx represents threshold Cmin (ng/mL) values used in simulation.



With the proposed market dosing, the virologic success on maraviroc with OBT was shown to be 67%. The probability of virologic success can be increased to 69% by doubling the dose in patients with Cmin <75 ng/mL. As seen from Table Q2, 75 ng/mL as a threshold will require 28% (150mg BID group) and 77% (300 mg BID group) to have dosing adjustments post Cmin assessment. Overall, 38% of clinical trial population on maraviroc BID had Cmin <75 ng/mL.The population benefit of monitoring therapeutic concentration is 2%. In addition to Cmin, several other patient and virus specific factors are important determinants of the virologic success.

The benefit of doubling the dose in patients with Cmin <75 ng/mL could be looked at differently. In the current simulations, we evaluated 399 patients out of which 146 (37%) patients needed dose doubling due to concentrations below 75 ng/mL. The current probability of the virologic success in those 146 patients is 56%. Dose doubling could increase the probability of virologic success to 62%, an 11% relative increase in the population that actually received dose change from monitoring therapeutic concentrations.

In conclusion, patients with Cmin >50-75 ng/mL (threshold not determined) have a better chance of virologic success. In addition to Cmin, the probability of success is also influenced by other patient specific factors such as baseline CD4+ count, baseline viral load and overall sensitivity score (OSS).

a. **With the sponsor's proposed dosing, ~67% of patients should achieve** <400 RNA copies/mL.

b. Concomitant drugs (such as CYP3A inhibitor or inducer after dose adjustment) or demographic factors were not the source of lower Cmin values.

c. The simulations indicate that by doubling the dose the probability of virologic success (<400 RNA copies/mL) can be increased from 56% to 62% in patients with Cmin <75 ng/mL. At the overall population level the probability of success increases from 67% to 69%.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Safety concerns raised by pre-clinical models and the Phase 1/2a studies include postural hypotension and QT prolongation. Exposure-response relationships are described below.

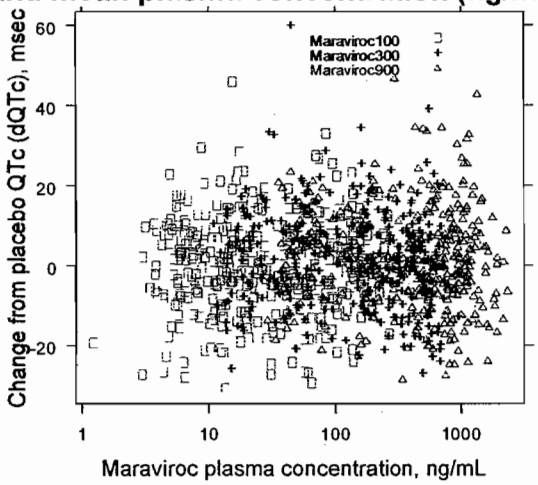
QT Interval

Results from hERG channel and dog isolated Purkinje fiber studies suggest that maraviroc has the potential to block the IKr current and affect cardiac repolarization 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 Cmax in HIV-1 infected patients at a dose of 300 mg BID (0.3 µM).

ECG parameters were monitored during early clinical studies with maraviroc. 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 Cmax at steady state after 600 mg QD was 333 ng/mL).

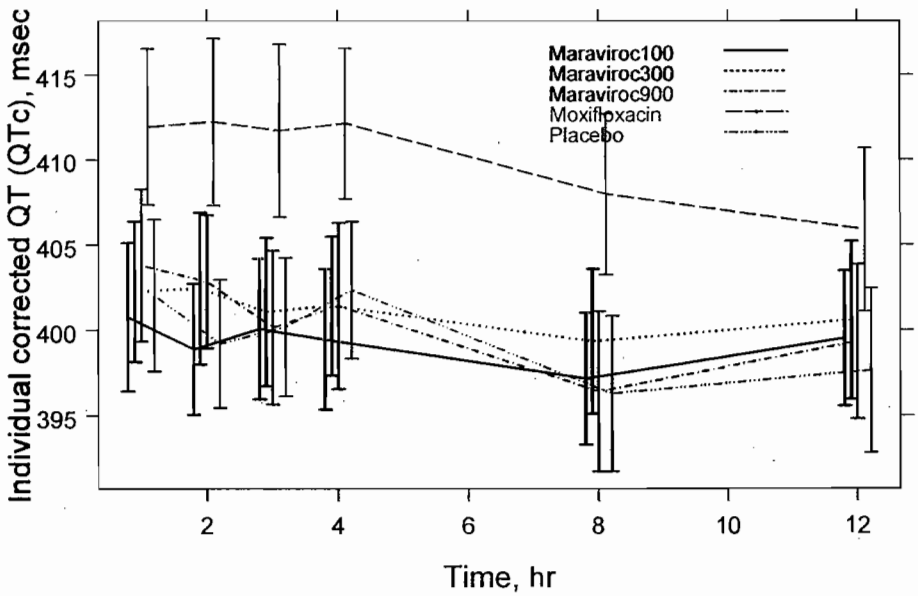
In order to assess the potential clinical significance of the results seen in A4001001, a prospectively designed QT study (A4001016) was conducted. No clear relationship between maraviroc plasma concentration and maximum increase in QTcI was observed at the time of the maximum increase from placebo, even at the 900-mg dose (Figure Q6). Similarly, there was no clear relationship between the changes from placebo in QTcI versus the maraviroc plasma concentrations at an individual's Tmax.

Figure Q6: The scatter plot for relationship between change from placebo QTc (dQTc), msec and mean plasma concentration (ng/mL) by dose groups



Additionally, the time course of QT, RR, QTc, dQTc was investigated. Figure Q7 shows the relationship between individual corrected QT (QTc) and time by dose groups.

Figure Q7 The relationship between individual corrected QT (QTc) and time by dose groups (mean ± 95% CI). The error bars are offset for clarity



The results from the moxifloxacin arm are unusual. It seems that moxifloxacin prolongs QT at all time points ($dQTc_{95\%\ upper\ confidence\ limit} > 10$ msec). Moxifloxacin concentrations were not collected, therefore, the source of these unusual findings is not resolved.

In conclusion, the change in QTc after administration of moxifloxacin minus the baseline QTc after placebo as a function of time was found to be unusual. The change was near maximal at 1 hour and remained unusually elevated at 12 hours. This unusual result means that assay sensitivity has not been demonstrated in this study; i.e., it is unclear

that had product administration prolonged the QTc, it could have been detected. At the time of this review, the IRT-QT team was uncertain whether administration of maraviroc prolongs the QTc above the threshold established in the ICH E14 guideline. Please refer to IRT-QT review for further details.

Cardiovascular Function

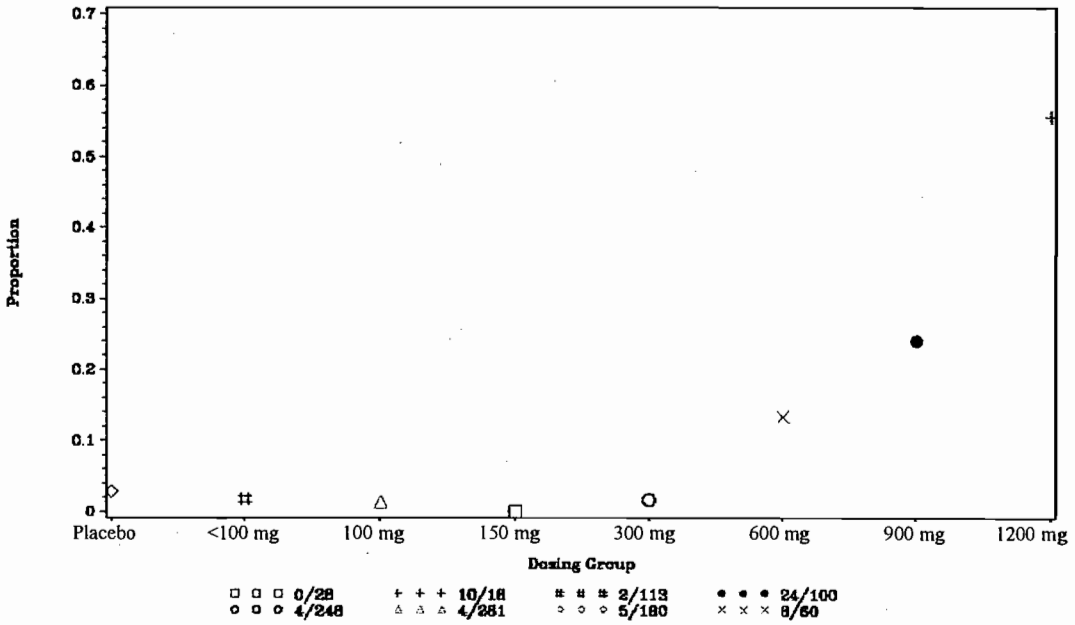
Maraviroc is a weak inhibitor of agonist binding to the human α2A adrenergic receptor and is an antagonist at alpha adrenergic receptors in canine venous tissue giving rise, in vitro, to vasodilatation. In Study A4001001, 4/9 subjects had dose limiting postural hypotension after a single maraviroc dose 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. Extensive profiling of the interaction of maraviroc with adrenergic receptors was performed, but there was no consistent adrenergic mediated activity by maraviroc.

In clinical studies, events of postural hypotension were rare at doses ≤300 mg where the incidence was similar to placebo, but the frequency increased 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 lightheadedness.

The observed incidence of postural hypotension across Phase 1/2a studies was plotted against unit dose as shown in Figure Q8, indicating that the incidence of postural hypotension increased above that of placebo at unit doses of ≥600 mg maraviroc.
In conclusion, events of postural hypotension are rare at 300 mg QD and BID (the doses used in the phase 2b/3 registrational studies).

In a Phase 1 study to investigate the haemodynamic effects of oral maraviroc, there was no apparent relationship between % change from baseline in ICG (Impedance Cardiography technology) parameters or change from baseline in supine blood pressure and pulse rate compared with maraviroc plasma concentration. However, 3/16 subjects experienced postural hypotension in the maraviroc treatment group (900 mg single dose) as compared to 0/3 subjects in the placebo group.

Figure Q8. Observed Occurrence of Postural Hypotension by Unit Dose of Maraviroc in Phase 1/2a Studies



2.2.4.3. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The proposed oral dose of 300mg BID (not administered with a potent CYP3A inhibitor) or 150 mg BID when administered with potent CYP3A inhibitors (including PIs (except tipranavir/ritonavir) and delavirdine) is consistent with the known exposure-response relationship. See detailed discussion in Section 2.2.4.1. It is acceptable to increase maraviroc dose to 600 mg when maraviroc is coadministered with efavirenz without PI. When maraviroc was coadministered with rifampin, maraviroc concentration was reduced by 63%, doubling maraviroc dose is sufficient to overcome the reduction. Nevirapine was not included in list of the CYP3A inducers that require dose doubling of maraviroc, because nevirapine did not reduce maraviroc concentrations in a Phase 1 study. See detailed discussion in Section 2.4.2.8.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

Following subsections describe the PK characteristics of maraviroc.

2.2.5.1 What are the single dose and multiple dose PK parameters?

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. Study A4001002 investigated pharmacokinetics of multiple oral doses of maraviroc in healthy male subjects. A single dose was given on day 1, followed by QD or BID dosing starting on day 3, with the final dose given on the morning of day 12. The study shows plasma maraviroc accumulates to a limited extent after both once- and twice-daily dosing (Table Q3). 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, Study A4001007, Table Q4). 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. Maraviroc has multiphasic elimination with a terminal half-life estimate from population pharmacokinetic modeling of data from oral tablet dosing of approximately 15 hours. The pharmacokinetic parameters in healthy subjects and HIV infected subjects are similar at 300 mg BID.

Table Q3. Summary of Multiple-Dose Pharmacokinetic Parameters in Healthy Subjects(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] $t_{½}$ only calculated for 4 subjects

[f] $t_{½}$ 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

Table Q4. Summary of Pharmacokinetic Parameters for HIV-1 Infected Subjects (A4001007, A4001015) on 300 mg doses.

Treatment	Day (n)	Mean Pharmacokinetic Parameter Value (range)					Accumulation Ratio[c]
		AUC_{12}[a] (ng.h/mL)	AUC_{24}[a] (ng.h/mL)	C_{max}[a] (ng/mL)	T_{max}[b] (h)	$t_{½}$[b] (h)	
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
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

2.2.5.2 How does the PK of the drug in healthy volunteers compare to that in patients?

The effect of HIV-1 infection on maraviroc pharmacokinetics was assessed in the population pharmacokinetic analysis of pooled Phase 1/2a data. 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.

2.2.5.3 What are the characteristics of drug absorption?

After single and multiple oral dosing, maraviroc Cmax generally occurs between 0.5 to 4 hours in both healthy subjects and HIV-1 infected patients (Tables Q3 and Q4). Maraviroc is a substrate of P-gp. The absolute bioavailability of maraviroc increases with dose, probably due to the saturation of P-gp with increased maraviroc concentrations in the gut, which results in more than a dose proportional increase in maraviroc exposure. The absolute bioavailability of a 100 mg dose is 23% and is predicted to be 31% at 300 mg. Maraviroc PK are approximately linear after intravenous (IV) administration (Table Q5).

Table Q5: Pharmacokinetic summary of maraviroc following intravenous administration (Study A4001009)

Parameter	UK-427,857 (Cohort 1)		
	3mg *iv* (N=8)	10mg *iv* (N=8)	30mg *iv* (N=8)
AUC_τ (ng.h/ml)[a]	57.6	201	670
AUC (ng.h/ml)[a]	NC	NC	687
C_{max} (ng/ml)[a]	36.9	122	397
T_{max} (h)[b]	0.94	0.94	0.91
$t_{1/2}$ (h)[b]	NC	NC	13.2
CL (L/h)[b]	NC	NC	44.0
CL_r (L/h)[b]	11.19	10.51	10.17
CL_{nr}(L/h)[b]	NC	NC	33.8
V_{ss} (L)[b]	NC	NC	194

[a]geometric means; [b]arithmetic means; NC (not calculated); CL (total clearance); CL_r (renal clearance); CL_{nr} (non-renal clearance); V_{ss} (volume of distribution at steady-state)

2.2.5.4 What are the characteristics of drug distribution?

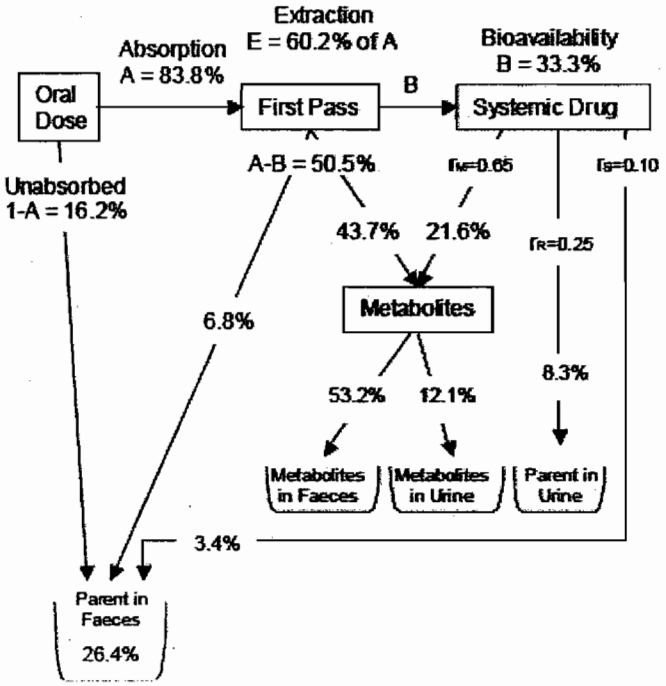
The steady state volume of distribution of maraviroc is approximately 194L following intravenous administration (Study A4001009). Maraviroc is bound (approximately 75%) to human plasma proteins, and shows moderate affinity for albumin and alpha-1 acid glycoprotein. Red blood cell partitioning was indirectly measured using whole blood and plasma radioactivity from a mass balance study when [14C] labeled maraviroc was administered to healthy subjects. Blood to plasma ratio was 0.6, suggesting maraviroc is predominantly confined to plasma with negligible distribution into red blood cells.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

The mass balance study suggested maraviroc is eliminated primarily by metabolism. A mass balance study was conducted using a single 300mg dose of ^{14}C-labeled maraviroc in healthy volunteers. Approximately 20% of the radiolabel was recovered in the urine and 76% was recovered in the feces over 168 hours. Maraviroc was the major component present in urine (mean: 8% of dose) and feces (mean: 26% of dose). The remainder was excreted as metabolites.

Using data from Study A4001010, combined with predictions of absorption of 83.8% for a 300 mg dose of maraviroc and the population modeled 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 Q9.

Figure Q9. Clearance and Mass Balance of Maraviroc after 300 mg Oral Dose



2.2.5.6 What are the characteristics of drug metabolism?

A mass balance study was conducted using a single 300mg dose of ^{14}C-labeled maraviroc in healthy volunteers. The major metabolites observed were UK-408,027 (22% of the administered dose), an amine analogue (11% of the administered dose) and UK-463,977 (5% of the administered dose). UK-408,027 and UK-463,977 have been evaluated in vitro and show no antiviral activity. In vitro studies indicate the major route of metabolism of maraviroc is via CYP3A4 and formation of the primary metabolite UK-408,027 is governed by CYP3A4. In clinical studies, potent CYP3A4 inhibitors and inducers were shown to modulate the kinetics of maraviroc and its primary metabolite. While 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. Furthermore, in Study A4001002, CYP2D6 phenotyping was conducted and there was no evidence that being a CYP2D6 poor metabolizer affected maraviroc exposure.

2.2.5.7 What are the characteristics of drug excretion?

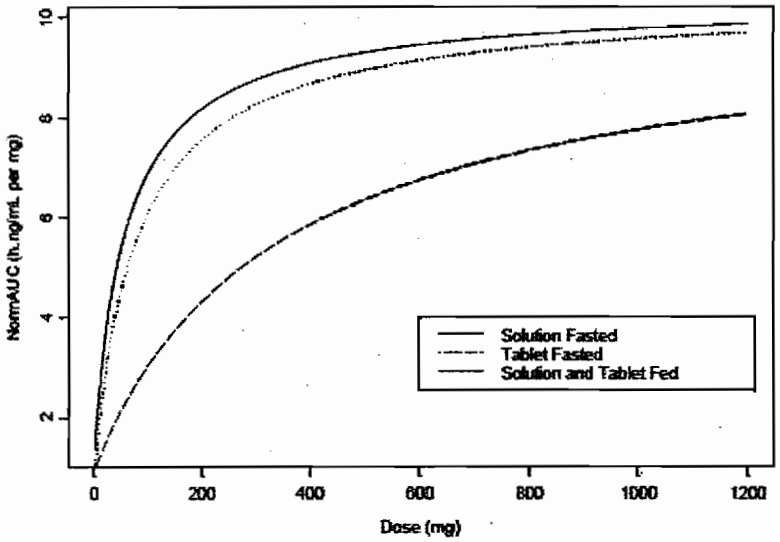
As shown in Section 2.2.5.5, renal clearance accounts for about 25% of the total clearance when 300 mg maraviroc is administered alone. However, data from several drug-drug interaction studies indicated when maraviroc is coadministered with CYP3A inhibitors, total maraviroc clearance is reduced while maraviroc renal clearance increases by 13 - 44% as compared to maraviroc administered alone; thus the percent of maraviroc clearance due to the renal route will increase with coadministration of CYP3A inhibitors. Therefore, the pharmacokinetics of maraviroc needs to be evaluated in subjects with impaired renal function.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

As shown in Section 2.2.5.1, Table Q3, maraviroc exposures increased in a more than dose proportional manner. 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. Using nonlinear mixed effects modeling a 2-compartment model was adapted to incorporate separate absorption and clearance components on bioavailability (referred to as the partition model). Bioavailability (F) was modeled as a product of extent of absorption (FABS) and fraction surviving first-pass elimination (FHEP) 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 FABS 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 modeling 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. Predictions for bioavailability of maraviroc at a 100 mg unit dose are very similar across the modeling analyses and are consistent with the calculated oral absolute bioavailability (23%) from Study A4001009. The data indicated that oral pharmacokinetics of maraviroc are nonproportional.

The IV kinetics of maraviroc are linear over the 3-30 mg IV dose range (Study A4001009, Table Q5), therefore, 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 efflux transporters (predominantly P-gp) that reduce 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 normalized AUC and Cmax using the nonlinear mixed effect modeling approach expressed the dose non-proportionality in quantitative terms to allow predictions for doses not studied. 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, so an Emax model was fitted to the normalized AUC (AUC divided by dose) versus dose data. These results showed the dose non-proportional behavior 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 normalized AUC dose relationship begins to reach a maximum (i.e. maximal absorption) (Figure Q10). Above 600 mg unit doses of maraviroc, dose proportional kinetics for maraviroc would be expected.

Figure Q10. Maraviroc Dose-Normalized Steady State



2.2.5.9 How do the PK parameters change with time following chronic dosing?

Based on Study AI4001002, apparent clearance decreased by less than 20% from Day 1 to Day 12 , the reduction was probably because of an underestimate of Day 1 AUC∞ due to concentrations close to the quantitation limit during the terminal phase. AUCτ on Day 7 and Day 12 are similar. The PK parameters in Phase 2b/3 population PK analysis are generally lower than those observed in Phase 1/2a, which could be due to concomitant medications, food effect, and compliance. There were no observed trough concentrations from the long-term study to determine whether PK parameters change with time following chronic dosing.

Table Q6: Geometric mean of pharmacokinetic parameters

Maraviroc Dose	AUCτ on Day 7	AUCτ on Day 12	AUC∞ after single dose	Ratio of AUCτ/AUC∞	Ratio of AUCτ Day 12 vs Day7
3 mg BID (Cohort 6)	6.6	4.2	-	-	0.70
10 mg BID (Cohort 6)	19.0	22.2	-	-	
25 mg BID (Cohort 4)	92.0	98.6	74.6	1.19	1.11
100 mg BID (Cohort 1)	636	686	579	1.19	1.08
300 mg BID (Cohort 2)	2641	3609	2422	1.49	1.37
600 mg QD (Cohort 3)	6981		6074	-	
600 mg QD (Cohort 5)		6440	5712	1.13	

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

In patients, the residual variability for sparsely sampled data in treatment experienced patients on varied OBT was 49.2% (constant over time) with a 53.9% between subject variability in residual variability. The drug interactions with other antiretrovirals in the OBT accounted for the largest component of interindividual variability in maraviroc concentrations

In a monotherapy study (A4001015) with treatment naïve patients, daily Cmin measurements were available from day 6 to day 10. A random effect approach was used to estimate inter-patient and within patient variability. The inter-patient variability (%CV=50%) was greater than within patient variability (%CV=33%).

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses? What dosage regimen adjustments are recommended for each of these groups?

The effect of HIV-1 infection on maraviroc pharmacokinetics was assessed in the population pharmacokinetic analysis of pooled Phase 1/2a data. This analysis included 365 healthy subjects and 48 HIV-1 infected patients. The results indicate HIV status (i.e. whether a subject was infected with HIV-1 or not) does not affect maraviroc pharmacokinetic parameters.

The effects of age, gender, weight, and race on maraviroc pharmacokinetics were also assessed in the population pharmacokinetic analysis of pooled Phase 1/2a data. The analysis appeared to indicate that age, gender and weight did not have an impact on maraviroc exposure. However, the results need to be interpreted with caution because no subjects over the age of 65 years were enrolled. Exposure appeared to be slightly (26.5%) increased in Asians (N=95). However, a specific study designed to evaluate PK differences between Caucasians and Singaporeans showed no difference between these two populations. Dose adjustments are not recommended.

The pharmacokinetics of maraviroc have not been evaluated in subjects with impaired renal function. Renal clearance accounts for about 25% of the total clearance when 300 mg maraviroc is administered alone. However, when maraviroc is coadministered with CYP3A inhibitors, total maraviroc clearance is reduced while maraviroc renal clearance increases by 13 - 44% as compared to maraviroc administered alone; thus the percent of maraviroc clearance due to the renal route will increase with coadministration of CYP3A inhibitors (phase 4 commitment).

Study	PI (CYP3A inhibitor)	CLr (L/h)		CLr Ratio
		MVC	MVC+ PI	MVC+PI vs MVC
1025	ATV	7.6	10.4	0.37
1021	LPV/RTV	8.5	11.8	0.39
1021	SQV/RTV	5.5	7.9	0.44
1021	SQV/LPV/RTV	10.9	12.3	0.13
1042	TPV/RTV	8.9	11.1	0.25

A single dose study in subjects with mild or moderate hepatic impairment is currently ongoing. Since maraviroc is metabolized by the liver, concentrations are likely to be increased in these subjects.

In vitro data suggest that none of the polymorphic enzymes (CYP2C9, CYP2C19 and CYP2D6) contribute significantly to the metabolism of maraviroc. Dose adjustments are not recommended.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure -response and what is the impact of any differences in exposure on response?

Food intake with maraviroc administration reduces the rate and extent of absorption of maraviroc to a similar extent in both healthy volunteers and HIV-1 infected patients. This food effect on maraviroc is less at higher doses (300 mg dose equivalent or above) and is less when doses are not taken at the same time as a meal as shown in Study A4001004. See details on Section 2.5.3

The potential for drug interactions is discussed in Section 2.4.2.

2.4.2. Drug-Drug Interactions

2.4.2.1. Is there any in vitro basis to suspect in vivo drug-drug interactions?

Yes. In vitro metabolism of maraviroc has been studied using human liver microsomes and recombinant cytochrome P450 enzymes. Maraviroc had a moderate clearance in these in vitro systems. Further investigations showed that this metabolism was inhibited by the CYP3A4 inhibitor ketoconazole but not by sulphaphenazole or quinidine (CYP2C9 and CYP2D6 inhibitors, respectively). The use of recombinant enzyme systems confirmed a role for CYP3A4 (and its orthologue, CYP3A5) in the metabolism of maraviroc, and showed that neither of the polymorphic P450 enzymes CYP2C19 or CYP2D6 contributes significantly to its metabolism. Furthermore, the formation of the circulating N-dealkylated metabolite UK-408,027 has been shown to be mediated by CYP3A4. CYP3A4 is therefore responsible for a large proportion of the metabolism of maraviroc and as a consequence its pharmacokinetics could be altered by coadministration of drugs that inhibit or induce this enzyme.

2.4.2.2. Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Maraviroc is a CYP3A4 substrate. None of the polymorphic enzymes (CYP2C9, CYP2C19 and CYP2D6) contribute significantly to its metabolism. See Section 2.4.2.1.

2.4.2.3. Is the drug an inhibitor and/or inducer of CYP enzymes?

The potential for maraviroc to inhibit the activity of the seven major cytochrome P450 enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 has been investigated in human liver microsomes, with and without preincubation. Probe enzyme activities and the substrate concentrations used are listed below.

CYP1A2- Phenacetin O-deethylase (20 μM phenacetin)
CYP2C9- Diclofenac 4-hydroxylase (18 μM diclofenac)

CYP2C19- (S)-mephenytoin-4-hydroxylase (37 μM S-mephenytoin)
CYP2D6- Dextromethorphan O-demethylase (4 μM dextromethorphan)
CYP3A4- Testosterone 6β-hydroxylase (120 μM testosterone)
CYP3A4- Felodipine oxidase (20 μM felodipine)
CYP3A4- Midazolam 1'-hydroxylase (3 μM midazolam)
CYP2B6- Bupropion 1-hydroxylase (100 μM bupropion)
CYP2C8- Rosiglitazone O-Desmethylase (9 μM rosiglitazone)

At the concentrations used in the studies (up to 30 μM), maraviroc did not inhibit any of these enzymes (IC50 > 30 μM). The in vitro data indicate maraviroc is unlikely to inhibit the metabolism of other cytochrome P450 substrates at clinical doses (I/KI <0.055).

Maraviroc has no clinically significant effect on a sensitive probe CYP3A substrate, midazolam. Maraviroc had no effect on the debrisoquine metabolic ratio (MR) at 300 mg BID or less in vivo. However, there was 230% increase in debrisoquine MR on treatment compared to baseline at 600 mg QD, suggesting potential inhibition of CYP2D6 at higher dose. It is not clear if maraviroc metabolite(s) inhibits CYP2D6, which could be significant when maraviroc is coadministered with CYP3A inducer at 600 mg BID (Phase 4 commitment).

Induction potential for maraviroc on CYP enzymes were not evaluated in vitro. Results from drug-drug interaction studies with midazolam, and another CYP3A substrate, ethinyl estradiol, indicate maraviroc is not an inducer of CYP3A enzyme. However, the potential of maraviroc to induce CYP1A2 has not been conducted (Phase 4 commitment).

2.4.2.4. Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

An in vitro permeability study of maraviroc and P-gp inhibitors in Caco-2 cells suggested that maraviroc is a substrate for P-gp. The efflux of maraviroc from Caco-2 cell monolayers has been studied in the presence of a number of P-gp inhibitors (ketoconazole, ritonavir, nelfinavir, saquinavir, and indinavir). Maraviroc shows limited permeability in the apical to basolateral direction (A-B) in Caco-2 cells in the absence of P-gp substrates, with Papp values of <1 $x10^{-6}$cm/s in all the studies. The rank order for inhibitory potency of maraviroc efflux was ketoconazole>ritonavir>nelfinavir>saquinavir >indinavir. Table Q7 shows inhibition of maraviroc efflux by ketoconazole.

Table Q7. Inhibition of efflux of 5μM maraviroc by the anti-fungal agent Ketoconazole at increasing concentrations.

Concentration Ketoconazole (μM)	Mean A-B Papp ($x10^{-6}$cm/s) (n=2)	Mean B-A Papp ($x10^{-6}$cm/s) (n=2)	Net Secretory Flux (nmol/cm^2/h)	Degree of inhibition of UK-427,857 efflux (%)
0	0.52 (0.55,0.50)	4.99 (4.59,5.39)	0.0805	
1	0.79 (0.86,0.72)	4.18 (3.74,4.62)	0.0611	24
3	0.97 (0.90,1.03)	2.89 (2.70,3.08)	0.0346	57
5	1.12 (1.23,1.00)	2.05 (1.91,2.19)	0.0168	79
7	1.24 (1.23,1.25)	1.67 (1.63,1.72)	0.0078	90
10	1.40 (1.24,1.56)	1.75 (1.63,1.88)	0.0064	92
25	1.55 (1.65,1.45)	1.44 (1.33,1.56)	-0.0021	103
50	1.66 (1.57,1.75)	1.37 (1.30,1.43)	-0.0053	107
75	1.59 (1.61,1.56)	1.37 (1.40,1.35)	-0.0039	105
100	1.61 (1.61,1.61)	1.53 (1.71,1.35)	-0.0013	102

P-gp inhibition potential for maraviroc has not been evaluated (Phase 4 commitment).

2.4.2.5. Are there other metabolic/transporter pathways that may be important?

No study was conducted to evaluate other transporter pathways.

2.4.2.6. Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

The proposed label provides dosing instructions when maraviroc is co-administered with inhibitors and inducers of CYP3A. The interaction potential between maraviroc and inhibitors/inducers of CYP3A has been evaluated in Phase I drug-drug interaction studies, as well as population PK analysis. See Section 2.4.2.8 for details.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Multiple co-medications are expected to be administered to the target populations, including inhibitors and inducers of CYP3A. Therefore, the proposed label provides dosing instructions when maraviroc is co-administered with inhibitors and inducers of CYP3A.

2.4.2.8. Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Effects of Other Drugs on Maraviroc

Maraviroc is a CYP3A and P-gp substrate. Since maraviroc will be coadministered with drugs that affect CYP3A and P-gp activity, such as protease inhibitors, the effects of drugs on maraviroc pharmacokinetics were studied in Phase I clinical trials. Table Q8 summarizes the effect of other drugs on maraviroc.

Table Q8. Summary of the Effect of Other Drugs on Maraviroc					
Co-administered drug and dose	**N**	**Maraviroc Dose**	**Ratio (90% CI) of maraviroc pharmacokinetic parameters with/without co-administered drug (no effect = 1.00)**		
			Cmin	**AUC_{tau}**	**Cmax**
CYP3A4 and/or P-gp Inhibitors					
Ketoconazole 400 mg QD	12	100 mg BID	3.75 (3.01-4.69)	5.00 (3.98, 6.29)	3.38 (2.38, 4.78)
Saquinavir (Fortovase™) 1200 mg TID	12	100 mg BID	4.50 (3.77-5.38)	4.25 (3.47, 5.19)	3.32 (2.45, 4.49)
Ritonavir 100 mg BID	8	100 mg BID	4.55 (3.37-6.13)	2.61 (1.92, 3.56)	1.28 (0.79, 2.09)
Saquinavir (Fortovase™)/r 1000 mg/100 mg BID	8	100 mg BID	9.10 (6.74-12.3)	8.32 (6.11, 11.3)	4.23 (2.60, 6.88)
Saquinavir (Fortovase™) /r 1000 mg/100 mg BID	11	100 mg BID	11.3 (8.96-14.1)	9.77 (7.87, 12.14)	4.78 (3.41, 6.71)
Kaletra™ 400 mg/100 mg BID	8	100 mg BID	6.23 (4.62-8.41)	3.83 (2.81, 5.21)	1.61 (0.99, 2.63)
Kaletra™ 400 mg/100 mg BID	11	300 mg BID	9.24 (7.98-10.7)	3.95 (3.43, 4.56)	1.97 (1.66, 2.34)
Atazanavir 400 mg QD	12	300 mg BID	4.19 (3.65-4.80)	3.57 (3.30, 3.87)	2.09 (1.72, 2.55)
Atazanavir/r 300 mg/100 mg QD	12	300 mg BID	6.67 (5.78-7.70)	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	0.55 (0.43-0.72)	0.552 (0.492, 0.620)	0.486 (0.377, 0.626)
Rifampicin 600 mg QD	12	100 mg BID	0.22 (0.17-0.28)	0.368 (0.328, 0.413)	0.335 (0.260, 0.431)
Nevirapine 200 mg BID (+ lamivudine 150 mg BID, tenofovir 300 mg QD)	8	300 mg SD	-	1.01 (0.65, 1.55)	1.54 (0.94, 2.51)
CYP3A4 and/or P-gp Inhibitors and Inducers					
Kaletra™ + efavirenz 400 mg/100 mg BID + 600 mg QD	11	300 mg BID	6.29 (4.72-8.39)	2.53 (2.24, 2.87)	1.25 (1.01, 1.55)

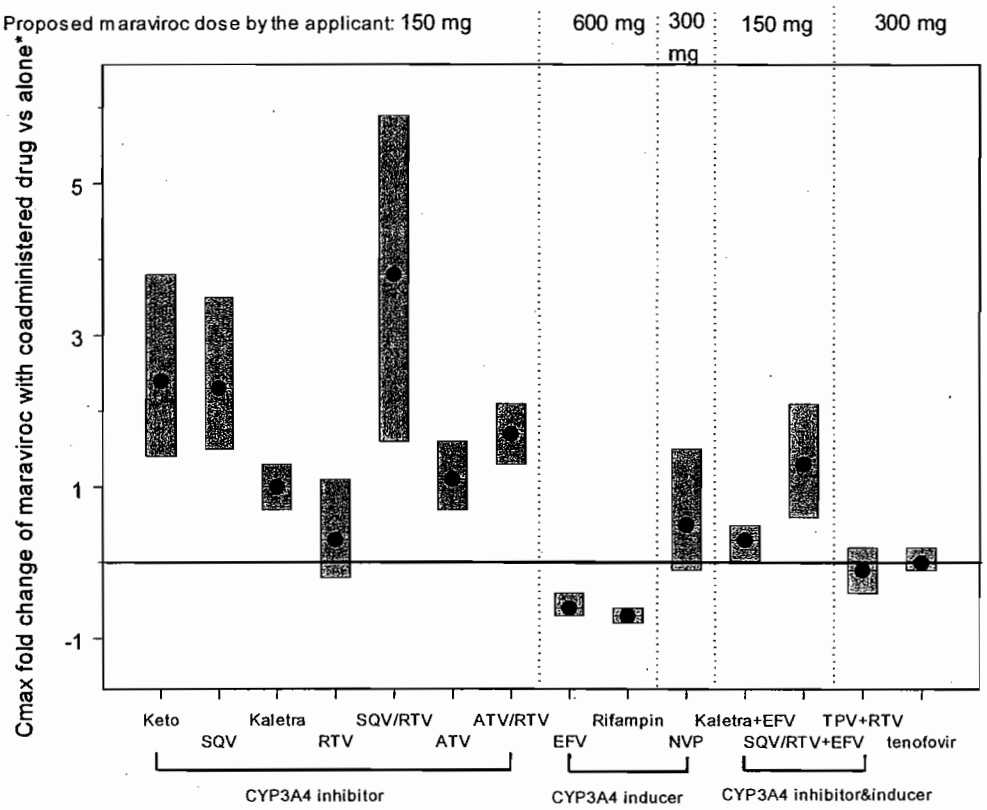
Table Q8. Summary of the Effect of Other Drugs on Maraviroc					
			Ratio (90% CI) of maraviroc pharmacokinetic parameters with/without co-administered drug (no effect = 1.00)		
Saquinavir(Fortovase™) /r + efavirenz 1000 mg/100 mg BID + 600 mg QD	11	100 mg BID	8.42 (6.46-10.97)	5.00 (4.26, 5.87)	2.26 (1.64, 3.11)
Tipranavir/r 500 mg/200 mg BID	12	150 mg BID	1.80 (1.55-2.09)	1.02 (0.850, 1.23)	0.86 (0.61, 1.21)
Renal					
Co-trimoxazole™ 800 mg/160 mg BID	15	300 mg BID	0.895 (0.80-1.00)	1.1 (1.04,1.37)	1.19 (1.01, 1.21)
Tenofovir 300 mg BID	12	300 mg BID	1.06 (0.94-1.20)	1.03 (0.980, 1.09)	1.04 (0.901, 1.19)

Figures Q11 and Q12 show the effect of CYP3A inhibitors or inducers (some are P-gp inhibitors or inducers as well) on the pharmacokinetics of maraviroc from Phase 1 studies. Tenofovir is also included in the figure, although it does not affect CYP3A or P-gp. The applicant proposes to reduce maraviroc dose to half (e.g., 150 mg BID) when it is coadministered with a CYP3A inhibitor with or without a CYP3A inducer, and increase maraviroc dose to 600 mg BID when it is coadministered with CYP3A inducer without a CYP3A inhibitor. The goal of the proposed dose reduction for maraviroc when coadministered with a CYP3A inhibitor is to reduce the Cmax to the value obtained with maraviroc 300 mg monotherapy. Although some potent CYP3A inhibitors such as saquinavir/ritonavir could increase maraviroc AUC by 8-fold, the increase of Cmax is much less. The reduction of maraviroc to half-dose in the presence saquinavir/ritonavir is not expected to result in a Cmax that exceeds the observed Cmax associated with postural hypotension (maraviroc Cmax at 600 mg). In contrast to other protease inhibitors, a maraviroc dose adjustment (to 150 mg BID) is not needed when tipranavir/ritonavir is part of the background therapy, based on Phase 1 drug interaction results. Maraviroc needs to reduce to 150 mg BID when maraviroc is coadministered with potent CYP3A inhibitors, but not mild or moderate inhibitors. We are concerned that reduction of maraviroc to 150 mg BID when a moderate or mild CYP3A inhibitor is administered (without other CYP3A inhibitor) may result in maraviroc concentrations lower than those observed in the clinical trials.

Although there are 45% and 63% reduction of maraviroc AUC by efavirenz and rifampin, respectively, the drug-drug interaction study indicated that maraviroc dose increase to 600 mg when combined with efavirenz and rifampin will increase the AUC to the value at maraviroc 300 mg alone.

The proposed regimens are the same as those used in the Phase 3 studies, except for maraviroc when given with efavirenz, where maraviroc 300 mg QD or BID was used in Phase 3 studies. The proposed regimens are acceptable based on Phase 1 drug-drug interaction studies and Phase 2b/3 population PK analysis.

Figure Q11: The effect of other drugs on Cmax of maraviroc (from Phase I drug interaction studies)



* Fold change is the ratio of Cmax of maraviroc when combined with other drug to the Cmax of maraviroc **when administered alone at the same dose** minus 1. The box is the 90% confidence interval (CI) for the fold change.

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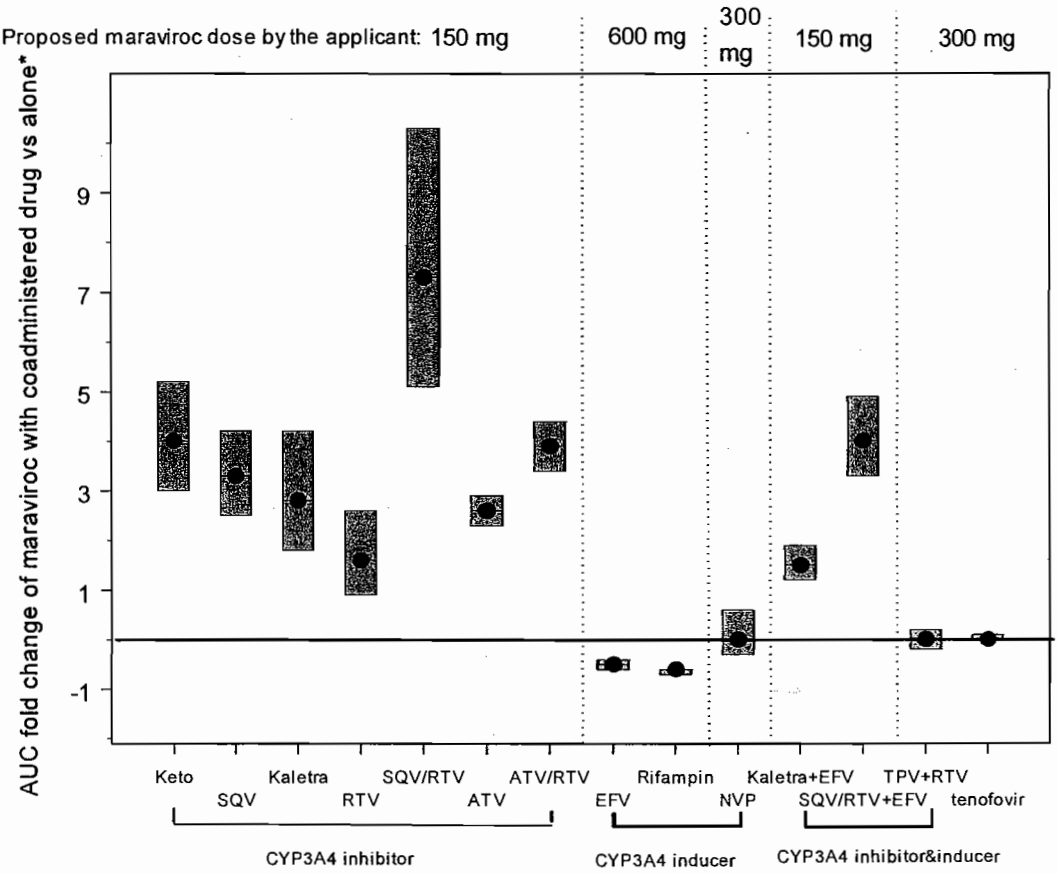
Figure Q12: The effect of other drugs on AUC of maraviroc (from Phase 1 drug interaction studies)



*Fold change is the ratio of AUC of maraviroc when combined with other drug to the AUC of maraviroc **when administered alone at the same dose** minus 1. The box is the 90% confidence interval (CI) for the fold change.

The data from Phase 2b/3 Studies 1027 and 1028 (**Table Q9**) show that when maraviroc 300 mg bid is taken with efavirenz without a protease inhibitor (n=10), arithmetic mean or geometric mean of AUC (or Cmin) was similar to the AUC (or Cmin) for maraviroc at the same dose when given with nevirapine without a protease inhibitor (n=9), and the AUC (or Cmin) for subjects who took maraviroc with tipranavir/ritonavir in 300 mg bid dose group (n=56). However, the median AUC and Cmin of maraviroc are lower in patients who took maraviroc with efavirenz as compared to median values in patients who took maraviroc with nevirapine or tipranavir/ritonavir. The median maraviroc concentrations in these studies in the presence of efavirenz are also lower than what have been observed for maraviroc 300 mg BID alone in Phase 2a study. The data from Phase 2a were used as reference because exposure-response analysis indicated that the exposure observed in Phase 2a with maraviroc 300 mg BID should be adequate for the efficacy. Therefore, maraviroc dose increase to 600 mg in presence of efavirenz (without CYP3A inhibitor) is acceptable.

For patients taking maraviroc with nevirapine or tipranavir/ritonavir, although arithmetic or geometric mean of maraviroc AUC is lower than the values observed in the Phase 2a study, maraviroc Cmin is comparable to the values observed in the Phase 2a study. In addition, the results from Phase 1 studies indicated that nevirapine and tipranavir/ritonavir have no effect on maraviroc concentrations. Therefore, no dose adjustment is needed for patients taking maraviroc with nevirapine or tipranavir/ritonavir.

Table Q9: Pharmacokinetics of Maraviroc when coadministered with nevirapine, efavirenz, and tipranavir/ritonavir on Studies 1027 and 1028 (pooled analysis) vs Phase 2a

Regimen	N	AUC (ng.h/mL)			Cmin (ng/mL)		
		Geometric Mean (CV%)	Mean (SD)	Median (Range)	Geometric Mean (CV%)	Mean (SD)	Median (Range)
300 mg MVC +NVP BID	10	1358 (80%)	1692 (1164)	1283 (613 – 3936)	33.2 (128%)	50.2 (46.9)	34.5 (9.2 -155.8)
300 mg MVC +EFV BID	9	1375 (74%)	1662 (1061)	1080 (505 – 3296)	34.1 (102%)	46.2 (36.9)	27.3 (9.6 – 106.4)
300 mg MVC+TPV/RTV	56	1238 (119%)	1545 (846)	1435 (7-4113)	31.4 (140%)	43.4 (31.4)	32.4 (0.1-145)
Phase 2a 300 mg MVC BID (s.s)	8	2552 (30%)	2649 (782)	1596 (1690-4060)	33.6 (63%)	39.9 (30.1)	30.8 (17-111)

Effects of Maraviroc on Other Drugs

Maraviroc is unlikely to inhibit the metabolism of co-administered drugs that are metabolized by cytochrome P450 enzymes, with the possible exception of CYP2D6, as explained below.

Maraviroc does not inhibit the seven major cytochrome P450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) at clinically relevant concentrations in vitro (IC_{50} > 30μM). Maraviroc had no clinically relevant effect on the pharmacokinetics of midazolam, the oral contraceptives ethinyl estradiol and levonorgestrel and had no effect on the urinary 6β-hydroxycortisol/cortisol ratio, suggesting no induction of CYP3A in vivo. Maraviroc had no effect on the debrisoquine metabolic ratio (MR) at 300 mg BID or less in vivo. However, there was a 230% increase in debrisoquine MR on treatment at a MVC dose of 600 mg QD compared to baseline, suggesting potential inhibition of CYP2D6 at higher doses. It is not clear if maraviroc metabolite(s) inhibits CYP2D6, which could be significant when maraviroc is coadministered with CYP3A inducer at 600 mg BID (Phase 4).

Drug interaction studies were performed with maraviroc and other drugs likely to be co-administered or commonly used as probes for pharmacokinetic interactions. **Table Q10** summarizes the effect of maraviroc on other drugs. Maraviroc had no effect on the

pharmacokinetics of zidovudine or lamivudine, suggesting no interactions with drugs eliminated through renal pathways.

Table Q10. 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)		
			Cmin	AUC_{tau}	Cmax
Ethinylestradiol (30µg QD) A4001005	15	100 mg BID	1.16 (1.08-1.26)	1.00 (0.95, 1.05)	0.98 (0.91, 1.06)
Levonorgestrel (150µg QD) A4001005	15	100 mg BID	0.99 (0.93-1.06)	0.98 (0.92, 1.04)	1.00 (0.93, 1.08)
Midazolam (7.5 mg SD) A4001012	12	300 mg BID	Not applicable	1.18 (1.04, 1.34)	1.21 (0.92, 1.60)
Zidovudine (300 mg BID) A4001020	11	300 mg BID	1.22 (0.99-1.49)	0.98 (0.79, 1.22)	0.92 (0.68, 1.24)
Lamivudine (150 mg BID) A4001020	11	300 mg BID	1.35 (1.14-1.61)	1.14 (0.98, 1.32)	1.16 (0.88, 1.54)

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Yes. The in vitro antiviral activity of maraviroc was evaluated in combination with standard and developmental antiviral agents. In total the antiviral activity of maraviroc was assessed in combination with 18 approved anti-HIV agents, [redacted]

Additive antiviral interactions were observed for all compounds in combination with maraviroc, with the exception of the protease inhibitors atazanavir and indinavir, and the entry inhibitor enfuvirtide, where synergy was observed in one experiment and additivity in a second experiment. There was no evidence of antagonistic interaction with any of the compounds investigated.

In the Phase 2b/3 studies, supine and standing blood pressure and pulse rate measurements were recorded at screening, Day 1, Weeks 2, 24 and 48 and (if applicable) at early termination. Postural hypotension at these timepoints was slightly more frequent in the 2 maraviroc treatment groups (300 mg QD and 300 mg BID) than in the placebo group. When the analysis was restricted to patients who were taking concomitant antihypertensives, nitrates, alpha blockers, and PDE5 inhibitors that are expected to lower blood pressure, the incidence of postural hypotension was likewise similar across treatment groups. At Week 2, for example, among patients who were receiving at least 1 of these concomitant agents, 10/147 (6.8%) patients receiving maraviroc QD, 9/172 (5.2%) receiving maraviroc BID and 4/75 (5.3%) receiving placebo met criteria for postural hypotension.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Maraviroc is highly soluble across the physiological pH range (pH 1.0 to 7.5), but has limited permeability and polarized transport across the cell monolayer (Caco-2 cells).

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

A pivotal BE study was conducted to compare the relative bioavailability of the proposed to-be-marketed formulation (commercial tablet) to the formulation used in the clinical trials (Research tablet). The study shows that the 90% CI for the geometric mean ratios for Cmax and AUC were within the range of 80% - 125% for bioequivalence. Therefore, the proposed to-be-marketed formulation is bioequivalent to the formulation used in the clinical trials.

Parameter (units)	Adjusted Means		Ratio/Difference Between Adjusted Means[a]	90% Confidence Interval
	Maraviroc 300mg Commercial Tablet N=42*	Maraviroc 2x 150mg Research Tablets N=42*		
AUC_{inf} (ng.h/ml)**	2700	2760	98.0%	(93.9%, 102.2%)
AUC_{last} (ng.h/ml)	2680	2730	98.4%	(94.3%, 102.6%)
C_{max} (ng/ml)	629	654	96.1%	(88.1%, 104.8%)
T_{max} (h)	2.49	2.45	0.04	(-0.33, 0.40)

* Subjects 18 and 19 were excluded from the analysis due to incomplete data.
[a] The ratios (Commercial/Research), expressed as percentages, are presented for AUCinf, AUClast and Cmax and the difference (Commercial-Research) for Tmax. ** N=41 for AUCinf because this parameter could not be calculated for Subject 1 in treatment period 2.

The results from Division of Scientific Investigations (DSI) indicated that the analytical site should correct the documentation issue cited in the Form FDA 483. The observation however, is not likely to have a significant impact on the study outcome. For the clinical site, DSI found that the authenticity of the dosage forms tested in Study A4001040 cannot be assured because the clinical facility did not select the dosage forms and retain reserve samples for the study. DSI issued Form 483, DAVP/OCP requested additional information from the applicant. The applicant provided the information (selection of samples for retention) and the BE study is acceptable.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Phase 1 food effect studies indicate there is a dose dependent and time dependent effect of food when maraviroc is administered with a high fat meal, which was independent of dosage form, as shown in **Table Q11**.

Table Q11. Summary of the Effect of Food on Maraviroc Pharmacokinetics

Study	Maraviroc Dose	Formulation	Timing of Food	Change of Cmax with food	Change of AUC_{inf} with food
1001	100 mg	Solution	With food	↓88%	↓63%
1004	100 mg	Research Tablet	1h before food	↑3%	↓20%
1004	100 mg	Research Tablet	With food	↓68%	↓52%
1004	100 mg	Research Tablet	1h after food	↓70%	↓49%
1004	100 mg	Research Tablet	2h after food	↓67%	↓42%
1004	100 mg	Research Tablet	4h after food	↓13%	↓21%
1043	300 mg	Commercial Tablet	With food	↓33%	↓33%
1003	600 mg	Research Tablet (4 x 150 tablets)	With food	↓36%	↓33%

Study 1043 showed that food reduced the exposure of maraviroc 300 mg by 33%. The food effect of maraviroc was also assessed in a 10-day Phase 2a study, 1015, to determine whether these effects translated into an effect on antiviral activity. The results of this study showed that although food reduced the Cmax and AUC of maraviroc by approximately 60% and 50% at 150 mg BID, respectively, there was little effect of food on the short-term antiviral activity (change from baseline in viral load log10 copies/mL) of maraviroc, with a -0.103 (90% CI -0.390, 0.185) difference between maraviroc 150 mg fasted and fed treatment groups on Day 11. Consequently, there were no food restrictions in Phase 3 studies.

In Phase 3 studies, almost 50% of subjects on 150mg BID took their dose within the food time window (food taken within 4 hours prior and 1 hour post last dose record) in 76 to 100% of their recorded occasions. For 300 mg BID group, approximately 57% of the subjects took their dose within the food time window in more than 50% of their recorded occasions. For BID patients in studies A4001027 and A4001028, the efficacy data (success endpoints at week 24 with viral load <50 and <400 copies/mL) were combined with the PK fed quartiles to test for any changes in efficacy with fed status. The success percentages show that there are no differences between the quartiles, so fed status does not appear to have an effect on efficacy at 24 weeks.

2.5.4 If different-strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Two strengths of maraviroc will be marketed: 300 mg and 150 mg tablets. Since these two strengths are totally proportional and use the same manufacture process, no bioequivalence study is required (see CMC review).

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What bioanalytical methods are used to assess concentrations?

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 Bioanalytical Group. 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 [redacted] mass spectrometric detection (MS/MS) assays by the analytical laboratories [redacted]. The assay methods are acceptable. See individual study review for details.

2.6.2 Which metabolites have been selected for analysis and why?

Maraviroc alone was selected for analysis. It was not necessary to measure concentrations of maraviroc metabolites, except for in the mass balance study, since in vitro data indicate that the principal metabolites did not have any pharmacological activities predicted to be biologically relevant.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Because protein binding of maraviroc (75.5%) is independent of concentration, total maraviroc concentrations were measured in the clinical pharmacology studies.

3 Page(s) Withheld

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Withheld Track Number: Clin Pharm/Bio-_____

4.2 Individual Study Review

4.2.1 Biopharmaceutic

A Study to Investigate the Pharmacokinetics, Safety and Toleration of Escalating Intravenous Doses of UK-427,857, and to Determine the Absolute Bioavailability of UK-427,857 after Oral Administration (Study A4001009)

Objectives: To investigate the safety and toleration of intravenous (*iv*) UK-427,857 and to determine the absolute bioavailability of a 100mg oral dose.

Study design: This study comprised two cohorts. Cohort 1 involved a double-blind (third party open), four-way crossover study, where eight subjects received escalating *iv* doses of UK-427,857 (3, 10 and 30mg) with placebo insertion. Cohort 2 involved an open, two-way crossover study where 12 subjects received 30mg UK-427,857 by *iv* infusion and 100mg UK-427,857 orally (under fasted conditions) in random order.

Formulations: UK-427,857 was supplied as solution in 100ml vials (2.5mg/ml), (formulation identification [FID] number S01237AB, Lot number 03-000901) and matching placebo, and as a 100mg tablet (FID number S01165AA, Lot number 8625-172).

Pharmacokinetic Evaluation: Blood samples (5ml) were collected at the following times: 0 (baseline pre-dose) and at 0.25 (*iv* dose only), 0.5, 0.75 (*iv* dose only), 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36 and 48 hours post-dose.

Urine samples were collected pre-dose and 0-6, 6-12 and 12-24 hours post-dose.

Analytical methods: Plasma and urine concentrations of maraviroc (UK-427,857) and urine concentrations of its major metabolite UK-408027 were determined by validated LC/MS/MS methods. All samples were analyzed within the demonstrated matrix and storage stability period. As shown in the following table, the analytical methods are acceptable.

Analytical methods for maraviroc

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
maraviroc (plasma)	0.5 – 200 (R^2 >0.98)	≤5.8	-5.6 to 8.0	• Stable at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for 3 freeze/thaw cycles at -20°C.
maraviroc (urine)	5 – 1000 (R^2 >0.99)	≤5.2	-7.3 to 10.7	• Stable at 37°C for 9 days • Stable at -20°C for 3 months, • Stable for 5 freeze/thaw cycles at -20°C.
UK-408027 (urine)	5 – 1000 (R^2 >0.99)	≤13.2	-2.5 to 5.0	N/A

Pharmacokinetic Results: The unadjusted mean plasma and urine pharmacokinetic parameter values for each *iv* dose in Cohort 1 are presented in the table below:

Parameter	UK-427,857 (Cohort 1)		
	3mg *iv* (N=8)	10mg *iv* (N=8)	30mg *iv* (N=8)
AUC_t (ng.h/ml)[a]	57.6	201	670
AUC (ng.h/ml)[a]	NC	NC	687
C_{max} (ng/ml)[a]	36.9	122	397
T_{max} (h)[b]	0.94	0.94	0.91
$t_{1/2}$ (h)[b]	NC	NC	13.2
CL (L/h)[b]	NC	NC	44.0
CL_r (L/h)[b]	11.19	10.51	10.17
CL_{nr}(L/h)[b]	NC	NC	33.8
V_{ss} (L)[b]	NC	NC	194

[a]geometric means; [b]arithmetic means; NC (not calculated); CL (total clearance); CL_r (renal clearance); CL_{nr} (non-renal clearance); V_{ss} (volume of distribution at steady-state)

The results of the power law analysis of the pharmacokinetic parameters (normalized to dose) in Cohort 1 are presented in the table below:

Parameter	Linearity	Common slope	Dose proportionality	
	p value	p value	estimate	95% CIs
AUC_t (ng.h/ml)[a]	0.500	0.626	1.065	1.012, 1.119
C_{max} (ng/ml)[a]	0.525	0.383	1.031	0.958, 1.105

[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)

The data show that 95% CI for Cmax includes 1, but 95% CI for AUC is greater than 1, indicating some degree of non-proportionality. The p values show that both AUC and Cmax are not significantly different from linearity and a common slope (slope =1). It was estimated that a doubling of the dose would produce a 2.1-fold increase (95% CI: 2.02, 2.17) in AUCt over this dose range. In addition, the non-proportionality could be due to more time points with concentrations below the level of quantitation for lower doses. Therefore, it can be concluded that there is no pharmacokinetically significant non-proportionality.

The plasma pharmacokinetic parameters for the 30mg *iv* and 100mg oral doses in Cohort 2 are summarized in the table below:

Parameter	UK-427,857 (Cohort 2)	
	30mg *iv* (N=12)	100mg oral (N=12)
AUC_t (ng.h/ml)[a]	645	492
AUC (ng.h/ml)[a]	656	506
C_{max} (ng/ml)[a]	374	122
T_{max} (h)[b]	0.98	3.08
$t_{1/2}$ (h)[b]	12.0	12.5
CL (L/h)[b]	46.2	NC
V_{ss} (L)[b]	182	NC

[a]geometric means; [b]arithmetic means; NC (not calculated)

The absolute bioavailabilty of the 100mg oral dose compared to a 100mg *iv* dose (normalized) was 23.1% (95% CIs: 19.2%, 27.8%).

Conclusion:

- The AUC and Cmax increased in a near dose-proportional manner after iv administration of UK-427,857.
- Following the 30mg *iv* dose, 21.9% of the dose was excreted in the urine over 24 hours as unchanged UK-427,857, and 3.6% of the dose was excreted as the metabolite UK-408,027 over the same time period.
- Following the 30mg *iv* dose, approximately 23% of the total clearance (44L/h) was accounted for by renal clearance (10.2L/h) and 77% by non-renal clearance (33.8L/h).
- The absolute bioavailabilty of the 100mg oral dose was 23.1%.

An Open, Randomized, 2 Way Crossover Study to Confirm Bioequivalence of The Maraviroc Research Tablet and the Commercial Tablet (Study A4001040)

Clinical Study Initiation Date: 17 January 2006
Clinical Study Completion Date: 14 April 2006

Objective:
The objectives of this study were 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.

Treatments:

Research formulation: Film coated tablets containing 150mg maraviroc (Lot No. 100407-066).
Commercial Image: Tablets containing 300mg maraviroc (Lot No. 3003035).

Study Design:
The study was an open-label, randomized, single dose, 2 way crossover study in 44 healthy subjects. The study drug medications were administered following an 8 hour overnight fast with 240 mL of water. Subjects received either two maraviroc 150 mg research formulation (2 x 150mg tablets) or one maraviroc 300mg commercial image formulation (1 x 300mg tablet), on Day 1 in each treatment period, according to the randomization schedule. There was a 5 day washout period between the periods.

Study Subjects:
Forty four (44) healthy subjects (33 males and 11 females) between the ages of 21 and 55 years participated in the study. The demography of the subjects is shown in the following table.

Table 3: Study Subjects

	Maraviroc 300mg Tablet Commercial → Research			Maraviroc 300mg Tablet Research → Commercial		
	Male	Female	Total	Male	Female	Total
Number of subjects	18	5	23	15	6	21
Age (years)*	28 (22–40)	31 (21-54)	29 (21-54)	25 (21-39)	26 (24-27)	26 (21-39)
Body Mass Index*	23 (19-30)	21 (20-23)	22 (19-30)	22 (20-24)	22 (19-27)	22 (19-27)

Forty two (42) subjects completed the study.

Sample Collection for Pharmacokinetic Measurements:
Blood samples (5ml) were collected at the following specified times during each Period for the determination of concentrations of maraviroc: pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours post dosing in plasma.

Bioanalytical Analysis:
A liquid chromatography [redacted] mass spectrometry system LC/MS/MS was used in determination of maraviroc concentration. The bioanalytical method performance is shown in the following table.

Assay Methodology Summary	
Method Validation Report	TNJR04-011 (A4009008)
Bioanalytical Method Reference	TNJM04011
Matrix	Human Plasma
Anticoagulant	Lithium Heparin
Type of Extraction	Protein Precipitation
Method of Detection	LC/MS/MS
Sample Aliquot Volume	50.0 µL
Regression, Weighting	linear, 1/conc. squared
Quantification	Peak Area Ratios
Analytical Systems Software	Analyst® Version 1.2 and 1.3.2 (PE Sciex) Watson™ Version 6.4.0.02 (Thermo Electron Corporation)
Calibration Range	0.500 to 500 ng/mL
LLOQ	0.500 ng/mL
ULOQ	500 ng/mL
Dilution Factors Employed	DF=10
Calibration Standard Distribution	Calibration standards were placed at the beginning and end of each bioanalytical batch run.
Quality Control (QC) Distribution	QC samples were distributed evenly throughout each bioanalytical batch run.
Assay Carryover Checks	A carryover blank was placed following the first ULOQ sample in each bioanalytical batch run.

Assay Performance		
QC Samples	Precision (%CV) 4.4	Accuracy (%RE) [redacted]
Batch Performance	No. of Acceptable Runs 12	No. of Failed Runs 3

Pharmacokinetic and Statistical Analysis:
The plasma pharmacokinetic parameters of maraviroc were determined (AUC, Cmax, Tmax, T1/2). The analysis of variance (ANOVA) with model of treatment, period, sequence, subject within sequence was carried out using log transformed pharmacokinetic parameters. The 90% confidence intervals were determined for AUCinf, AUClast and Cmax. The geometric mean and the point estimate (ratio of the commercial to the research formulations), and 90% confidence interval are shown in the following two tables.

Summary of Plasma Pharmacokinetic Parameters:

Parameter (units)	Maraviroc 300mg Commercial Tablet N=43*	Maraviroc 300mg Research Tablet N=42
AUC_{inf} (ng.h/ml)	2720	2760
AUC_{last} (ng.h/ml)	2700	2730
C_{max} (ng/ml)	638	654
T_{max} (h)	2.47	2.45
$t_{½}$ (h)	10.4	10.5

Bioequivalence Evaluation Summary statistics:

Parameter (units)	Adjusted Means		Ratio/Difference Between Adjusted Means[a]	90% Confidence Interval
	Maraviroc 300mg Commercial Tablet N=42*	Maraviroc 300mg Research Tablet N=42*		
AUC_{inf} (ng.h/ml)**	2700	2760	98.0%	(93.9%, 102.2%)
AUC_{last} (ng.h/ml)	2680	2730	98.4%	(94.3%, 102.6%)
C_{max} (ng/ml)	629	654	96.1%	(88.1%, 104.8%)
T_{max} (h)	2.49	2.45	0.04	(-0.33, 0.40)

* Subjects 18 and 19 were excluded from the analysis due to incomplete data.
[a] The ratios (Commercial/Research), expressed as percentages, are presented for AUCinf, AUClast and Cmax and the difference (Commercial-Research) for Tmax. ** N=41 for AUCinf because this parameter could not be calculated for Subject 1 in treatment period 2.

Protocol Deviations:
Subject number 10010518 took multi-vitamin six days prior to first dosing. The 30 minute blood sample was collected 15 minutes late in period one for subject number 10010008. The 2 hour blood sample was collected 15 minutes late in period one for subject number 10010033. These deviations should not affect the results of this study

Adverse Events:
Two subjects discontinued from the study due to an adverse event. Subject 18, a 30 year old female, reported dizziness, of moderate severity, on Day 8 of the study and on Day 1 of the post-treatment. Subject 19, a 25 year old female, reported syncope which was considered to be a serious adverse event due to the subject being hospitalized for neurological examinations. Other adverse events are shown in the following table.

Number of subjects with:	Maraviroc 300mg Commercial Tablet	Maraviroc 300mg Research Tablet
Subjects evaluable for adverse events	44 (44)	42 (42)
Subjects with adverse events	17 (7)	20 (9)
Number of adverse events	20 (9)	25 (12)
Vessel puncture site bruise	8 (0)	10 (0)
Headache	4 (4)	4 (4)
Somnolence	1 (1)	2 (2)
Myalgia	0	2 (2)

Conclusion:
The 300 mg commercial image formulation is bioequivalent to (2X150 mg) research formulation under fasting conditions.

4.2.2 General Pharmacokinetics

Double Blind, Placebo Controlled, Dose Escalating Crossover Study to Investigate the Safety, Toleration and Pharmacokinetics of Single Oral Doses (Solution) of UK-427,857 in Healthy Male Volunteers in the Fed and Fasted State (Study A4001001)

Objectives:

- To determine the pharmacokinetic profile of single oral doses of UK-427,857;
- To assess the effect of food;
- To assess the relationship between UK-427,857 plasma concentration over time and the mean concentration required to inhibit 90% of virus replication *in vitro* (IC90) for primary isolates.

Study design: This was a double-blind study, with the sponsor unblinded, placebo controlled, cross-over, dose escalation study. Two cohorts of 12 subjects each (9 active, 3 placebo) participated. Subjects in cohort A received single doses of 1, 10, 100, and 900 mg in the fasted state and a single 100 mg dose in the fed state (a high fat, high calorie meal). Subjects in cohort B received single oral doses of 3, 30, 300, and 1200 mg in the fasted state.

Formulations: UK-427,857 (Lot No. R1) and placebo (Lot No. 99EXC190) were supplied as powder for oral solution.

Pharmacokinetic Evaluation: Blood samples were collected at 0 (baseline pre-dose) and at 15min, 30min, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours post dose. Subjects who received 900 mg and 1200 mg (fasted) and 100 mg (fed) also had samples taken at 36 and 48 hours post-dose. Urine was collected over the 0-6 and 6-24 hour post-dose intervals.

Analytical methods: Plasma and urine concentrations of maraviroc (UK-427,857) were determined by validated [redacted] extraction and [redacted] chromatography methods. All samples were analyzed within the demonstrated matrix and storage stability period. As shown in the following table, the analytical methods are acceptable.

Analytical methods for maraviroc

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
maraviroc (plasma)	0.25 – 50 (R^2 >0.993)	≤10.9	-7.0 to 2.9	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.
maraviroc (urine)	5 – 1000 (R^2 >0.996)	≤ 6.1	6.5 to 13.4	• Stable at 37°C for 9 days • Stable at -20°C for 3 months, • Stable for 5 freeze/thaw cycles at -20°C.

Plasma PK Results: As shown in the following table, concentrations increased greater than dose-proportionally over the dose range of 1-1200 mg.

Parameter	Cohort A					Cohort B			
	1 mg	10 mg	100 mg	900 mg	100 mg (fed)	3 mg	30 mg	300 mg	1200 mg
AUC∞ (ng*hr/mL)[a]	[c]	17.2[d]	619	7360	222	2.25[d]	117	2310	11400
Cmax (ng/mL)[a]	[c]	2.92	172	1630	19.3	0.58	15.3	621	2810
Tmax (hr)[b]	[c]	2.5	3.1	1.9	2.9	2.1	2.9	1.6	1.8
T1/2 (hr)[b]		n/c	9.9	11.3	14.0	n/c	8.9	10.6	12.5

[a]Geometric mean; [b]arithmetic mean; [c]only 2 subjects with quantifiable data; [d]AUCt presented because AUC∞ could not be calculated; n/c- not calculated.

As shown in the following table, urine PK results indicate that the percentage of UK-427,857 dose excreted unchanged in urine increased from 1.5% following 1 mg to 12% following 1200 mg. Renal clearance did not change with dose- it was 10.3 to 12.9 L/hr following doses of 30 to 1200 mg. The renal data is consistent with finding of non-linear absorption and linear PK after intravenous administration from other studies.

Dose (mg)	Ae_t µg (% of dose)[a]	CL_r (l/hr)[a]
1	15 (1.5%)	n/c
3	47 (1.6%)	n/c
10	232 (2.3%)	n/c
30	916 (3.1%)	10.5
100	6098 (6.1%)	10.3
100 (fed)	2140 (2.1%)	12.6
300	28400 (9.5%)	12.9
900	86966 (9.7%)	11.5
1200	144156 (12.0%)	12.7

[a]Arithmetic mean; n/c =not calculated.

As shown in the following table, coadministration with food decreased AUC by 63% and Cmax by 88%, which is consistent with the results from Study A4001004.

Parameter	UK-427,857		Ratio (%)[c] /difference[d]	90% CIs
	100mg (fasted)	100mg (fed)		
AUC (ng.h/ml)[a]	591	221	Ratio=37.4	30.5,45.9
C_{max} (ng/ml)[a]	158	19.3	Ratio=12.2	8.3,17.9
T_{max} (h)[b]	3.0	2.9	Difference=-0.17	-0.79,0.45
t½ (h)[b]	11.1	13.8	Difference=2.66	0.62,4.70

[a]Adjusted geometric means; [b]adjusted arithmetic means; [c]fed/fasted; [d]fed minus fasted.

At the 100 mg (fasted) dose, UK-427,857 plasma concentrations were almost always above the IC_{90} (4.7 ng/mL) at 12 hours post-dose.

The 900-mg dose was considered the maximum tolerated dose, with postural hypotension at 1200 mg being the dose-limiting event (4/9 subjects). There were 5 subjects with asthenia at 900 mg.

The 12-lead ECG data showed there were no subjects with QTcB ≥450ms or an increase from baseline of ≥60ms. There was, however, evidence of a QTc interval increase after the 1200-mg dose. Using Bazett's and Fridericia's correction for heart rate, mean increases from baseline two hours post-dose were 20.3 and 10.7 ms, respectively. Using a population correction factor, the change from baseline was 7.8 ms.

Conclusion:

- UK-427,857 absorption was rapid and rate of absorption did not alter significantly with dose.
- Concentrations increased greater than dose-proportionally over the dose range of 1-1200 mg.
- About 1.5% to 12% of UK-427,857 was excreted unchanged in the urine up to 24 hours post-dose. CLr was not affected by dose.
- Food decreased AUC by 63% and Cmax by 88% at 100mg.
- Following a 100mg dose, plasma concentrations were maintained above the IC90 for approximately 12 hours.
- UK-427,857 was tolerated up to 900mg. The 1200 mg dose was associated with postural hypotension, headache and increased the pulse rate.
- Although there was some evidence that 1200 mg may increase QTc from baseline, there were no subjects with a QTcB ≥450ms or an increase from baseline of ≥60ms.

A Double Blind, Parallel Group, Placebo Controlled Single Dose and Multiple Escalating Oral Dose Study to Investigate the Safety, Toleration and Pharmacokinetics of UK-427,857 in Healthy Male Volunteers (Study A4001002)

Objectives: To investigate the safety, toleration and pharmacokinetics of multiple oral doses of UK-427,857 in healthy male subjects.

Study design: This is a double blind (3rd party open), parallel group, placebo controlled single dose and multiple escalating oral dose study. The study included the following cohorts:
Cohort 1: 100mg BID UK-427,857 or placebo (ratio 3:1)
Cohort 2: 300mg BID UK-427,857 of placebo (ratio 3:1)
Cohort 3: 600mg QD UK-427,857 or placebo (ratio 3:1)
Cohort 4: 25mg BID UK-427,857 or placebo (ratio 3:1)
Cohort 5: 600mg QD UK-427,857 or placebo (ratio 3:1)
Cohort 6: 3mg BID, 10mg BID UK-427,857 or placebo (ratio 5:5:2)

A single dose was given on day 1, followed by QD or BID dosing starting on day 3, with the final dose given on the morning of day 12. Subjects fasted of all food and drink, except water, from midnight until at least two hours post-dose, except on Days –1, 1, 7 and 12 when they fasted until four hours post-dose.

Evaluations included PK; CCR5 receptor saturation; debrisoquine metabolic ratio in presence and absence of UK-427,857 (CYP2D6 inhibition); and 6β-OH-cortisol/cortisol ratio (CYP3A4 induction).

Formulations: UK-427,857 was supplied as powder (Lot No. R101) for oral solution (for doses of 3, 10, 25, 100, and 300 mg), and as 150mg tablets [formulation identification number (FID) S01167AA, Lot 6825-173] for 600 mg dose. The matching placebo powder for oral solution and a matching placebo tablet (FID S00118AA, Lot 6825-193). Denatonium benzolate (FID No. S00013DA; Lot No. 99EXC190) was supplied as an excipient and debrisoquine HCl was supplied as a 10mg tablet (Lot No. 8978-072).

Pharmacokinetic Evaluation: Blood samples were taken pre-dose on Day 1 and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours post-dose. Cohorts 1 to 5 also had samples taken 18, 24 and 48 hours post-dose (the 48 hour sample was equivalent to the Day 3 pre-dose sample).

During the multiple dose phase, samples were taken pre-dose in the morning on Days 3 to 12 and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours post-dose on Days 7 and 12: Samples were also taken 18, 24, 48 and 72 hours post-dose on Day 12. Cohort 3 stopped dosing on Day 7, so the additional samples were taken post-Day 7 instead of post-Day 12. Cohort 6 did not have a blood sample 72 hours post-dose on 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 10mg debrisoquine, urine was then collected from 0 to 8 hours post-debrisoquine dose. On Day 10 debrisoquine phenotyping was performed as on Day –1 for Cohorts 1, 2, 4 and 5.

On Day -1 and 9, Cohorts 1 to 5 had their urine collected up to 24 hours post-dose for determination of 6β-OH-cortisol/cortisol ratios.

Analytical methods: Plasma and urine concentrations of maraviroc (UK-427,857) were determined by validated [redacted] extraction and [redacted] chromatography methods. Debrisoquine and 4-OH-debrisoquine were measured using a partially validated HPLC method. 6β-OH cortisol and cortisol concentrations were determined by a previously validated LC-MS-MS method. As shown in the following table, the analytical method for maraviroc plasma concentrations is acceptable. The detailed analytical methods for urine maraviroc urine concentrations, debrisoquine, 4-OH-debrisoquine, 6β-OH cortisol, and cortisol are not provided. All samples were analyzed within the demonstrated matrix and storage stability period.

Analytical methods for maraviroc

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
maraviroc (plasma)	0.5 – 200 (R^2 >0.999) for Cohort 1-5 0.1 -10 (R^2 =1) for Cohort 6	≤8.6 ≤12.6	-1.3 to 1.7 -1.3 to 1.6	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.

Pharmacokinetic Results: The table below summarizes the UK-427,857 plasma pharmacokinetic parameter data.

Dose	Day (n)	AUCτ[a] (ng*hr/mL)	AUCt[a] (ng*hr/mL)	AUC∞[a] (ng*hr/mL)	Cmax[a] (ng/mL)	Tmax[b] (hr)	T1/2[b] (hr)
3 mg BID	1 (5)	-	2.66	-	0.67	0.90	-
(Cohort 6)	7 (5)	6.57	6.57	-	1.32	1.10	-
	12 (4)	4.2	5.3	-	0.83	0.56	-
10 mg BID	1 (5)	11.8	11.8	-	2.26	1.80	-
(Cohort 6)	7 (5)	19.0	19.0	-	2.71	1.90	-
	12 (5)	22.2	38.4	44.8	3.33	1.30	15.2
25 mg BID	1 (9)	46.1	55.2	74.6	8.72	3.33	10.8
(Cohort 4)	7 (8)	92.0	92.0	-	18.6	3.13	-
	12 (8)	98.6	147	236	16.2	3.25	13.9
100 mg BID	1 (9)	512	556	579	187	2.17	7.76
(Cohort 1)	7 (9)	636	636	-	159	2.50	-
	12 (9)	686	987	1018	181	2.53	18.5
300 mg BID	1 (9)	2157	2322	2422	538	1.64	8.63
(Cohort 2)	7 (9)	2641	2641	-	674	1.47	-
	12 (9)	3609	4490	4561	854	2.61	16.4
600 mg QD	1 (9)	5877	5877	6074	1317	3.33	7.74
(Cohort 3)	7 (9)	6982	7576	7650	1351	2.61	15.3
	12 (9)	-	-	-	-	-	-
600 mg QD	1 (9)	5545	5545	5712	1322	2.08	7.83
(Cohort 5)	7 (9)	-	-	-	1204	2.83	-
	12 (-)	6440	7069	7177	1361	2.31	17.2

[a]Geometric mean; [b]arithmetic mean; - = not calculated; [c]AUC and T1/2 only calculated for 5 subjects

Mean accumulation ratios on Day 12 were 1.34 (95% CI: 1.07, 1.68) to 2.06 (95% CI: 1.62, 2.62) following BID dosing, with less accumulation at higher doses. Mean accumulation ratio was 1.23 at 600 mg QD. Visual assessment of trough plasma concentrations suggested that steady-state was achieved at all doses by Day 9 (after 7 days of multiple dosing).

The T1/2 assessment following a single dose (day 1) was compromised by the sampling schedule. Thus, it is not possible to determine whether PK is time independent.

Less than 15% of the dose was excreted as unchanged UK-427,857 in the urine over 24 hours (increased with increased dose except cohort 5). CL_R is about 11.3 L/h for all the doses, except for Cohort 5, where CL_R is about 9.5 l/h. The data are consistent with that obtained from Study A4001001.

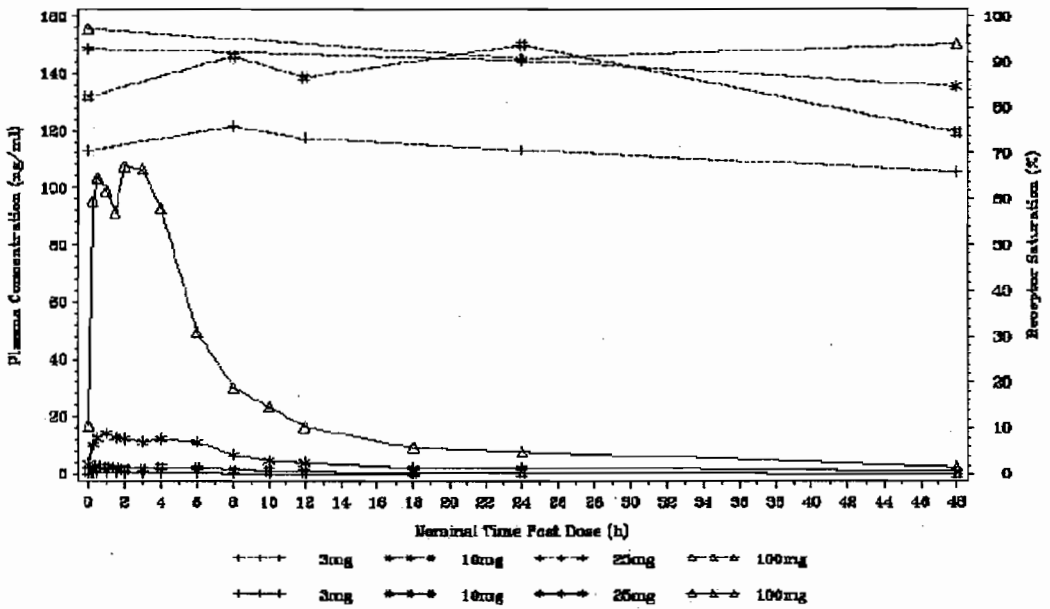
UK-427,857 Dose	Day (n)	Ae_t (% of dose excreted)	CL_R (l/h)
25mg BID	1[a] (9)	2.78	11.44
	7[b] (8)	2.15	11.12
	12[a](8)	5.62	11.03
100mg BID	1[a] (9)	6.40	11.26
	7[b] (9)	3.73	11.27
	12[a] (9)	9.14	11.12
300mg BID	1[a] (9)	8.59	11.22
	7[b] (9)	5.45	12.80
	12[a] (9)	13.91	10.33
600mg QD (Cohort 3)	1[a] (9)	11.78	11.96
	7[a] (9)	13.26	11.60
600mg QD (Cohort 5)	1[a] (9)	8.92	9.21
	7[b] (9)	9.57	9.95
	12[a] (9)	10.31	9.55

Debrisoquine metabolic ratio (MR) data indicated no CYP2D6 inhibition at doses up to and including 300 mg BID. At 600 mg QD, there was 230% increase in debrisoquine

MR on treatment compared to baseline, as shown in the following table. 6β-OH-cortisol/cortisol ratio data showed no apparent difference on or off treatment, suggesting there is no CYP3A4 induction at any dose evaluated. This result is consistent with no effect of maraviroc on midazolam (Study A4001012).

Treatment group	Debrisoquine MR	
	Baseline	On-treatment
25mg BID	0.86	0.72
100mg BID	0.63	0.65
300mg BID	1.52	1.13
600mg QD (Cohort 3)	-	-
600mg QD (Cohort 5)	1.23	4.11
Placebo	0.96	0.85

The CCR5 receptor saturation increased with dose. The figure below shows the mean UK-427,857 plasma concentration and receptor saturation on Day 12 (The four line on the top are for receptor saturation). Due to the range of data collected, it was not possible to determine a relationship between receptor occupancy and plasma UK-427,857 concentration.



Dosing was terminated for Cohort 3 (600 mg QD) because 3 subjects had severe symptomatic postural hypotension four hours post-dose on day 7 (2 on UK-427,857, 1 on placebo). The dose was repeated in Cohort 5, with 1 episode of mild transient postural hypotension. There were dose related increases in the mean maximum decreases from baseline for standing systolic BP at 300 mg BID and 600 mg QD and for standing diastolic BP at 600 mg QD.

There was no obvious clinically relevant dose-related or concentration-related effect on the QTc interval over the dose range studied.

There were 8 subjects (all on UK-427,857) with transaminase levels above the ULN,

which tended to increase through the last day of treatment and then decrease. There were apparent dose-related increases in total cholesterol and LDL-cholesterol.

Conclusion:

- UK-427,857 was rapidly absorbed after single and multiple dosing with Tmax occurring between 0.5 and 4 hours.
- Mean accumulation ratios on Day 12 were 1.34 (95% CI: 1.07, 1.68) to 2.06 (95% CI: 1.62, 2.62) following BID dosing, with less accumulation at higher doses. Mean accumulation ratio was 1.23 at 600 mg QD.
- Steady state was achieved after seven days of multiple dosing.
- Less than 15% of the dose was excreted in the urine as parent drug over 24 hours. Renal clearance was consistent across the dose range studied.
- UK-427,857 showed weak inhibition of CYP2D6 at a dose of 600mg QD, but no inhibition of CYP2D6 at a dose of 300 mg or less.
- UK-427,857 showed no evidence of CYP3A4 induction at any dose studied.
- At doses of UK-427,857 up to 300mg BID, there were few adverse effects. However, at 600mg QD, severe symptomatic postural hypotension was experienced in 2/9 subjects on 600mg QD and 1/3 subjects on placebo in Cohort 3.
- Minor effects on blood pressure and pulse rate occurred, mainly after 600mg QD. These included dose related increases in the mean maximum decrease from baseline for standing diastolic and systolic blood pressure, an increase in the maximum change from baseline for standing pulse rate, a mean postural decrease in diastolic and systolic blood pressure and an increase in mean postural change in pulse rate compared to placebo.

An Open, Randomized, 5-Way Crossover Study in Healthy Male Volunteers to Investigate the PK of UK-427,857 Single Oral Tablet Doses of 50 mg, 100 mg, and 600 mg (Fed/Fasted) and a Single Oral Solution Dose of 100 mg (Study A4001003)

Objectives: to investigate the pharmacokinetics of single oral tablet doses of UK-427,857 50, 100 and 600mg, the effect of food on a single 600mg tablet dose, the relative oral bioavailability of the 100mg tablet vs 100mg oral solution doses and the safety and tolerability of single oral 50, 100 and 600mg doses.

Study design: This was an open, randomized, five-way crossover study. Fifteen healthy male subjects received all 5 treatments, with a washout period of at least 5 days between periods. For the four fasted periods, subjects fasted, except for water, from 10:00 pm the evening before each dose until at least four hours post-dose. For the fed period, subjects ate a high fat breakfast in twenty minutes or less, and received the study drug within five minutes after completing the meal. The breakfast was comprised of ~1000 kcal, ~50% derived from fat.

Formulations: UK-427,857 was supplied as 50mg (formulation identification (FID) No. S01163AA; Lot No. 8625-171), 100mg (FID No S01165AA; Lot No. 8625-172) and 150mg (FID No. S01167AA; Lot No. 8625-173) tablets and as a bulk powder for oral solution.

Pharmacokinetic Evaluation: Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours post-dose.

Analytical methods: Plasma concentrations of maraviroc (UK-427,857) were determined by a validated LC/MS/MS method. All samples were analyzed within the demonstrated matrix and storage stability period. As shown in the following table, the analytical method is acceptable.

Analytical methods for maraviroc

Analyte	**Standard Curve Range (ng/mL)**	**Between Run Precision (%CV)**	**Between Run Bias (% Dev.)**	**Validation and sample for stability and conditions**
maraviroc (plasma)	0.5 – 200 (R^2 >0.98)	≤11.7	-6.5 to 10.4	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.

Pharmacokinetic Results: The table below shows the unadjusted mean pharmacokinetic parameter values for each treatment.

Parameter	50 mg tablet (fasted)	100 mg tablet (fasted)	600 mg tablet (fasted)	100 mg solution (fasted)	600 mg tablet (fed)
AUCt (ng*hr/mL)[a]	209	555	5636	638	3715
AUC∞ (ng*hr/mL)[a]	227	576	5703	654	3805
Cmax (ng/mL)[a]	55.0	154	1221	170	783
Tmax (hr)[b]	3.00	2.33	3.30	2.77	3.07
T1/2 (hr)[b]	14.4	13.3	11.5	12.6	13.6
Kel (1/hr)[c]	0.048	0.052	0.060	0.055	0.050

[a]Geometric mean; [b]arithmetic mean; [c]harmonic mean

The relative bioavailability of the tablet compared to the solution, as assessed by AUC ratio, was 88% (90% CI: 74 to 105%). The Cmax ratio was 90% (90% CI: 69 to 118%). Tmax was similar for both formulations.

Mean exposure at 600 mg was lower when administered following food compared to when administered fasting. The fed/fasted percent ratios were 67% (90% CI: 56 to 80%) and 64% (90% CI: 49 to 84%) for AUC and Cmax, respectively. Administration with food did not alter Tmax. Variability was higher for the fed treatment- %CV for AUC was 26.4% for the fasted treatment and 38.5% for the fed treatment. AUC was lower for 13/15 subjects in the fed state. AUC was at least 30% lower in the fed state for 7/15 subjects.

There was a greater than dose proportional increase in AUC and Cmax, following tablet doses of 50 to 600 mg.

All adverse events were mild or moderate in severity. Asthenia, headache and dyspepsia were the only treatment related adverse events that were reported by more

than one subject in any treatment group.

Conclusion:

- The relative bioavailability of the tablet compared to the solution in the fasted state was 88% (90% CI; 74,105%).
- Food reduced the exposure to the 600mg tablet by approximately 33% (90% CI; 20, 44%) and reduced Cmax by 36% (90% CI; 16, 51%).
- There were no clinically relevant differences in Tmax or t1/2 with formulation or food.
- There was a greater than dose proportional increase in AUC and Cmax, following tablet doses of 50 to 600 mg.

An Open Study to Investigate the Absorption, Metabolism and Excretion of [14C]-UK-427,857 (Study A4001010)

Objectives:

- To quantify drug related radioactivity in whole blood and plasma and cumulative amount of radioactivity excreted in urine and feces.
- To quantify plasma UK-427,857 concentrations and any metabolites where possible.
- To characterize fecal and urinary radioactivity and identify metabolites of UK-427,857 where possible.

Population: 3 healthy males aged 45 to 65 years with a weight between 60 and 100kg with a Quetelet index (Body Mass Index, BMI) between 18 and 28.

Study design: This was a single center, single dose, open study. Oral solution of 14C UK-427,857 (300 mg) was administered to healthy subjects. Subjects fasted from 22:00 on the evening before dosing until four hours post-dose on Day 1 when they had a standard lunch.

Formulations: UK-427,857 was supplied as a 300mg powder for oral solution [Formulation identification (FID) number S01310AA; Lot No 10082-006] in 125ml biotainers, containing 14C UK-427,857 equivalent to a maximum radioactive dose of 48µCi. Each dose was prepared by adding 10ml of 0.01M hydrochloric acid and 90ml water to the 300mg powder, to produce a 100ml solution of 3mg/ml 14C UK-427,857.

Pharmacokinetic Evaluation: Blood samples for pharmacokinetic analysis were collected at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 96 and 120h post-dose.

Urine samples were collected pre-dose and during the following intervals; 0-6, 6-12, 12-24, 24-36, 36-48, 48-72, 72-96 and 96-120 hours post-dose.

Feces were collected pre-dose and for at least 120 hours post-dose on Day 1 or until

[redacted] of the administered reactivity had been recovered or the daily excretion was <1%.

Analytical methods: Maraviroc was analyzed in plasma by LC/MS/MS. Metabolic profiling of maraviroc in plasma, urine, and feces was also performed by LC/MS/MS. Relative quantitation of the components of mixed regions was achieved by on-line LC-MS resolution, either collecting fractions for off-line counting (for faecal regions) or using MRM quantitation (for urine). Total radioactivity in plasma, blood, urine, and feces was performed by liquid scintillation counting. All samples were analyzed within the demonstrated matrix and storage stability period. As shown in Table 1, the analytical methods for maraviroc plasma samples, and UK-463,977 plasma and urine samples are acceptable.

Table 1: Analytical method for maraviroc

Analyte	Standard Curve Range (µg/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
Maraviroc (plasma)	0.5 – 200 (R^2 > 0.98)	≤5.4 %	-6.7% to 3.0%	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.
UK-463,977 (plasma)	0.1 – 5.0 (R^2 > 0.998)	≤11.3 %	-1.5% to 5.0%	Only 2 concentrations, 0.2 and 5.0 ng/mL, were studied. UK-463,977 was stable after 3 freeze-thaw cycles, 24 hrs at Rm temp, 4°C, and -20°C for 5 ng/mL but not for 0.2 ng/mL. For nominal concentration of 0.2 ng/mL, the concentration after storage was increased by 20% to 33%. The difference was not expected to have a significant effect on the study results.
UK-463,977 (urine)	10-1000 (R^2 > 0.999)	≤4.2%	4.5% to 14%	Nominal concentrations of 10 and 1000 ng/mL were studied. UK-463,977 was stable after 3 freeze-thaw cycles, 24 hrs at Rm temp, 4°C, and -20°C

Pharmacokinetic Results:

Radioactivity in Plasma and Whole Blood

The maximum observed UK-427,857 plasma and whole blood concentrations of radioactivity occurred within a mean of 1.5 hours (range 1-2 hours) of dosing. The following table summarizes the total radioactivity for pharmacokinetic parameters in plasma and blood. There was a higher amount of radioactivity in plasma than in blood. The blood/plasma ratio was 0.624 for AUC_t and 0.612 for Cmax.

Parameter	Medium	UK-427,857 300mg	Blood/Plasma Ratio
AUC_t (ng equiv.h/g)[a]	Plasma	4497	-
	Blood	2251	0.624[c]
C_{max} (ng equiv/g)[a]	Plasma	800	-
	Blood	489	0.612
T_{max} (h)[b]	Plasma	1.33	-
	Blood	1.33	-

[a]geometric mean; [b]arithmetic mean; [c]AUC_t ratio determined using time- matched AUC_t values.

UK-427,857 Pharmacokinetics

The pharmacokinetic results show that a single 300mg UK-427,857 dose was rapidly absorbed with a mean Tmax of approximately one hour. There was low inter-individual variation in these results. The following table shows the mean values for the pharmacokinetic parameters derived from the plasma UK-427,857 concentration data.

Parameter	UK-427,857 300mg
AUC_t (ng.h/ml)[a]	2055
AUC (ng.h/ml)[a]	2086
C_{max} (ng/ml)[a]	496
T_{max} (h)[b]	0.83
$t_{1/2}$ (h)[b]	23.0

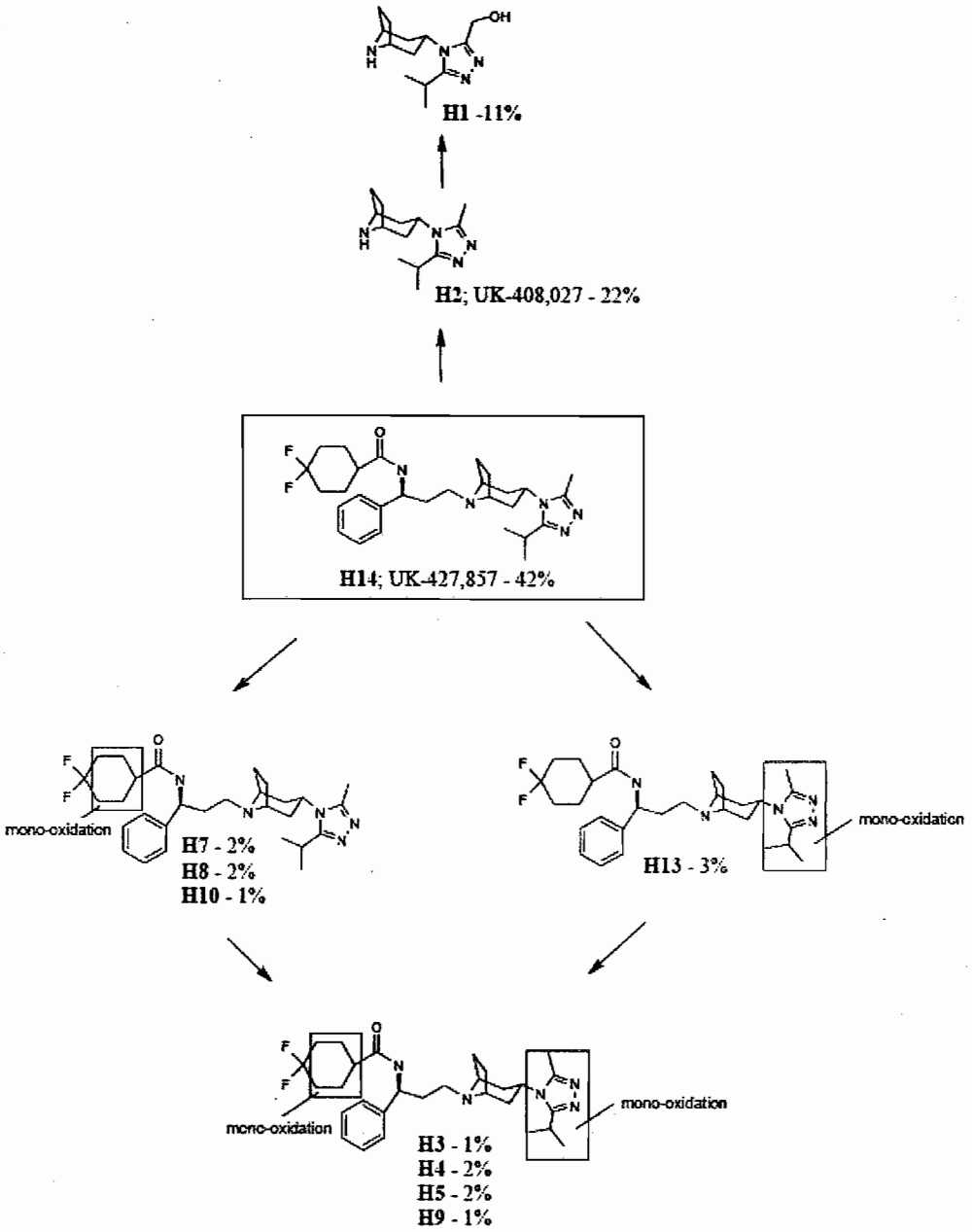
[a]geometric mean; [b]arithmetic mean

UK-427,857 accounted for approximately 40% of the total plasma radioactivity. The plasma UK-427,857 concentration/ total plasma radioactivity ratio for AUCt was 0.402. The mean ratio for Cmax was 0.622.

Metabolites in Plasma

As shown in the following figure, unchanged UK-427,857 was the major circulating component in plasma, accounting for a mean of 42% of the circulating radioactivity. The secondary amine metabolite resulting from N-dealkylation (UK-408,027) and an analogue of the amine involving oxidation of the methyl group in the triazole ring were also identified in human plasma, accounting for 22 and 11% of the circulating radioactivity, respectively.

DRUG-RELATED COMPONENTS IDENTIFIED IN HUMAN PLASMA FOLLOWING SINGLE ORAL (300mg) ADMINISTRATION OF [14C]-UK-427,857, WITH %AUC DATA FOR COMPOSITE (0-18H) SAMPLES



Radioactivity in Urine and Feces

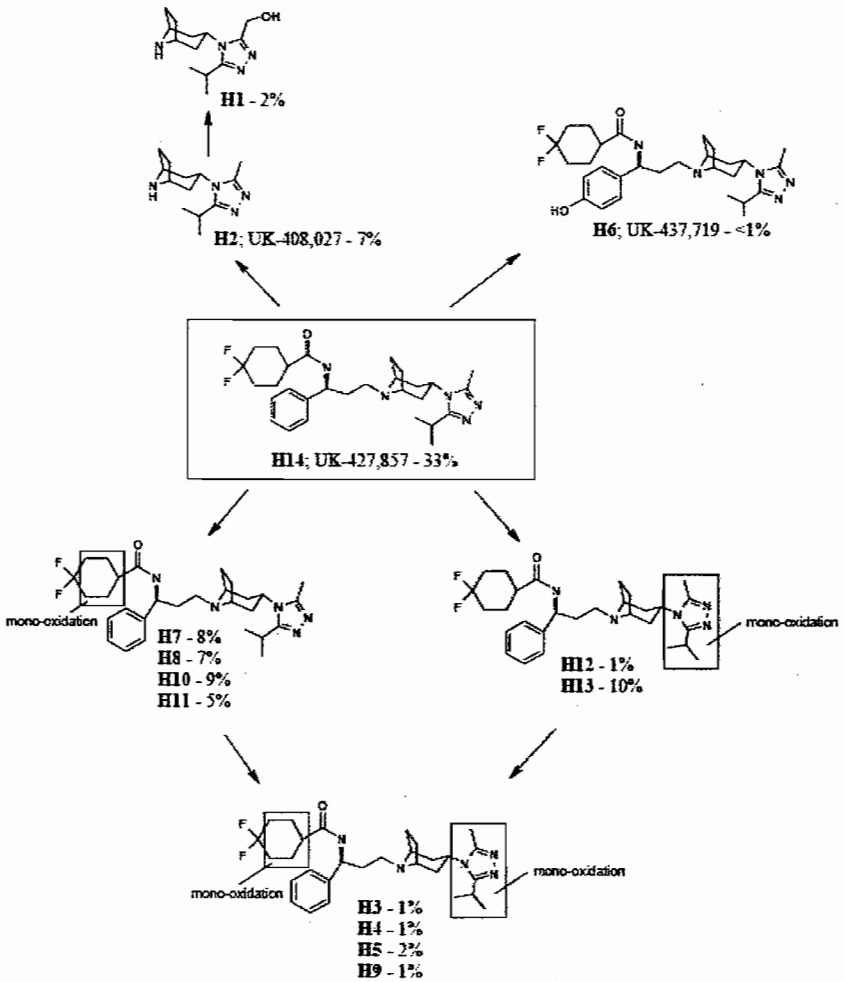
The mean amount of radioactivity excreted in the urine was 19.6% with a coefficient of variation of 12.9% and the majority was excreted in the first 36 hours. The mean amount of radioactivity excreted in the feces was 76.4% with a coefficient of variation of 3.4% and the majority was excreted in the first 96 hours. There was low inter-individual

variation. The mean total recovery of dosed radioactivity was 96% over the sample collection period of 168 hours.

Metabolites in Urine and Feces

HPLC profiling of human urine and extracted fecal homogenates showed similar and extensive metabolism in all subjects. As shown in the following figure, 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 UK-427,857, accounting for a mean of 33% of the dose, four metabolites involving mono-oxidation in the diflurocyclohexane ring, each accounting for between 6 and 9%, a metabolite resulting from oxidation in the triazole group (10%) and a secondary amine, UK-408,027 which resulted from N-dealkylation adjacent to the tropane moiety (7%). The N-dealkylation mechanism also yielded an unlabelled carboxylic acid metabolite (UK-463,977) which was quantified in human urine. UK-463,977 was shown to be present in urine at levels equivalent to a mean of 3% of the dose.

PROPOSED METABOLIC PATHWAYS IN HUMAN EXCRETA FOLLOWING SINGLE ORAL (300mg) ADMINISTRATION OF [14C]-UK-427,857, WITH % TOTAL EXCRETED DOSE (MEAN OF THREE SUBJECTS)



Conclusion:

- The maximum observed UK-427,857 plasma and whole blood concentrations of radioactivity occurred within a mean of 1.5 hours of dosing. There was a higher amount of radioactivity in plasma than in blood.
- The pharmacokinetic results show that a single 300mg UK-427,857 dose was rapidly absorbed with low inter-individual variation.
- There was [redacted] of the dose recovered in this study. Most UK-427,857 was excreted via the feces (76.4%) with 19.6% excreted via the urine.
- Unchanged UK-427,857 was the major circulating component in plasma, accounting for a mean of 42% of the circulating radioactivity. The secondary amine metabolite resulting from N-dealkylation (UK-408,027) and an analogue of the amine involving oxidation of the methyl group in the triazole ring were also identified in human plasma, accounting for 22 and 11% of the circulating radioactivity, respectively.
- UK-427,857 was the major component present in urine (mean: 8% of dose) and feces (mean: 26% of dose).
- Metabolite analysis of urine and feces showed that UK-427,857 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 UK-427,857, four metabolites involving mono-oxidation in the diflurocyclohexane ring, a metabolite which resulted from oxidation in the triazole group and a secondary amine UK-408,027 and an unlabelled carboxylic acid UK-463,977, both produced from N-dealkylation adjacent to the tropane moiety.

A Double-Blind, 3rd Party Open, Placebo-Controlled, Parallel Group Study to Investigate the Safety, Toleration and Pharmacokinetics of Multiple Escalating Oral Doses of Uk-427,857 in Healthy Subjects (Study A4001019)

Objectives: to investigate the safety, toleration and pharmacokinetics of multiple oral doses of UK-427,857 and the effect of dose escalation on toleration.

Study design: This was a randomized, double blind, 3rd party open, placebo-controlled, parallel group study. Total of 36 subjects were randomized into one of the following three cohorts.

Cohort	Day 1 to 7	Days 8 to 14
1	UK-427,857 300mg BID or placebo	UK-427,857 600mg BID or placebo
2	UK-427,857 600mg BID or placebo	UK-427,857 900mg BID or placebo
3	UK-427,857 900mg QD or placebo	UK-427,857 1200mg QD or placebo

BID=twice daily; QD=once daily. Within each cohort subjects were assigned to receive either UK-427,857 at the appropriate doses or placebo a 3:1 ratio.

In each cohort, subjects received UK-427,857 or placebo at a lower dose level for seven days (Days 1 to 7), with an escalation to a higher dose level for Days 8 to 14 inclusive (dependent on safety and toleration). Subjects randomized to placebo remained on placebo throughout the study. There were at least seven days between consecutive cohorts, to allow for a review of safety and toleration data.

Formulations: UK-427,857 was supplied as 100mg tablets [formulation identification (FID) No. S01165AA; Lot No. 8625-171] and placebo tablets (FID No. S001173AA; Lot No. 9255-004).

Pharmacokinetic Evaluation: Blood samples for UK-427,857 and UK-408,027 were collected pre-morning dose on Days 1 to 14 and also at 0.5, 1, 2, 4, 6, 8 and 12 hours post-morning dose on Days 1, 7 and 14. Urine samples for UK-427,857 were collected pre-dose and from 0 to 12 hours post-morning dose on Day 1 and from 0 to 12 hours post-morning dose on Days 7 and 14.

Analytical methods: UK-427,857 and UK-408,027 concentrations were measured in plasma using [redacted] extraction [redacted] and liquid chromatography-mass spectrometry-mass spectrometry. UK-427,857 was measured in urine using [redacted] and liquid chromatography-mass spectrometry-mass spectrometry. All samples were analyzed within the demonstrated matrix and storage stability period. As shown in the following table, the analytical methods are acceptable.

Analytical methods for maraviroc

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
maraviroc (plasma)	0.5 – 200 (R^2 >0.99)	≤7.8	-1.6 to 4.5	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.
UK-408,027 (plasma)	0.5 – 200 (R^2 >0.98)	≤9.1	-7.2 to 6.7	• Stable at room temperature and 4°C for up to 48 hours, • Stable after 5 freeze-thaw cycles and • **Stable at –20°C for 7 weeks.**
maraviroc (urine)	05 – 1000 (R^2 >0.99)	≤7.8	-1.3 to 11.3	• Stable at 37°C for 9 days • Stable at -20°C for 3 months, • Stable for 5 freeze/thaw cycles at -20°C.

Pharmacokinetic Results: The following table summarizes the plasma pharmacokinetic parameter data.

UK-427,857 Dose	Day	AUC_{12}[a] (ng.h/ml)	C_{max}[a] (ng/ml)	T_{max}[b] (h)
300mg BID →	1	1900	770	1.83
	7	2100	807	2.00
600mg BID	14	4980	1810	2.00
600mg BID →	1	3230	1100	2.00
	7	3870	1180	2.25
900mg BID	14	5880	1630	2.25
900mg QD →	1	5990	1990	1.72
	7	6550	1960	2.00
1200mg QD	14	10400	2990	1.83

[a]unadjusted geometric mean, [b]unadjusted arithmetic mean

The following table summarizes the statistical analysis of the pharmacokinetic parameters with the 95% CIs.

UK-427,857 Dose	Comparison	AUC_{12} as ratio % (95% CIs)	C_{max} as ratio % (95% CIs)	T_{max} as h difference (95% CIs)
300mg BID	Day 7/Day 1	121 (106,140)	114 (93.2, 140)	0.19 (-0.26, 0.63)
→ 600mg BID	Day 14/ Day 7	237 (210, 267)	224 (181, 277)	0.00 (-0.22, 0.22)
600mg BID	Day 7/Day 1	120 (104, 137)	107 (87.5, 132)	0.25 (-0.19, 0.69)
→ 900mg BID	Day 14/ Day 7	152 (135, 172)	138 (112, 171)	0.00 (-0.22, 0.22)
900mg QD	Day 7/Day 1	109 (95.7, 125)	98.3 (81.1, 119)	0.28 (-0.14, 0.70)
→ 1200mg QD	Day 14/ Day 7	159 (142, 178)	152 (125, 186)	-0.17 (-0.38, 0.04)

The mean accumulation ratio was 1.21 and 1.20 after 300 and 600mg BID for seven days, respectively and Cmax increased by 14 and 7%, respectively. The accumulation ratio was 1.09 after 900mg QD for seven days with no Cmax increase.

In Cohort 1, a doubling in dose from 300 to 600mg BID increased AUC and Cmax by 2.4 and 2.2 fold, respectively. In Cohort 2, a 1.5 fold dose increase from 600 to 900mg BID increased AUC and Cmax by 1.5 and 1.4 fold, respectively. In Cohort 3, a 1.3 fold increase in dose from 900 to 1200mg QD increased AUC and Cmax by 1.6 and 1.5 fold, respectively. The data from trough UK-427,857 plasma samples show that steady state was reached by Day 7.

Total urinary recovery of unchanged drug (Aet), Aet (%) of the administered dose and renal clearance (CLR) were similar across all doses and regimens throughout the study. The following table presents the unadjusted arithmetic mean Aet, Aet (%) and CLR on Days 1, 7 and 14 for each UK-427,857 dose.

UK-427,857 Dose	Day	Ae_t (µg)	Ae_t (%)	CL_R (L/h)
300mg BID	1	18200	6.07	9.70
	7	18600	6.21	9.12
→ 600mg BID	14	47700	7.95	9.44
600mg BID	1	40000	6.67	12.6
	7	38400	6.39	12.6
→ 900mg BID	14	66500	7.39	11.8
900mg QD	1	64800	7.20	10.8
	7	80100	8.89	12.2
→ 1200mg QD	14	82100	6.83	7.58

Steady state for the metabolite UK-408,027 was reached by Day 7. Steady state exposure (AUC12) of UK-408,027 increases corresponded with dose increases. UK-408,027 accumulation was approximately 50 and 39% for BID dosing and 11% for QD dosing.

Conclusion:

- In all treatment groups, UK-427,857 was rapidly absorbed after single and multiple dosing and steady state was reached by Day 7.
- UK-427,857 accumulation was approximately 20% for BID dosing and 9% for QD dosing.
- The exposure of UK-427,857 increased more than dose-proportionally at dose less than 600 mg BID and toward dose-proportional at higher dose.
- The renal clearance was similar across all doses and regimens throughout the study. Less than 10% of the dose excreted unchanged in urine.

- There were small reductions in standing blood pressure and increases in standing pulse rate at all doses with the largest effects in the 900mg QD → 1200mg QD cohort. There was no significant effect on supine blood pressure but there were small increases in pulse rate at some doses.

4.2.2 Intrinsic Factors

An Open, Two Centre Study, to Compare the Pharmacokinetics of a Single Oral Dose of Maraviroc (UK-427,857) 300mg in Asian and Caucasian Healthy Subjects (Study A4001038)

Objectives: To compare the pharmacokinetics of a single 300mg dose of maraviroc between Asian and Caucasian healthy male subjects.

Study design: This is an open, single dose study in 12 Asian and 12 Caucasian healthy male subjects who received a single 300mg oral dose of maraviroc under fasted conditions.

Formulations: Maraviroc was supplied as a 100mg tablet; formulation identification No. S01165AA; Lot No. 03-001060.

Pharmacokinetic Evaluation: Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16 and 24 hours post-dose on Day 1.

Analytical methods: Plasma and urine concentrations of maraviroc (UK-427,857) were determined by validated LC/MS/MS methods. All samples were analyzed within the demonstrated matrix and storage stability period. As shown in the following table, the analytical methods are acceptable.

Analytical methods for maraviroc

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
maraviroc (plasma)	0.5 – 500 (R^2 >0.993)	≤6.1	-3.3 to 13.1	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.
maraviroc (urine)	5 – 5000 (R^2 >0.999)	N/A*	-6.0 to -1.3	• Stable at 37°C for 9 days • Stable at -20°C for 3 months, • Stable for 5 freeze/thaw cycles at -20°C.

* Insufficient data for calculation

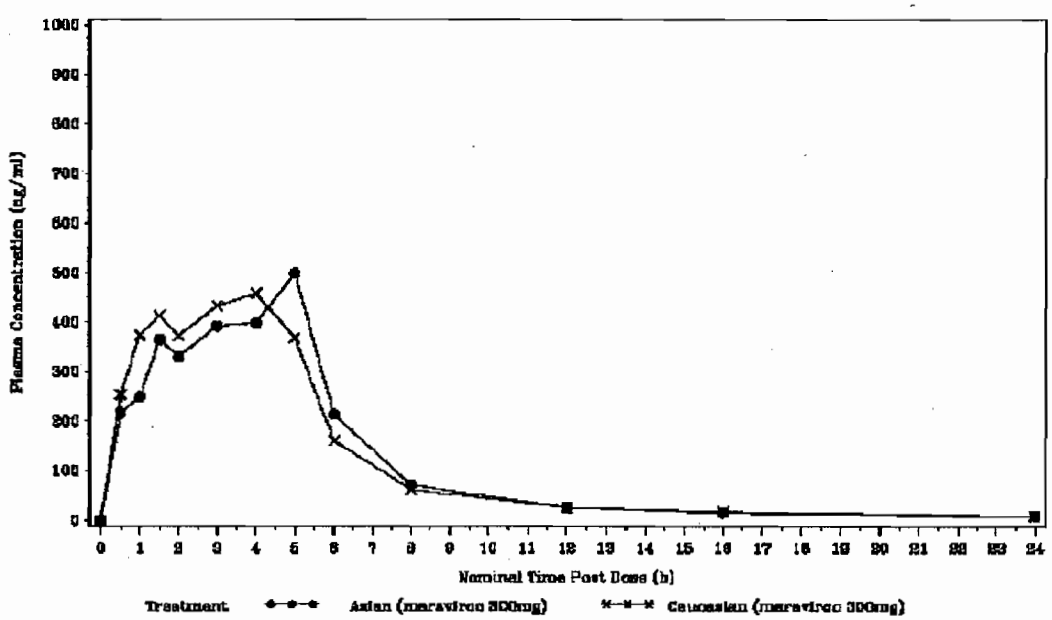
Pharmacokinetic Results: The pharmacokinetics of a single oral dose of 300mg maraviroc is similar in Asians and Caucasians. The mean ratios and 90% CIs were 111% (90.3, 137%) for Cmax, 99.2% (84.5, 116%) for AUC12 and 98.8% (84.0, 116%) for AUC24. Figure S1 plots the mean maraviroc plasma concentration by race.

Table S2. Statistical analysis of the pharmacokinetic parameters between the Asian and Caucasian groups.

Parameter	Group		Ratio%[a]/difference[b]	90% CI
	Asian	Caucasian		
AUC_{12} (ng.h/ml)[c]	2470	2490	99.2	84.5 to 116
AUC_{24} (ng.h/ml)[c]	2640	2680	98.8	84.0 to 116
C_{max} (ng/ml)[c]	741	666	111	90.3 to 137
T_{max} (h)[d]	3.5	3.0	0.5	-0.66 to 1.66

[a]Ratio for AUC_{12}, AUC_{24} and C_{max} (Asian divided by Caucasian); [b]difference for T_{max} (Asian minus Caucasian); [c]adjusted geometric means; [d]adjusted arithmetic means; CI=confidence interval.

Figure S1. The mean maraviroc plasma concentrations for the Asian and Caucasian groups up to 24 hours post-dose.



By examining the individual concentration-time profiles, we found that most of the subjects have two peaks, indicating possible enterohepatic cycling. This phenomenon has been seen in other studies after oral maraviroc administration. We have also seen dual peak in concentration-time profiles in some patients after iv administration (Study A4001009).

Total % urinary recovery of unchanged drug (A_{et}%) for Asian and Caucasian subjects are [redacted], respectively. Renal clearance (CL_R) for Asian and Caucasian subjects are 9.1 L/h and 10.2 L/h, respectively.

Conclusion:

- The pharmacokinetics of a single oral dose of 300mg maraviroc is similar in Asians and Caucasians.
- Enterohepatic cycling may occur after absorption of maraviroc, as observed in both Asian and Caucasian subjects.

4.2.3 Extrinsic Factors

An Open, Randomized, Single Dose, Five Way Incomplete Block Design Crossover Study in Fed and Fasted Healthy Volunteers to Investigate the Effects of Timing of Food Intake on the Pharmacokinetics of a 100 mg Dose of UK-427,857 Tablets (Study A4001004)

Objectives: To investigate the effects of food administration at different times relative to oral dosing on the pharmacokinetics of a single 100mg dose of UK-427,857 in tablet form.

Study design: This is an open, randomized, five way cross-over study in a group of 15 healthy male subjects, using single doses of 100mg tablets of UK-427,857. Each subject was randomized to receive a fasted treatment, and four of the following five fed treatments.

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

Doses were separated by a minimum of 5 days. The meal was a high fat (approximately 50% of total caloric content of the meal), high calorie (approximately 150 protein calories, 250 carbohydrate calories and 500-600 fat calories, totaling approximately 1000 calories) breakfast and was consumed within 20 minutes.

Formulations: UK-427,857 was supplied as 100mg tablets (lot number 8625-172, formulation identification number S01165AA).

Pharmacokinetic Evaluation: Blood samples (5ml) were taken at times: 0 (baseline pre-dose) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours post dose.

Analytical methods: Plasma concentrations of maraviroc (UK-427,857) were determined by a validated LC/MS/MS method. All samples were analyzed within the demonstrated matrix and storage stability period. As shown in the following table, the analytical method is acceptable.

Analytical methods for maraviroc

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
maraviroc (plasma)	0.5 – 200 (R^2 >0.98)	≤5.9	-7.2 to 3.8	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.

Pharmacokinetic Results: The table below presents the statistical analysis for PK parameters of UK-427,857.

Comparison	Ratio % (90% CI)		Difference between means (90% CI)
	AUC	Cmax	Tmax
Dosing 1 hr prior to food vs fasted	79.5 (67.0, 94.3)	98.6 (71.8, 135.5)	-0.99 (-1.96, -0.02)
Dosing with food vs fasted	48.0 (40.7, 56.7)	31.8 (23.1, 43.7)	0.10 (-0.88, 1.07)
Dosing 1 hr post food vs fasted	50.0 (42.4, 59.0)	32.6 (24.0, 44.4)	0.58 (-0.35, 1.52)
Dosing 2 hr post food vs fasted	55.2 (46.5, 65.5)	34.6 (25.2, 47.6)	0.34 (-0.63, 1.31)
Dosing 4 hr post food vs fasted	80.3 (68.1, 94.7)	83.4 (60.7, 114.6)	-0.46 (-1.42, 0.51)

The effect of food on UK-427,857 exposure was greatest when the drug was administered immediately after food, but the effect was similar when UK-427,857 was administered 1 or 2 hours after food. The effect is diminished when UK-427,857 is administered 1 hour before or 4 hours after a meal.

Conclusions:

- The effect of food on Cmax and AUC was greatest when UK-427,857 was administered immediately after food (about 50% reduction in AUC and 67% reduction in Cmax), however the extent of the effect was similar when UK-427,857 was give one and two hours post food intake.
- When administered four hours post food intake, the effect was significantly reduced (20% reduction in AUC and 17% reduction in Cmax) and similar to that seen when UK-427,857 was given one hour prior to food intake.
- There were no clinically relevant effects of food on Tmax or t1/2.

An Open, Randomized, 2 Way Crossover Study to Confirm the Effect of Food on the Pharmacokinetics of Maraviroc (300mg Commercial Tablet) (Study A4001043)

Objectives: To determine the effect of food on the pharmacokinetics of maraviroc (300mg commercial formulation).

Study Design: This was an open-label, randomized, single dose, 2 way crossover study performed in 12 healthy subjects. Subjects were randomized to 1 of the following 2 treatment sequences.

Treatment Sequence	Treatment Period 1	Treatment Period 2
I	300mg commercial tablet fed	300mg commercial tablet fasted
II	300mg commercial tablet fasted	300mg commercial tablet fed

There was a minimum 5 day washout period between fasted and fed doses. For the fed treatment period, a high fat (50% of total calorific value of the meal) and high calorie (approximately 800 to 1000 calories) breakfast was given 30 minutes prior to maraviroc dosing. The meal was composed of approximately 150, 250 and 500 to 600 calories from protein, carbohydrate and fat, respectively.

Formulations: 300 mg maraviroc commercial tablets (formulation identification number D0501962 Lot No. 3003035).

Pharmacokinetic Evaluation: Blood samples (5ml) were taken at times: 0 (baseline pre-dose) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours post dose.

Analytical methods: Plasma concentrations of maraviroc (UK-427,857) were determined by a validated LC/MS/MS method. All samples were analyzed within the demonstrated matrix and storage stability period. As shown in the following table, the analytical method is acceptable.

Analytical methods for maraviroc

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
maraviroc (plasma)	0.5 – 500 (R^2 >0.99)	≤4.0	-9.0 to 2.1	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.

Pharmacokinetic Results: The mean plasma pharmacokinetic parameters following single doses of maraviroc 300mg, as a commercial tablet, are summarized in Table S2. Results of the treatment comparisons (food effect) are summarized in Table S3.

Table S2. Summary of maraviroc plasma pharmacokinetic parameters

Parameter (units)	Maraviroc 300mg Fed N=12	Maraviroc 300mg Fasted N=12
AUC_{inf} (ng.h/ml)	2084	3117
AUC_{last} (ng.h/ml)	2047	3079
C_{max} (ng/ml)	454	674
T_{max} (h)	3.96	3.04
$t_{½}$ (h)	10.3	11.0

Means are geometric for AUC_{inf}, AUC_{last} and C_{max} and arithmetic for T_{max} and $t_{½}$.

Table S3. Summary of treatment comparisons

Parameter (units)	Ratio/Difference Between Adjusted Means[a]	90% Confidence Interval
AUC_{inf} (ng.h/ml)	66.9%	(57.1%, 78.3%)
AUC_{last} (ng.h/ml)	66.5%	(56.5%, 78.2%)
C_{max} (ng/ml)	67.4%	(49.0%, 92.7%)
T_{max} (h)	0.92	(-0.60, 2.43)

[a] The ratios, expressed as percentages, are presented for AUC_{inf}, AUC_{last} and C_{max} and the difference for T_{max}.

The data show that administration of the 300mg commercial tablet with food reduced both AUC and Cmax of maraviroc by approximately 33%. Mean Tmax was prolonged by approximately 1 hour after food. There was no notable difference in t½ following administration with food.

Conclusion: Administration with food reduced the AUC and Cmax following administration of the 300mg maraviroc commercial tablet by approximately 33%. Mean Tmax was prolonged by approximately 1 hour when maraviroc was administered after food.

A Randomized, Double Blind, Placebo Controlled, Two Way Crossover Study to Investigate the Pharmacokinetics, Safety and Toleration of UK-427,857 in Healthy Young Women and to Investigate the Effect of UK-427,857 on the Pharmacokinetics of Oral Contraceptive Steroids (Study A4001005)

BACKGROUND: UK-427,857 is an antagonist of the human chemokine receptor CCR5. The sponsor is developing this drug for the treatment of HIV-1 infection. As with all drugs developed to treat HIV infection, the potential for an interaction with oral contraceptives (OCs) is of interest. The sponsor conducted an in vivo study to evaluate the effect of UK-427,857 on the PK of oral contraceptives. In vitro drug metabolism data indicate little potential for an effect of UK-427,857 on CYP enzymes. In spite of the low potential for UK-427,857 to affect CYP-mediated drug metabolism, there are other potential mechanisms for drugs to alter OC pharmacokinetics.

Study Design: Fifteen women received the following two treatments in a random order:
A: UK-427,857 100 mg BID on days 1-10 and once on day 11; OC QD on days 2-28
B: Placebo BID on days 1-10 and once on day 11; OC QD on days 2-28

UK-427,857 was supplied as a 100 mg tablet. The OC was Microgynon 30 (ethinyloestradiol [EE] 30 µg and levonorgestrel [LN] 150 µg).

An abbreviated UK-427,857 PK profile was determined on day 1. A full UK-427,857 PK profile was determined on day 11. Full PK profiles of EE and LN were determined on day 8 of both treatment periods.

Results: Administration of UK-427,857 did not alter the PK profiles of EE or LN.

Analyte	PK parameter	% ratio and 90% CI for OC + UK vs OC alone
LN	AUC	97.7 (92.0, 104.0)
	Cmax	100 (92.9, 107.9)
EE	AUC	99.6 (94.5, 104.9)
	Cmax	98.4 (91.3, 106)

Conclusion: There is not a concern regarding the use of OCs with UK-427,857. However, the decision regarding the use of OCs in specific studies will need to be made on a case-by-case basis, due to the potential for interactions between OCs and other antiretroviral agents.

A Randomized, Double Blind, Placebo-Controlled, Two-Period Crossover Study to Investigate the Effects Of Steady State UK-427,857 on the Pharmacokinetics of a Single Oral Dose of Midazolam (Study A4001012)

Background: This study is designed to assess the effects of steady state UK-427,857 on the PK of a single dose of midazolam, to determine if UK-427,857 is a CYP3A4 inducer or inhibitor. Midazolam is a CYP3A4 probe substrate for investigating potential drug interactions.

UK-427,857 dose of 300mg bid was chosen because this is the highest anticipated clinical dose. A single dose oral dose of 7.5 mg midazolam was selected to avoid excessive sedation during UK-427,857 treatment.

Objectives: To investigate the effect of the steady state UK-427,857 on the PK of single oral dose of midazolam and to investigate the safety & tolerance of UK-427,857 and midazolam when coadministered.

Study design: This is a randomized, double blind, placebo-controlled, 2-period crossover with a minimum of a seven day washout. Healthy male & female subjects (12), aged 18-45 years were enrolled. Each subject was assigned to one of the following treatment sequences:

Sequence	Period 1	Period 2
I	A	B
II	B	A

Where the treatments to be administered were:

A: UK-427,857 300mg BID for seven days + midazolam 7.5mg on the morning of Day 7

B: Placebo BID for seven days + midazolam 7.5mg on the morning of Day 7

The medications were administered under fasted conditions on Day 7.

PK measurement:

UK-427,857	Midazolam
Trough at pre-dose on days 1, 4, 7	Pre-dose, & at intervals up to 24 hours (0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, & 24 hours) post dose on day 7

Analytical method:

	Midazolam	UK-427,757
Method	LCMS	LCMS
Calibration ranges	0.1-100ng/ml	0.2-200ng/ml

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Results: Midazolam PK parameters are shown below.

Parameter	Mean for UK-427,857 + midazolam	Mean for placebo + midazolam	Ratio %[c] /difference[d]	90% confidence interval
AUC_t (ng.h/ml)[a]	120	102	118	104, 134
AUC (ng.h/ml)[a]	122	104	118	104, 134
C_{max} (ng/ml)[a]	46.9	38.7	121	92.2, 160
T_{max} (h)[b]	1.00	0.79	0.21	-0.72, 1.14
$t_{½}$ (h)[b]	5.34	5.25	0.083	Not calculated

[a] = geometric mean [b] = arithmetic mean
[c] = Ratio for AUC_t, AUC and C_{max}. [d] = Difference for T_{max} and $t_{½}$

Conclusion:

- The UK-427,857 dose (300mg bid) studied in current protocol is acceptable
- Twice daily dosing with UK-427,857 increased midazolam AUC by 18% and Cmax by 21% compared with placebo.
- UK-427,857 is considered to be a sensitive CYP3A4 probe. One should not anticipate bigger CYP3A4 inhibitory effect on other CYP3A4 substrates by UK-427,857. UK-427,857 does not induce CYP3A.

A Double Blind, Third Party Open, Randomized, Placebo Controlled, Two-Period Crossover Study to Investigate the Effects of Steady State UK-427,857 on the Steady State Pharmacokinetics of Combivir™ in Healthy Subjects (Study A4001020)

Objectives: To investigate the effect of steady state UK-427,857 on the steady state pharmacokinetics of Combivir™.

Study Population: 12 healthy male and female subjects aged 18 to 45 years.

Study Design: This was a double-blind, third party open (*ie.* subject and investigator blinded, but sponsor unblinded to treatment with UK-427,857 and placebo), randomized, placebo-controlled, two period crossover study. Each subject attended two treatment periods (each lasting seven days with a minimum washout of seven days between treatment periods). In each treatment period, subjects received Combivir™ and either 300mg UK-427,857 or placebo twice daily (BID) on Days 1 to 6 with the final dose on the morning of Day 7. The medications were administered under fasted conditions on Day 7.

Formulations:

Study Drug	Dosage Form	Dose, Frequency and Duration	Lot Number	FID Number
UK-427,857	100mg tablet	300mg BID for six days, and a final dose on the morning of Day 7	9255-190	S01165AA
Matched placebo for UK-427,857	Tablet	Three tablets BID for six days, and a final dose on the morning of Day 7	9522-004	S01173AA
Combivir™ (150mg 3TC 300mg AZT)	Tablet	One tablet BID for six days, and a final dose on the morning of Day 7	Supplied by study centre	

3TC: lamivudine; AZT: zidovudine.

Pharmacokinetic Evaluation: Two 5ml blood samples, one for lamivudine (3TC) and one for zidovudine (AZT) plasma assay were collected pre-dose on the morning of Days 1, 2, 4 and 6, and pre-dose, 30 minutes, 1, 2, 4, 6, 8, 10 and 12 hours post-dose on Day 7. AUC12, Cmax and Tmax on Day 7 were calculated.

Urine for 3TC and AZT assay was collected pre-dose (immediately before dosing) and up to 12 hours post-dose on Day 7. Aet, Aet (%) and CLr on Day 7 were calculated.

Analytical methods: Plasma and urine samples were assayed for 3TC and AZT using a previously validated method employing [redacted] extraction and liquid chromatography followed by [redacted] mass spectrometric detection (LC-MS-MS). All samples were analyzed within the demonstrated matrix and storage stability period. As shown in the following table, the analytical methods are acceptable.

Analytical methods for lamivudine and zidovudine

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
lamivudine (plasma)	2 – 1000 (R^2 >0.991)	≤6.9	-12.1 to -1.2	NA
lamivudine (urine)	2 – 1000 (R^2 >0.996)	≤3.8	-5.6 to 4.2	NA
zidovudine (plasma)	2 – 1000 (R^2 >0.993)	≤8.0	-5.0 to 0.8	NA
zidovudine (urine)	2 – 1000 (R^2 >0.997)	≤2.9	-4.1 to -0.8	NA

Pharmacokinetic Results: UK-427,857 had a small, non-clinically significant effect on the plasma PK of 3TC and AZT, when administered as 300mg BID for seven days with Combivir™, as shown in the following table.

The Effect of UK-427,857 on the PK of Lamivudine + Zidovudine

	AUC_{12}[a] (ng.h/ml) Ratio of Means (%) [90% CI]	C_{max}[a] (ng/ml) Ratio of Means (%) [90% CI]	T_{max}[b] (h) Difference Between Means [90% CI]
Lamivudine (3TC)	114 [98.4 - 132.3]	116 [87.5 - 154.2]	0.1 [-0.7 - 0.8]
Zidovudine (AZT)	98.2 [78.9 – 122.2]	91.8 [67.7 – 124.4]	0.0 [-0.3 – 0.3]

[a] Log transformed parameters; [b] Untransformed parameters.

UK-427,857 had no effect on the urine PK of lamivudine + zidovudine. The following table shows the unadjusted arithmetic means for Aet, Aet (%) and CLr by treatment group for 3TC and AZT:

Pharmacokinetic Parameter	Lamivudine (3TC)		Zidovudine (AZT)	
	UK-427,857 + Combivir™ (N=11)	Placebo + Combivir™ (N=11)	UK-427,857 + Combivir™ (N=11)	Placebo + Combivir™ (N=11)
Ae_t(µg)	119	110	37.7	36.3
Ae_t (%)	79.6	73.5	12.6	12.1
CL_r (L/h)	21.9	22.3	24.1	21.4

N: number of subjects.

Conclusion: UK-427,857 had a small, non-clinically significant effect on the plasma PK and no effect on the urine PK of 3TC and AZT, when administered as 300mg BID for seven days with Combivir™.

An Open, Randomized, Placebo-Controlled, Two-Period Crossover Study to Investigate the Effects of Co-Trimoxazole on the Steady-State Pharmacokinetics of UK-427,857 in Healthy Volunteers (Study A4001018)

Objectives: To determine the effect of co-trimoxazole on the steady-state pharmacokinetics of UK-427,857.

Study Design: This was an open label, randomized, placebo-controlled, two-period crossover study. Sixteen healthy subjects received either UK-427,857 (300mg) + co-trimoxazole (960mg) or UK-427,857 (300mg) + placebo (12 subjects received both treatments) separated by at least seven days. The medications were administered under fasted conditions on Day 7.

Formulations: UK-427,857 was supplied as 100mg tablets: Formulation Identification number (FID no.) S01165AA, Lot No. 8625-172. Placebo was supplied as a non-matching tablet, FID no. S00425AB, Lot No. 8625-145. Co-trimoxazole was supplied as 800mg/160mg tablets, Lot No. 47124.

Pharmacokinetic Measurements: On Days 1 to 6 in each study period, blood samples were collected for assay of UK-427,857 pre-morning dose and on Day 7 pre-dose and at 30 min, 1, 1.5, 2, 3, 4, 6, 8, 12 hours post-dose. Urine UK-427,857 concentration was determined from urine collected from 0 to 6 hours and 6 to 12 hours post-dose on Day 7.

Analytical methods: Plasma concentrations of maraviroc (UK-427,857) were determined by a validated LC/MS/MS method. All samples were analyzed within the demonstrated matrix and storage stability period. As shown in the following table, the analytical method is acceptable.

Analytical methods for maraviroc

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
maraviroc (plasma)	0.5 – 200 (R^2 >0.997)	≤7.6	-3.3 to 6.3	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.
maraviroc (urine)	5 – 1000 (R^2 >0.997)	≤4.4	-3.7 to 6.0	• Stable at 37°C for 9 days • Stable at -20°C for 3 months, • Stable for 5 freeze/thaw cycles at -20°C.

Pharmacokinetic Results: As shown in the following table, co-trimoxazole had an effect on the exposure of UK-427,857 with small increases in AUC12 (10.5%) and Cmax (19.4%). Tmax was similar for both treatment groups. UK-427,857 CL_R was slightly lower accounting for the small increases in AUC12 and Cmax when given in combination with co-trimoxazole compared to when given with placebo. The following table shows the comparison between log transformed AUC12 and Cmax and untransformed Tmax and CLR and the corresponding 90% CI for the two treatment groups.

Parameter	Ratio (%)[a] /Difference[b]	90% CI
AUC_{12} (ng.h/ml)[a]	111	101, 121
C_{max} (ng/ml)[a]	119	104, 137
T_{max} (h)[b]	0.25	-0.82, 1.32
CL_R (L/h)[b]	-0.59	-1.49, 0.306

Source: Tables 5.4.2 & 5.4.3. [a]ratio=UK-427,857 + co-trimoxazole divided by UK-427,857 + placebo; [b]difference = UK-427,857 + co-trimoxazole minus UK-427,857 + placebo. CI=confidence interval

It should be noted that the 90% CI for AUC12 and Cmax do not include 100%, whereas the difference in CLR does span zero. Steady state concentrations were reached by Day 7 for both treatment groups. Because trimethoprim is an inhibitor of the renal cation transporter, it could reduce the rate of renal elimination of UK-427,857, resulting in higher plasma concentrations.

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Conclusion:

- Co-trimoxazole caused a non-clinically significant increase in the systemic exposure to UK-427,857 probably related to the small reduction in renal clearance.
- Steady state pharmacokinetics were reached by Day 7 for both treatment groups.

An Open, Randomized, 2 Way Crossover Study to Investigate the Effect of Co-Administration of Tenofovir on the Pharmacokinetics of UK-427,857 in Healthy Subjects (Study A4001022)

Objectives: To investigate the effect of tenofovir on the pharmacokinetics of multiple oral doses of UK-427,857 (300mg BID).

Study Design: This was an open, randomized, placebo-controlled, two-way crossover study conducted in healthy male and female subjects. Subjects received UK-427,857 300mg twice daily (BID) + tenofovir 300mg once daily (QD) or placebo on Days 1–7. Subjects returned for their second treatment period following a washout period of at least 14 days. UK-427,857 was dosed under fasted conditions, with breakfast 1h after dosing. Tenofovir or placebo was administered 30min after breakfast started (1.5h after the morning dose of UK-427,857).

Formulations: The sponsor supplied the following study medication:

Table S2. Lot and Formulation Identification (FID) Numbers

Study Drug	Dosage Form	Lot Number	FID Number
UK-427, 857	50mg Tablet	03-001014 (9255-189)	S01163AA
Tenofovir disoproxil fumarate (Viread®)	300mg Tablet	FBK149D	-
Placebo (non-matching)	Tablet	165 (8625-145)	S00425AB

Pharmacokinetic Measurements: Blood samples (5ml) were taken to provide 2ml plasma for UK-427,857 pharmacokinetic analysis. Samples were taken at the following times:

Days 1, 3–6: 0 hour pre-morning dose of UK-427,857
Day 7: 0 hours (pre-dose), 30min, 1, 2, 4, 6, 8, 12h post-dose morning dose of UK-427,857

Urine was collected for analysis of UK-427,857 over 0-12 hours post morning dose of UK-427,857 on Day 7.

Analytical methods: Plasma and urine concentrations of maraviroc (UK-427,857) were determined by a validated LC/MS/MS method. All samples were analyzed within the

demonstrated matrix and storage stability period. As shown in the following table, the analytical methods are acceptable.

Analytical methods for maraviroc

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
maraviroc (plasma)	0.5 – 500 (R^2 >0.997)	≤8.8	-2.0 to 5.2	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.
maraviroc (urine)	5 – 5000 (R^2 >0.997)	≤3.8	-4.5 to 8.0	• Stable at 37°C for 9 days • Stable at -20°C for 3 months, • Stable for 5 freeze/thaw cycles at -20°C.

Pharmacokinetic Results: The 90% CIs for UK-427,857 Cmax and AUC_{12} were within the 80-125% range (Table S3). Tmax appeared to be unaffected by tenofovir. UK-427,857 Cmax and AUC at 300 mg BID are higher than what were observed in other studies.

Table S3. UK-427,857 Plasma Pharmacokinetic Parameters and Statistical Analysis

	Adjusted mean values for UK-427,857		
	AUC_{12} [a] (ng.h/ml)	C_{max} [a] (ng/ml)	T_{max} [b] (h)
UK-427,857 + tenofovir (N=12)	3600	1240	2.0
UK-427,857 + placebo (N=11)	3490	1200	1.9
Ratio of means* (90% CI)	103% (98, 109%)	104% (90, 119%)	0.13 (-0.13, 0.38)

a = geometric mean; b = arithmetic mean; * difference between means for T_{max}

As shown in the following table, the cumulative amount of unchanged drug excreted in the urine over 12 hours was approximately 10% for UK-427,857 with and without administration of tenofovir. Renal clearance of UK-427,857 was approximately 8L/h with and without administration of tenofovir.

	Arithmetic mean values for UK-427,857		
	Ae_{12} (mg)	Ae_{12} (% dose excreted)	CL_R (L/h)
UK-427,857 + tenofovir (N=12)	28.3	9.44	7.81
UK-427,857 + placebo (N=11)	30.6	10.2	8.50

Conclusion:

- As the 90% CIs for the Cmax and AUC12 ratios (Day 7) for UK-427,857 were within 80-120%, no drug interaction between tenofovir and UK-427,857 can be concluded.
- UK-427,857 Tmax also appeared to be unaffected by tenofovir.
- The amount of unchanged UK-427,857 in urine and renal clearance of UK-427,857 were the same for UK-427,857 administered with or without tenofovir.

An Open, Randomized, Parallel Group Study to Investigate the Effect of Rifampicin and Efavirenz on the Steady State Pharmacokinetics of UK-427,857 in Healthy Volunteers (Study A4001011)

Objectives:

- To investigate the effects of rifampicin and efavirenz on the steady state pharmacokinetics of UK-427,857.
- To investigate whether UK-427,857 dose adjustment can compensate for the effects of rifampicin and efavirenz.

Study Design: This was an open, randomized, placebo controlled, parallel group study. The following table shows the dosing sequence for the three treatment regimens.

Group	Study Days			
	1 to 7	8 to 21	22 to 27	28
1	UK-427,857 100mg BID	UK-427,857 100mg BID + Rifampicin 600mg QD	UK-427,857 200mg BID + Rifampicin 600mg QD	UK-427,857 200mg QD + Rifampicin 600mg QD
2	UK-427,857 100mg BID	UK-427,857 100mg BID + Efavirenz 600mg QD	UK-427,857 200mg BID + Efavirenz 600mg QD	UK-427,857 200mg QD + Efavirenz 600mg QD
3	UK-427,857 100mg BID	UK-427,857 100mg BID + Placebo QD	UK-427,857 100mg BID + Placebo QD	UK-427,857 100mg QD + Placebo QD

BID=twice daily; QD=once daily.

On Days 7, 21 and 28, subjects fasted from the previous midnight until four hours post-morning dose.

Formulations: UK-427,857 was supplied as 50mg tablets [formulation identification (FID) No. S01163AA; Lot No. 8625-171] and 100mg tablets [FID No S01165AA; Lot No. 8625-172]. Non-matching placebo tablets [Lot No. 8625-145] were also supplied. Rifampicin was supplied as 300mg capsules [Lot No. 02F05] and efavirenz was supplied as 200mg capsules [Lot No. HS59050].

Pharmacokinetic Measurements: Blood samples were collected pre-dose on Days 1, 4, 8 to 20 and 22 to 27, pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 10, 12 hours post-dose on Days 7 and 21 and pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36 and 48 hours post-dose on Day 28.

Urine was collected from 0 to 12 hours post-dose on Days 7 and 21.

Analytical methods: Plasma concentrations of maraviroc (UK-427,857) were determined by a validated LC/MS/MS method.

Plasma concentrations of UK-408027 (maraviroc's metabolite) were measured using high performance liquid chromatography with [redacted] mass spectrometric detection. Only samples taken on Days 7, 21 and 28 from subjects who received UK-427,857 + placebo or UK-427,857 + rifampicin were assayed.

The 6β-OH-Cortisol/ Cortisol Ratio was measured in urine using previously validated LC-MS-MS method.

All samples were analyzed within the demonstrated matrix and storage stability period. As shown in the following table, the analytical methods are acceptable.

Analytical methods

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
Maraviroc (plasma)	0.5 – 200 (R^2 >0.98)	≤5.7	-5.6 to 4.0	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.
UK-408027 (plasma)	1– 200 (R^2 >0.99)	≤15.0	-4.4 to 0.1	• Stable at room temperature and 4°C for up to 48 hours, • Stable after 5 freeze-thaw cycles and • **Stable at –20°C for 7 weeks.**
Cortisol (urine)	5 - 1000 (R^2 >0.99)	≤3.3	0 to 4.6	NA
6ß-hydroxycortisol (urine)	10 - 2000 (R^2 >0.99)	≤7.6	-5.3 to 0.9	NA

Pharmacokinetic Results: The following table summarizes the statistical analysis of AUCτ, Cmax and Tmax between Days 21 and 7 and Days 28 and 7 for each study drug group.

Group	Parameter	Comparison	Ratio %[a] /difference[b]	90% CI
UK-427,857 + rifampicin (Group 1)	AUC_τ (ng.h/ml)	Day 21 v Day 7	36.8	32.8, 41.3
		Day 28 v Day 7	104	88.5, 122
	C_{max} (ng/ml)	Day 21 v Day 7	33.5	26.0, 43.1
		Day 28 v Day 7	96.6	72.4, 129
	T_{max} (h)	Day 21 v Day 7	-1.04	-2.08, -0.01
		Day 28 v Day 7	-0.92	-1.93, 0.10
UK-427,857 + efavirenz (Group 2)	AUC_τ (ng.h/ml)	Day 21 v Day 7	55.2	49.2, 62.0
		Day 28 v Day 7	115	97.7, 135
	C_{max} (ng/ml)	Day 21 v Day 7	48.6	37.7, 62.6
		Day 28 v Day 7	116	87.1, 155
	T_{max} (h)	Day 21 v Day 7	-0.33	-1.37, 0.70
		Day 28 v Day 7	-0.67	-1.68, 0.35
UK-427,857 + placebo (Group 3)	AUC_τ (ng.h/ml)	Day 21 v Day 7	113	101, 127
		Day 28 v Day 7	105	89.5, 124
	C_{max} (ng/ml)	Day 21 v Day 7	112	86.5, 144
		Day 28 v Day 7	99.9	74.9, 133
	T_{max} (h)	Day 21 v Day 7	-0.33	-1.37, 0.70
		Day 28 v Day 7	0.46	-0.55, 1.47

[a]Ratio for AUC_τ and C_{max} (Day 28 or 21 divided by Day 7); [b]difference for T_{max} (Day 28 or 21 minus Day 7); CI=confidence interval.

The AUCτ (AUC over 12 hours) and Cmax after UK-427,857 100mg BID at steady state decreased by 67 and 70%, respectively in the presence of rifampicin and by 51 and 56%, respectively in the presence of efavirenz (Day 21 v Day 7 adjusted for placebo). The AUCτ and Cmax returned approximately to previous values when the UK-427,857 dose was increased to 200mg BID (Day 28 v Day 7). The mean values for Tmax and t1/2 were similar across study drug groups.

Rifampicin and efavirenz increased the placebo adjusted 6β-OH cortisol/ cortisol ratio between Days 7 and 21 by 423% and 93%, respectively.

The following table shows the mean pharmacokinetic parameter values for UK-408,027 for subjects who received UK-427,857 + rifampicin and UK-427857 + placebo.

Parameter	UK-427,857 + rifampicin			UK-427,857 + placebo		
	Day 7	Day 21	Day 28	Day 7	Day 21	Day 28
AUC_τ (ng.h/ml)[a]	148	214	489	142	136	129
C_{max} (ng/ml)[a]	19.6	28.5	63.1	18.5	18.4	15.7
T_{max} (h)[b]	3.8	2.5	2.8	3.8	2.8	4.3
$t_{1/2}$ (h)[b]	-	-	9.7	-	-	11.3

[a]geometric means; [b]arithmetic means; -=not calculated.

The mean UK-408,027 exposure in the UK-427,857 + rifampicin group, increased from Days 7 to 21 due to induced UK-427,857 metabolism and it increased further from Days 21 to 28 due to the doubling of the UK-427,857 dose. The mean exposure to UK-408,027 in the UK-427,857 + placebo group was similar throughout the study.

Conclusion:

- The CYP3A4 isozyme inducing drugs rifampicin and efavirenz reduce the exposure of steady state UK-427,857 and this effect can be adequately compensated for by doubling the UK-427,857 dose.
- As expected, the mean UK-408,027 exposure in the UK-427,857 + rifampicin group, increased from Days 7 to 21 due to induced UK-427,857 metabolism and it further increased from Days 21 to 28 due to the doubling of the UK-427,857 dose. Also as expected, the mean exposure to UK-408,027 in the UK-427,857 + placebo group was similar throughout the study.
- Increases in the placebo adjusted 6β-OH cortisol/ cortisol ratio between Days 7 and 21 indicated that, as expected, rifampicin strongly induced CYP3A4 activity (423% increase) while efavirenz moderately induced it (93% increase).

An Open, Randomized, Placebo Controlled, 2 Way Crossover Study to Investigate the Effect of Ketoconazole and Saquinavir on the Steady State Pharmacokinetics, Safety and Toleration of UK-427,857 in Healthy Volunteers (Study A4001006)

Objectives: To access the effect of ketoconazole and saquinavir on the steady state pharmacokinetics, safety and toleration of UK-427,857 in healthy volunteers

Study Population: Twenty healthy volunteers (males and females) completed the study.

Study Design: This was an open, two-period study involving two cohorts of 12 healthy subjects, as shown below.

Cohort 1: UK-427,857 100 mg every 12 hours (Days 1-7)
Saquinavir 1200 mg or placebo every 8 hours (Days 1-9)

Cohort 2: UK-427,857 100 mg every 12 hours (Days 1-7)
Ketoconazole 400 mg or placebo QD (morning) (Days 1-9)

Subjects attended both study periods. Dosing periods were separated by a minimum of seven days. Food restrictions were in place throughout the study. Cohort 1 was fasted from food and drink (except water) from six hours prior to the morning dose of UK-427,857 until one hour post morning dose, while Cohort 2 were fasted from 00:00 hours until four hours post UK-427,857 morning dose on Days 1 and 7. Water was restricted for both cohorts from one hour prior to dosing to one hour post dose. Cohort 1 had a high fat breakfast, lunch and dinner 30 minutes prior to the morning, afternoon and evening doses of saquinavir while Cohort 2 were permitted a standard lunch, dinner and snacks up to one hour prior and after one hour post UK-427,857 doses.

Formulations: UK-427,857 was administered as 50-mg tablets.

Pharmacokinetic Measurements: Blood samples (5 ml) for UK-427,857 assay were collected at the following times (relative to the morning dose of UK-427,857):

Day 1 0 and 1, 2, 4, 8 and 12 hours post dose.
Days 2-6: 0 (baseline pre- dose)
Day 7: 0 (baseline pre-dose) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48 and 72 hours post dose.

Pharmacodynamic Measurements: Supine and standing BP and pulse rate and 12 lead ECGs were recorded at the following times:

Day –1: 0 (baseline), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18 and 24 hours
Day 1: 0 (baseline pre dose), 1, 2, 4, 8 and 12 hours post dose
Days 2 to 6: 2 and 4 hours post dose
Day 7: 0 (baseline pre dose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18 and 24 hours post dose.

An additional visit for ECG collection during a controlled exercise regimen occurred between screening and Day –1, between the two study periods, after the second period or at or after follow up.

Analytical methods: Plasma concentrations of maraviroc were determined by a validated LC/MS/MS method. All samples were analyzed within the demonstrated matrix and storage stability period. As shown in the following table, the analytical method is acceptable.

Analytical method for maraviroc

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
maraviroc (plasma)	0.5 – 200 (R^2 >0.98)	≤6.3	-4.0 to 1.3	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.

Results: Saquinavir and ketoconazole had similar effects on Cmax, but ketoconazole caused a greater increase in AUC_τ as shown in the following table. The effect may be due to inhibition of CYP3A, Pgp, or both.

Effect of saquinavir and ketoconazole on UK-427,857 exposure

Comparison	Ratio (%); 90% CI		Difference; 90% CI	
	AUC	Cmax	Tmax	T1/2
UK-427,857 + SQV vs UK-427,857 + placebo	425% (347, 519)	332% (245, 449)	0.21 (-0.39, 0.81)	-0.38 (-1.80, 1.03)
UK-427,857 + keto vs UK-427,857 + placebo	501% (398, 629)	338 (238, 478)	-0.33 (-0.97, 0.30)	-2.81 (-5.80 (0.19)

The time profiles for systolic and diastolic BP and pulse rate were similar for each of the treatments within each cohort. QTcI (the QT individual correction factor) absolute values and change from baseline did not differ between treatment groups.

The incidence of adverse events was higher in Cohort 1 after UK-427,857 + SQV compared to UK-427,857 + placebo. In Cohort 2, the incidence of adverse events was similar after both treatments. There was one case of postural hypotension with UK-427,857 + SQV. There were minor elevations in AST and ALT, predominantly on UK-427,857 + SQV.

Conclusion:

- Saquinavir and ketoconazole had similar effects on Cmax but ketoconazole caused a greater increase in AUC_τ. Saquinavir increased exposure of UK-427,857 by 325% and 232% for AUC_τ and Cmax, respectively. Ketoconazole increased exposure of UK-427,857 by 400% and 237% for AUC_τ and Cmax, respectively.
- There was no major effect on Tmax or t½ when UK-427,857 was coadministered with either ketoconazole or saquinavir. Steady state was achieved by Day 7 in all study periods.
- The data suggests no evidence of a significant difference between treatments on systolic and diastolic (supine and standing) BP and pulse rate and QTcI.

An Open Label, Randomized, Placebo Controlled, Four Treatment, Four Group, Parallel Group Study to Explore the Steady State Pharmacokinetics of UK-427,857 when Co-Administered With Ritonavir, Saquinavir Plus Ritonavir or Lopinavir Plus Ritonavir (Kaletra™) (Study A4001013)

Objectives: To access the effects of ritonavir, saquinavir plus ritonavir and lopinavir plus ritonavir on the steady state pharmacokinetics of UK-427,857, to explore whether UK-427,857 dose adjustment can compensate for the effects of ritonavir, saquinavir plus ritonavir and lopinavir plus ritonavir on the steady state pharmacokinetics of UK-427,857.

Study Design: This was an open label, randomized, placebo controlled, four treatment, four group, parallel group study. Thirty-two healthy subjects were randomized to one of four treatment groups as follows:

Treatment group	Days 1 to 7	Days 8 to 21	Days 22 to 28*†
UK-427,857 + ritonavir	UK-427,857 100mg BID	UK-427,857 100mg BID and ritonavir 100mg BID	UK-427,857 50mg BID and ritonavir 100mg BID
UK-427,857 + saquinavir plus ritonavir	UK-427,857 100mg BID	UK-427,857 100mg BID and saquinavir 1000mg BID plus ritonavir 100mg BID	UK-427,857 25mg BID and saquinavir 1000mg BID plus ritonavir 100mg BID
UK-427,857 + lopinavir plus ritonavir	UK-427,857 100mg BID	UK-427,857 100mg BID and lopinavir 400mg BID plus ritonavir 100mg BID	UK-427,857 50mg BID and lopinavir 400mg BID plus ritonavir 100mg BID
UK-427,857 + placebo	UK-427,857 100mg BID	UK-427,857 100mg BID and placebo BID	UK-427,857 100mg BID and placebo BID

BID = twice daily. * Only the morning dose was taken on Day 28

† UK-427,857 dose was determined from magnitude of interaction observed during second phase

On Days 7 to 28, subjects were fasted of all food from at least two hours before until one hour after UK-427,857 dosing.

Formulations: UK-427,857 was supplied as 100mg tablets [formulation identification number (FID no) S01165AA, Lot no. 43 (8625-172)], 25mg tablets [FID no. S01229AA, Lot no. 354 (9255-070)] and 5mg tablets [FID no. S01227AA, Lot no. 353 (9255-069)]. Ritonavir (Norvir®, Abbott) was supplied as 100mg capsules (Lot no. 95494VA02J01). saquinavir (Fortovase®, Roche) was supplied as 200mg capsules (Lot. no. B145101J16) and lopinavir co-formulated with ritonavir (KaletraTM, Abbott) was supplied as 133.3mg/33.3mg capsules (Lot no. 01524VA02K16). Non-matching placebo tablets [FID no. S00425AB, Lot no. 8625-145] were supplied.

Pharmacokinetic Measurements: Blood samples (5ml) were taken to provide 2ml plasma for assay of concentrations of UK-427,857 at the following times (relative to the morning dose of UK-427,857):
Days 1, 4, 8, 10, 12, 14, 16, 19, 22, 24 and 26: pre-dose
Days 7, 21 and 28: pre-dose and 1, 2, 3, 4, 6, 8, 10 and 12 hours post-dose
Day 17: pre-dose and 2 and 4 hours post-dose

Analytical methods: Plasma concentrations of maraviroc were determined by a validated LC/MS/MS method. As shown in the following table, the analytical method is acceptable. All samples were analyzed within the demonstrated matrix and storage stability period.

Analytical method for maraviroc

Analyte	**Standard Curve Range (ng/mL)**	**Between Run Precision (%CV)**	**Between Run Bias (% Dev.)**	**Validation and sample for stability and conditions**
maraviroc (plasma)	0.5 – 200 (R^2 >0.99)	≤6.9	-5.6 to 4.2	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.

Pharmacokinetic Results: The following table summarizes the statistical analysis of AUCτ, Cmax and Tmax between Days 21 (PI(s) +maraviroc) and 7 (maraviroc alone) and Days 28 (PI(s) +maraviroc with dose reduction) and 7 within each treatment group.

Treatment group	Parameter	Comparison	Ratio (%)[a] or difference[b]	90% CI
UK-427,857 + ritonavir	AUC_τ (ng.h/ml)	Day 21 v Day 7	233	188, 290
		Day 28 v Day 7	80.2	63.2, 102
	C_{max} (ng/ml)	Day 21 v Day 7	177	125, 249
		Day 28 v Day 7	52.6	37.0, 74.6
	T_{max} (h)	Day 21 v Day 7	-0.3	-1.1, 0.6
		Day 28 v Day 7	-0.5	-1.3, 0.3
UK-427,857 + saquinavir plus ritonavir	AUC_τ (ng.h/ml)	Day 21 v Day 7	743	597, 924
		Day 28 v Day 7	127	99.7, 161
	C_{max} (ng/ml)	Day 21 v Day 7	582	413, 822
		Day 28 v Day 7	85.9	60.5, 122
	T_{max} (h)	Day 21 v Day 7	-0.6	-1.5, 0.3
		Day 28 v Day 7	-1.1	-1.9, -0.3
UK-427,857 + lopinavir plus ritonavir	AUC_τ (ng.h/ml)	Day 21 v Day 7	342	275, 425
		Day 28 v Day 7	139	110, 177
	C_{max} (ng/ml)	Day 21 v Day 7	222	158, 314
		Day 28 v Day 7	73.5	51.8, 104
	T_{max} (h)	Day 21 v Day 7	-1.1	-2.0, -0.2
		Day 28 v Day 7	-1.6	-2.4, -0.8
UK-427,857 + placebo	AUC_τ (ng.h/ml)	Day 21 v Day 7	89.2	71.7, 111
		Day 28 v Day 7	88.1	69.4, 112
	C_{max} (ng/ml)	Day 21 v Day 7	138	97.6, 194
		Day 28 v Day 7	140	98.6, 199
	T_{max} (h)	Day 21 v Day 7	-0.4	-1.3, 0.5
		Day 28 v Day 7	-0.6	-1.4, 0.2

Source: Tables 5.4.1 and 5.4.2

[a] Ratio for AUC_τ and C_{max} (Day 28 or 21 divided by Day 7); [b] Difference for T_{max} (Day 28 or 21 minus Day 7); CI = confidence interval

Conclusion: All of the interactants increased the exposure of steady state UK-427,857, with saquinavir plus ritonavir having the greatest effect, followed by lopinavir plus ritonavir and then ritonavir alone. Dose adjustment from 100mg to 25mg BID UK-427,857 in the presence of saquinavir plus ritonavir, and from 100mg to 50mg BID UK-427,857 in the presence of lopinavir plus ritonavir and ritonavir alone, adequately compensated for the increases in AUC_τ seen.

An Open, Randomized, Placebo-Controlled, 2-Way Crossover Study to Investigate the Effect of Co-Administration of Efavirenz with Kaletra™, Efavirenz with Boosted Saquinavir and Efavirenz with Both Kaletra™ and Saquinavir on The Pharmacokinetics of UK-427,857 in Healthy Subjects (Study A4001021)

Objectives:

- To investigate the effect of co-administration of efavirenz and Kaletra™ on the steady state pharmacokinetics of UK-427,857 300mg BID
- To investigate the effect of efavirenz and boosted saquinavir on the steady state pharmacokinetics of UK-427,857 100mg BID

- To investigate the effect of co-administration of efavirenz with Kaletra™ and saquinavir on the steady state pharmacokinetics of UK-427,857 100mg BID
- To investigate the effect of Kaletra™ on the steady state pharmacokinetics of UK-427,857 300mg BID
- To investigate the effect of boosted saquinavir on the steady state pharmacokinetics of UK-427,857 100mg BID
- To investigate the effect of co-administration of saquinavir and Kaletra™ on the steady state pharmacokinetics of UK-427,857 100mg BID

Study Design: This is an open, randomized, placebo-controlled, two-way crossover study in 36 healthy male and female subjects. Subjects were randomized to one of three cohorts (Table S1, 12 subjects per cohort) and to a treatment sequence within the cohort. The treatment periods were separated by a washout period of at least 14 days.

Table S1 Treatments Administered

	Period 1*	Period 2*
Cohort 1	UK-427,857 300mg BID + Kaletra™ BID (Days 1-21) plus efavirenz 600mg QD (Days 8-21)	UK-427,857 300mg BID + placebo BID (Days 1-21) plus placebo QD (Days 8-21)
Cohort 2	UK-427,857 100mg BID + boosted saquinavir BID (Days 1-21) plus efavirenz 600mg QD (Days 8-21)	UK-427,857 100mg BID + placebo BID (Days 1-21) plus placebo QD (Days 8-21)
Cohort 3	UK-427,857 100mg BID + saquinavir 1000mg BID + Kaletra™ BID (Days 1-21) plus efavirenz 600mg QD (Days 8-21)	UK-427,857 100mg BID + placebo BID (Days 1-21) plus placebo QD (Days 8-21)

Kaletra™ = lopinavir 400mg + ritonavir 100mg Boosted saquinavir = saquinavir 1000mg + ritonavir 100mg

* Subjects were randomised to treatment sequence and could receive the treatments in either order

UK-427,857 was given under fasted conditions. Efavirenz were co-administered with the morning dose of UK-427,857. Kaletra™/placebo (Cohort 1), boosted saquinavir/placebo (Cohort 2) or saquinavir/placebo and Kaletra™/placebo (Cohort 3) were administered to subjects 30 minutes after meal (approximately 1.5 after administration of UK-427,857).

Formulations: The following medications were supplied:

Study Drug	Dosage Form	Lot Number	FID Number
UK-427,857	100mg tablet	9255-190 (03-001060*)	S01165AA
UK-427,857	50mg tablet	9255-189 (03-001041*)	S01163AA
Saquinavir (Fortovase™)	200mg capsule	B4053	-
Lopinavir/ritonavir (Kaletra™)	133.3mg/33.3mg capsule	11311VA	-
Ritonavir (Norvir™)	100mg capsule	03719VA	-
Efavirenz (Sustiva™)	600mg capsule	EQK431AA	-
Non-matching placebo	Tablet	8625-145 (165*)	S00425AB

* Clinicopia Lot No.

Pharmacokinetic Measurements:
Blood samples (6ml) were taken to provide 2.5ml plasma for assay of concentrations of UK-427,857 (all samples) and its metabolite, UK-408,027 (Days 7 and 21 only). Samples were taken at the following times:

Days 1, 3-6, 8 and 10-20: 0 hours (pre-morning dose of UK-427,857).
Days 7 and 21: 0 hours (pre-dose) and 30 minutes, 1, 2, 4, 6, 8 and 12 hours post-morning dose of UK-427,857.

Analytical methods: Plasma and urine concentrations of maraviroc (UK-427,857) and plasma concentrations of its major metabolite UK-408027 were determined by validated LC/MS/MS methods. All samples were analyzed within the demonstrated matrix and

storage stability period. As shown in the following table, the analytical methods are acceptable.

Analytical methods for maraviroc

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
maraviroc (plasma)	0.5 – 500 (R^2 >0.997)	≤8.0	0 to 1.8	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.
UK-408027 (plasma)	0.5 – 500 (R^2 >0.994)	≤8.3	-4.7 to 0.8	• Stable at room temperature and 4°C for up to 48 hours, • Stable after 5 freeze-thaw cycles and • Stable at –20°C for 7 weeks.
maraviroc (urine)	.5 – 5000 (R^2 >0.998)	≤3.8	-4.4 to 6.7	• Stable at 37°C for 9 days • Stable at -20°C for 3 months, • Stable for 5 freeze/thaw cycles at -20°C.

Pharmacokinetic Results: The mean plasma pharmacokinetic parameters are shown in Tables S4 and S5. Twice daily dosing with Kaletra™ in combination with UK-427,857 300mg BID (Cohort 1) increased UK-427,857 AUC12 by 295% and Cmax by 97% compared with placebo on Day 7. This effect was reduced when efavirenz was co-administered with KaletraTM and UK-427,857, with increases in AUC12 and Cmax of 153% and 25%, respectively, compared with placebo on Day 21.

Twice daily dosing with boosted saquinavir in combination with UK-427,857 100mg BID (Cohort 2) increased UK-427,857 AUC12 by 877% and Cmax by 378% compared with placebo on Day 7. This effect was reduced when efavirenz was co-administered with boosted saquinavir and UK-427,857, with increases in AUC12 and Cmax of 400% and 126%, respectively, compared with placebo on Day 21.

There was evidence of an increase in UK-427,857 AUC12 and Cmax when saquinavir and Kaletra™ were co-administered with UK-427,857 100mg BID, compared with placebo (Cohort 3), based on mean values for six subjects (placebo period) and three subjects (saquinavir and KaletraTM period). There were no clinically relevant differences in UK-427,857 Tmax between the treatment periods in each cohort. Two subjects in Cohort 1, one subject in Cohort 2 and all subjects in Cohort 3 were excluded from the statistical analysis as they did not have pharmacokinetic results for both treatment periods.

Mean values for UK-427,857 urine pharmacokinetic parameters are shown in Table 6. Renal clearance is increased by 37% and 43%, respectively, when UK-427,857 is combined with Kaletra™ or boosted Saquinavir, which could be due to inhibition of metabolic pathway. This trend has been seen when UK-427,857 is combined with other PIs.

Table S4 Mean Values for UK-427,857 Plasma Pharmacokinetic Parameters

Cohort	Treatment	AUC_{12} (ng.h/ml)[a]		C_{max} (ng/ml)[a]		T_{max} (h)[b]	
		Day 7	Day 21	Day 7	Day 21	Day 7	Day 21
1	UK-427,857 300mg BID + LPV ÷ RTV± EFV	10100	6200	1810	1070	2.40	2.15
	UK-427,857 300mg BID ÷ placebo	2570	2450	920	854	2.00	2.00
2	UK-427,857 100mg BID + SQV + RTV ± EFV	4740	2710	894	437	2.00	2.15
	UK-427,857 100mg BID ÷ placebo	486	543	187	194	1.50	1.85
3	UK-427,857 100mg BID + SQV + LPV + RTV ± EFV	2950*	-	413*	-	1.67*	-
	UK-427,857 100mg BID ÷ placebo	451	-	119	-	1.75	-

[a] = geometric mean [b] = arithmetic mean * Mean of data for three subjects only
Means are adjusted means for Cohorts 1 and 2 and raw means for Cohort 3

Table S5 Summary of Statistical Analysis of UK-427,857 Plasma Pharmacokinetic Parameters

Cohort	Treatment comparison	Day	AUC_{12} (ng.h/ml)		C_{max} (ng/ml)		T_{max} (h)	
			Ratio (%)	90% CIs	Ratio (%)	90% CIs	Difference	90% CIs
1	UK-427,857 300mg BID +LPV+RTV±EFV vs UK-427,857 300mg BID + placebo	7	395	343, 456	197	166, 234	0.40	-0.34, 1.14
		21	253	224, 287	125	101, 155	0.15	-0.52, 0.82
2	UK-427,857 100mg BID +SQV+RTV±EFV vs UK-427,857 100mg BID + placebo	7	977	787, 1210	478	341, 671	0.50	0.13, 0.87
		21	500	426, 587	226	164, 311	0.30	-0.59, 1.19

Table 6 Raw Mean Values for UK-427,857 Urine Pharmacokinetic Parameters

Cohort	Treatment	n (D7)	n (D21)	Ae_{12} (mg)		Ae_{12} (%)		CL_r (l/h)	
				D 7	D 21	D 7	D 21	D 7	D 21
1	UK-427,857 300mg BID + LPV ÷ RTV ± EFV	11	10	118	68.7	39.3	22.9	11.8	10.9
	UK-427,857 300mg BID ÷ placebo	11	10	21.7	23.6	7.24	7.88	8.51	9.61
2	UK-427,857 100mg BID ÷ SQV + RTV ±EFV	11	10	37.5	21.7	37.5	21.8	7.89	8.22
	UK-427,857 100mg BID ÷ placebo	10	10	2.85	3.76	2.87	3.78	5.51	6.44
3	UK-427,857 100mg BID +SQV+LPV+RTV±EFV	6	-	19.8	-	19.8	-	12.3*	-
	UK-427,857 100mg BID ÷ placebo	6	-	5.17	-	5.15	-	10.9	-

Means are arithmetic means * n = 3

Larger decreases in mean standing SBP were observed during co-administration of Kaletra™, boosted saquinavir, and Kaletra™ and saquinavir, compared with UK-457,857 alone (*ie* with placebo). There were no notable changes from baseline in ECGs.

There were no serious adverse events (AEs) during the study. In Cohort 1, two subjects discontinued due to AEs (treatment related hyperlipemia and raised alanine transaminase) and one subject had a temporary interruption to study treatment due to unrelated nausea and vomiting. In Cohort 2, one subject discontinued due to an unrelated respiratory tract infection and one subject discontinued after withdrawing her consent. In Cohort 3, four subjects discontinued due to treatment related AEs [bilirubinaemia (two subjects), malaise and nausea] and two subjects had a temporary interruption to study treatment due to treatment related gastrointestinal AEs; all 12 subjects in Cohort 3 were subsequently discontinued when the sponsor stopped the cohort due to treatment related gastrointestinal AEs.

Conclusion:

- Kaletra™, boosted saquinavir, and saquinavir plus Kaletra™ all increased the exposure of steady state UK-427,857, with boosted saquinavir having the greatest effect (increase in AUC12 of 295%, 877% and 554%, respectively, compared with UK-427,857 + placebo). This effect was reduced by approximately 50% by the co-administration of efavirenz with UK-427,857 and KaletraTM or UK-427,857 and boosted saquinavir (increase in AUC12 of 153% and 400%, respectively, compared with UK-427,857 + placebo).
- Renal clearance of UK-427,857 is increased by 37% and 43%, respectively, when UK-427,857 is combined with Kaletra™ or boosted Saquinavir, which could be due to inhibition of metabolic pathway.

An Open Study to Investigate the Range of Maraviroc Exposures Following a 150mg Single Dose in HIV Positive Patients Receiving Antiretroviral Therapy Containing Boosted Saquinavir (Study A4001046)

Objectives: 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 (SQV/r). To justify 150 mg dose is the right dose for maraviroc when combined with boosted saquinavir.

Study Design: This was an open, single period, single centre study. Eight HIV positive subjects receiving antiviral therapy containing SQV/r (1000/100 mg) took a single 150mg maraviroc dose. All subjects took SQV/r once on the day before dosing and on Day 1 to evaluate the single dose effect of SQV/r. Four subjects took concomitant abacavir, saquinavir and tenofovir, and three subjects took lamivudine. It is not clear if additional saquinavir will increase maraviroc further. The sponsor did not provide individual concomitant drug information.

Formulations: The sponsor supplied maraviroc as a 150mg tablet; Lot No. 10082-197

Pharmacokinetic Measurements: Blood samples were taken pre-dose and 1, 2, 4, 6, 8 and 12 hours post-dose on Day 1.

Analytical methods: Plasma concentrations of maraviroc were determined by a validated LC/MS/MS method. All samples were analyzed within the demonstrated matrix and storage stability period. As shown in the following table, the analytical method is acceptable.

Analytical methods for maraviroc

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
maraviroc (plasma)	0.5 – 500 (R^2 >0.99)	≤11.7	-4.3 to 3.3	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.

Pharmacokinetic Results: The mean AUC and Cmax following maraviroc 150 mg in the presence of SQV/r was 4588ng.h/ml (range 2470 to 12000ng.h/ml) and 756ng/ml (range 498 to 1550ng/ml), respectively. The inter-subject variability for the pharmacokinetic parameters was consistent with that seen in other studies with maraviroc in subjects with HIV.

The following table summarizes the mean plasma maraviroc plasma pharmacokinetic parameters, with the range and coefficient of variation % (CV%) for the eight subjects.

Table 6. Maraviroc Plasma Pharmacokinetic Results

Parameter	Mean (range)	CV%
AUC (ng.h/ml)[a]	4588 (2470-12000)	58
AUC_{last} (ng.h/ml)[a]	4145 (2330-11200)	61
C_{max} (ng/ml)[a]	756 (498-1550	45
T_{max} (h)[b]	1.6 (1-2)	32
$t_{1/2}$ (h)[b]	18.4 (13.3-25.5)	23

[a]geometric mean; [b]arithmetic mean; CV=coefficient of variation.

Conclusion: The mean AUC and Cmax following maraviroc 150 mg in the presence of SQV/r was 4588ng.h/ml (range: 2470 to 12000) and 756ng/ml (range: 498 to 1550), respectively. The inter-subject variability for the pharmacokinetic parameters was consistent with that seen in other studies with maraviroc 300 mg BID in subjects with HIV at Phase 2a. This study did not raise any safety or toleration issues, thus 150 mg maraviroc QD or BID can be used in patients coadministered with SQV/RTV in Phase III studies.

An Open, Placebo-Controlled, Randomized, 2 Way Crossover Study to Investigate the Effect of Co-Administration of Atazanavir Alone and Boosted with Ritonavir on the Pharmacokinetics of UK-427,857 in Healthy Subjects (Study A4001025)

Objectives: To investigate the effects of atazanavir (alone and boosted with ritonavir) on the pharmacokinetics of multiple oral doses of UK-427,857 and to investigate the safety and toleration of UK-427,857 when administered with atazanavir (alone and boosted with ritonavir).

Study Design: This was an open, randomized, placebo-controlled, two-period crossover study. Healthy subjects (12) were randomized to receive UK-427,857 300mg twice daily (BID) on Days 1 to 13 and once daily (QD) on Day 14 plus atazanavir 400mg QD on Days 1 to 7 and boosted atazanavir (atazanavir 300mg and ritonavir 100mg QD) on Days 8 to 14 of one treatment period, and UK-427,857 300mg BID (QD Day 14) plus placebo QD on Days 1 to 14 of the other treatment period. The treatment periods were separated by a washout period of at least 14 days.

All subjects received their morning dose of UK-427,857 between 8 am and 10 am under fasted conditions. The evening dose of UK-427,857 was administered 12h after the morning dose (2.5 h before dinner and 1.5 h after lunch). Subjects received their morning dose of atazanavir 400mg or placebo 30min after commencing breakfast (i.e. 1.5 h post the morning dose of UK-427,857).

Formulations: Table S2 shows the formulation information of all the medication used in the study.

Table S2 Lot and Formulation Identification (FID) Numbers

Study Drug	Dosage Form	Lot Number	FID Number
UK-427,857	50mg tablet	03-001041 (9255-189)	S01163AA
Atazanavir (Reyataz™)	150mg capsule	MLA20	-
Atazanavir (Reyataz™)	200mg capsule	MJA10	-
Non-matching placebo for atazanavir	Tablet	165 (8625-145)	S00425AB
Ritonavir (Norvir™)	100mg capsule	04186E22	-

Pharmacokinetic Measurements: Blood samples (5ml) were taken at the following times:
Days 1, 3-6, 8 and 10-13: 0 hours (pre-morning dose of UK-427,857).
Days 7 and 14: 0 hours (pre-dose) and 30 minutes, 1, 2, 4, 6, 8 and 12 hours post-morning dose of UK-427,857.

Urine for analysis of UK-427,857 was collected from 0 to 12 hours after the morning dose of UK-427,857 on Days 7 and 14.

Pharmacodynamic Measurements: Blood pressure and pulse rate were recorded using a semi-automated sphygmomanometer. Measurements were made after subjects had rested supine for five minutes; subjects then sat for two minutes and a further measurement was made once the subject had stood for a further two minutes.

Analytical methods: Plasma and urine concentrations of maraviroc (UK-427,857) were determined by validated LC/MS/MS methods. All samples were analyzed within the demonstrated matrix and storage stability period. As shown in the following table, the analytical methods are acceptable.

Analytical methods for maraviroc

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
maraviroc (plasma)	0.5 – 500 (R^2 >0.999)	≤10.0	-6.7 to 1.6	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.
maraviroc (urine)	5 – 5000 (R^2 >0.997	≤5.6	-5.6 to 9.3	• Stable at 37°C for 9 days • Stable at -20°C for 3 months, • Stable for 5 freeze/thaw cycles at -20°C.

Pharmacokinetic Results: Visual inspection of trough values suggests that steady state UK-427,857 was achieved by Day 7. As shown in Table S3, once daily dosing with atazanavir 400mg increased UK-427,857 AUC12 by 257% and Cmax by 109% compared with placebo on Day 7. The increase in UK-427,857 AUC12 and Cmax was greater when UK-427,857 was administered with boosted atazanavir (atazanavir 300mg and ritonavir 100mg QD), with increases of 388% and 167%, respectively, compared with placebo on Day 14. Mean values for Tmax were similar during both treatment periods.

Table S3 Summary of Statistical Analysis of UK-427,857 Plasma Pharmacokinetic Parameters

Parameter	Day	Mean for UK-427,857 + atazanavir	Mean for UK-427,857 + placebo	Ratio %[c] /difference[d]	90% confidence interval
AUC_{12} (ng.h/ml)[a]	7	9970	2790	357	330, 387
	14	12800	2610	488	440, 541
C_{max} (ng/ml)[a]	7	1910	915	209	172, 255
	14	2440	914	267	232, 308
T_{max} (h)[b]	7	2.50	2.00	0.50	0.01, 0.99
	14	2.00	1.92	0.08	-0.07, 0.23

[a] = adjusted geometric mean [b] = adjusted arithmetic mean [c] = Ratio for AUC_{12} and C_{max} [d] = Difference for T_{max}

Mean values for UK-427,857 urine pharmacokinetic parameters are shown in Table S4. Renal clearance is increased by 25%- 36%, when UK-427,857 is combined with atazanavir, which could be due to inhibition of metabolic pathway.

Table S4 Summary of Mean Values for UK-427,857 Urine Pharmacokinetic Parameters

Parameter	Mean for UK-427,857 + atazanavir		Mean for UK-427,857 + placebo	
	Day 7	Day 14	Day 7	Day 14
Ae_{12} (mg)	93.3	132	22.2	19.3
Ae_{12} (%)	31.1	44.0	7.38	6.42
CL_r (L/h)	9.66	10.4	7.70	7.63

Means are arithmetic means

Pharmacodynamic Results: Mean values for the pharmacodynamic parameters are shown in Table S5.

Table S5 Summary of Mean Values for Pharmacodynamic Parameters

Parameter	UK-427,857 + atazanavir	UK-427,857 + placebo
Maximum decrease from baseline in standing SBP (mmHg)	-28.1	-13.6
Maximum decrease from baseline in standing DBP (mmHg)	-20.3	-13.4
Maximum increase from baseline in standing PR (bpm)	27.9	30.0
Maximum decrease from baseline in supine SBP (mmHg)	-18.0	-13.0
Maximum decrease from baseline in supine DBP (mmHg)	-15.2	-11.7
Maximum increase from baseline in supine PR (bpm)	20.1	24.2

Means are arithmetic means

The data show that the mean maximum decrease from baseline in standing SBP and DBP was larger during the UK-427,857 + atazanavir treatment period (-28.1mmHg and -20.3mmHg, respectively) compared with the UK-427,857 + placebo treatment period (-13.6mmHg and -13.4mmHg, respectively).

There were no notable differences between the treatment periods in mean maximum increase from baseline in standing or supine PR.

Conclusion:

- Atazanavir and boosted atazanavir both increased the exposure of steady state UK-427,857, with boosted atazanavir having the greatest effect (increase in AUC12 of 257% and 388%, and Cmax of 109% and 167%, respectively, compared with UK-427,857 + placebo).

- The mean maximum decrease from baseline in standing or supine SBP and DBP was larger during the UK-427,857 + atazanavir treatment period compared with the UK-427,857 + placebo treatment period.

An Open, Randomized, 2 Way Crossover Study to Investigate the Effect of Tipranavir/Ritonavir on the Pharmacokinetics of Maraviroc in Healthy Subjects (Study A4001042)

Objectives: To investigate the effects of tipranavir administered in combination with ritonavir, [boosted tipranavir (tipranavir 500mg + ritonavir 200mg)] twice daily (BID) 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.

Study Population: Healthy (12) male and female subjects aged 18 to 55 years with a Body Mass Index between approximately 18 to 30kg/m2 and a body weight >50kg.

Study Design: This was an open, randomized, placebo-controlled, two-period crossover study. Subjects took maraviroc 150mg at the same time with either boosted tipranavir (500mg tipranavir/200mg ritonavir) or placebo BID on Days 1 to 7, with a final dose on the morning of Day 8. The treatment periods were separated by a washout period of at least 14 days. Meals were taken at least 2 hours before or one hour after the morning and evening doses. Subjects were fasted on the morning of day 8 until 4 hours post dose.

Formulations: The sponsor supplied maraviroc as 150mg oral film coated tablets [Formulation identification number (FID) 0401103; Lot No. 10082-197] and non-matching placebo tablets (FID S00425AB; Lot No. 8625-145). Boehringer Ingelheim GmbH supplied tipranavir as 250mg oral capsules (Lot No. PD-2555) and the study centre supplied ritonavir (Norvir™) as 100mg oral capsules (Lot No. 17932VA 04C11).

Pharmacokinetic Measurements: Blood samples for maraviroc were taken pre-morning dose on Days 1 to 7 and pre-dose and 0.5, 1, 2, 3, 4, 6, 8 and 12 hours post-dose on Day 8. Blood samples fro tipranavir and ritonavir were taken pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 hours post-dose on Day 8.

Urine sample for maraviroc were taken pre-dose on Day 8 and up to 12 hours post-dose.

Analytical methods: Plasma and urine concentrations of maraviroc (UK-427,857) and plasma concentrations of tipranavir and ritonavir were determined by validated LC/MS/MS methods. All samples were analyzed within the demonstrated matrix and storage stability period. As shown in the following table, the analytical methods for maraviroc and tipranavir are acceptable.

Analytical methods

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
maraviroc (plasma)	0.5 – 500 (R^2 >0.997)	≤3.8	1.5 to 7.3	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months;

				• Stable for three freeze/thaw cycles at -20°C.
maraviroc (urine)	5 – 5000 (R^2 >0.993)	≤8.1	--1.3 to 13.2	• Stable at 37°C for 9 days • Stable at -20°C for 3 months, • Stable for 5 freeze/thaw cycles at -20°C.
tipranavir (plasma)	1,000 – 100,000 (R^2 >0.99)	≤3.7	4.3 to 12.0	
ritonavir (plasma)	25 – 2,500	NA	NA	

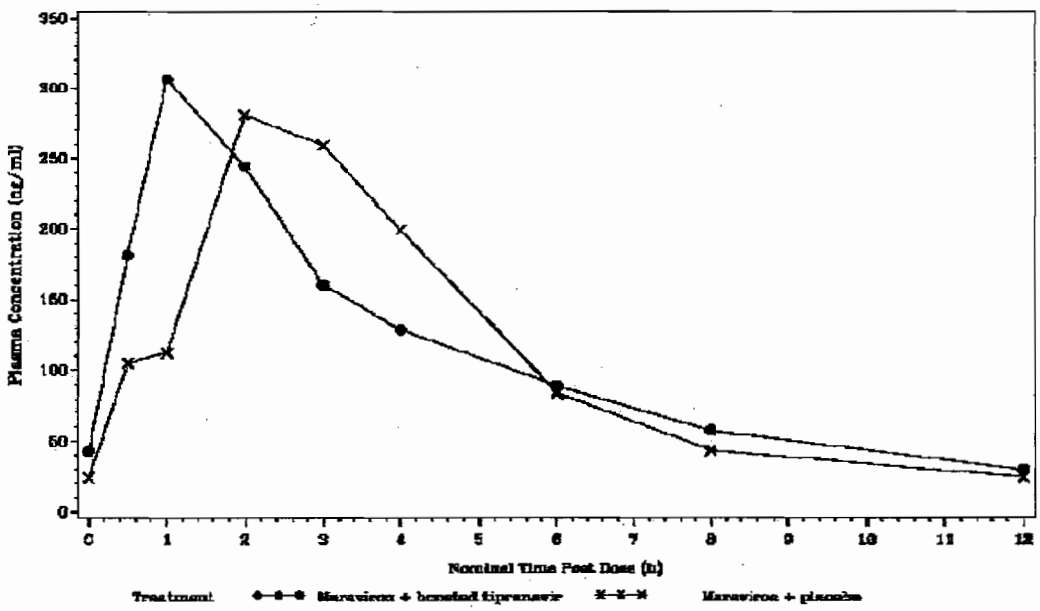
Pharmacokinetic/Pharmacodynamic Results: Table S2 summarizes the mean plasma maraviroc pharmacokinetic parameters on Day 8 for the two treatment groups. Analysis of maraviroc AUC_{0-12}, Cmax and Tmax suggested that boosted tipranavir did not have a clinically significant effect on the pharmacokinetics of maraviroc. Figure 1 shows the mean plasma maraviroc concentration at Day 8 for the two treatment groups.

Table S2. Maraviroc Plasma Pharmacokinetic Results

Treatment group	AUC_{0-12}[a] (ng.h/ml)	C_{max}[a] (ng/ml)	T_{max}[b] (h)
Maraviroc + boosted tipranavir	1282	298	1.5
Maraviroc + placebo	1260	347	2.6

[a]geometric mean; [b]arithmetic mean.

Figure 1. Mean Plasma Maraviroc Concentration at Day 8



The following table summarizes the statistical analysis of the mean plasma maraviroc pharmacokinetics on Day 8.

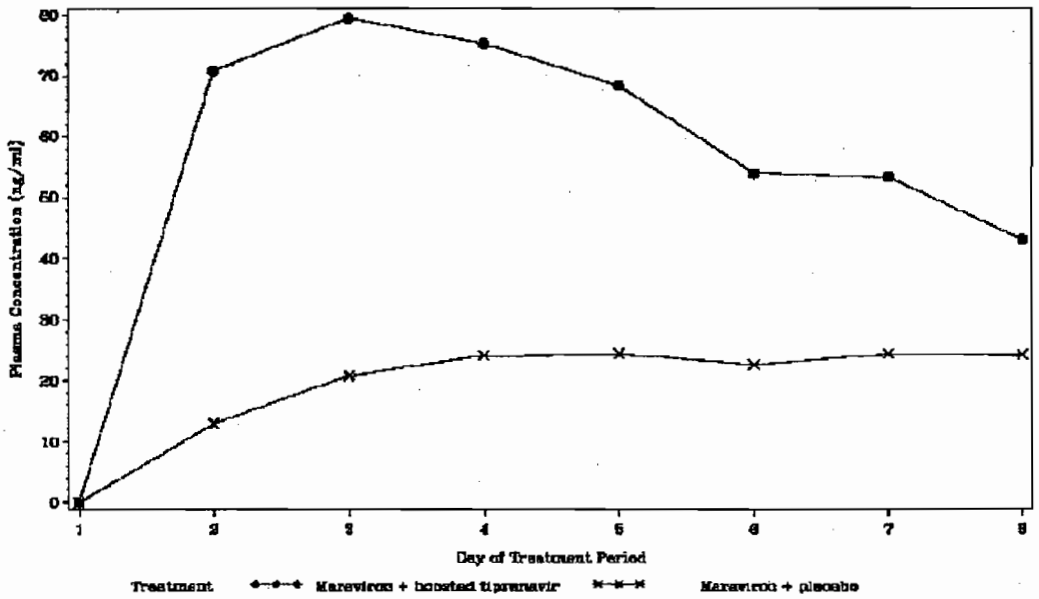
Table S3. Statistical Analysis of the Plasma Maraviroc Pharmacokinetic Results

Parameter	Ratio (%)[a] or difference[b]	90% CI
AUC_{0-12} (ng.h/ml)	102	85,123
C_{max} (ng/ml)	86	61,121
T_{max} (h)	-1.1	-1.7,-0.6

[a]ratio for AUC_{0-12} and C_{max} (maraviroc + boosted tipranavir divided by maraviroc + placebo); [b]difference for T_{max} (maraviroc + boosted tipranavir minus maraviroc + placebo); CI=confidence interval.

Figure 2 shows that maraviroc trough concentrations increased over Days 1 to 4 and decreased thereafter when administered with boosted tipranavir, which suggests that there was initial CYP3A inhibition, but at steady-state the net CYP3A inhibition and net P-gp induction of tipranavir/ritonavir cancel out.

Figure 2. Mean Trough Plasma Maraviroc Concentration



Renal clearance is increased by 25%- 36%, when maraviroc is combined with boosted tipranavir. Table 9 summarizes the arithmetic mean urine maraviroc pharmacokinetic parameters on Day 8 for the two treatment groups.

Table 9. Maraviroc Urine Pharmacokinetic Results

Treatment group	Ae_{0-12} (mg)	Ae_{0-12} (%)	CL_R (L/h)
Maraviroc + boosted tipranavir	14.5	9.7	11.1
Maraviroc + placebo	11.4	7.6	8.9

The range of ritonavir and tipranavir trough concentrations was similar to those reported previously for subjects who received boosted tipranavir. The geometric mean tipranavir AUC0-12 was 376ng.h/ml (623µM); Cmax was 59.3µg/ml (98.4µM) and C12 was 11.6µg/ml (10.3µM). The following table summarizes the tipranavir and ritonavir non-compartmental steady state pharmacokinetics when co-administered with maraviroc.

Table 10. Tipranavir and Ritonavir Plasma Pharmacokinetics

Treatment group	AUC (μg.h/ml)[a]	C_{max} (μg/ml)[a]	C_{12} (μg/ml)[a]	T_{max} (h)[a]
Tipranavir (N=12)	376	59.3	11.6	2.2
Ritonavir (N=12)	6.89	1.79	0.0421	2.3

[a]geometric means.

The effects on blood pressure and pulse rate after were similar for both dose groups.

Conclusion:

- Boosted tipranavir did not have a clinically significant effect on Day 8 maraviroc plasma or urine pharmacokinetics.
- Maraviroc trough concentrations increased over Days 1 to 4 and decreased thereafter when administered with boosted tipranavir, which suggests that there was initial inhibition followed by induction of maraviroc metabolism and is consistent with the known mechanism of boosted tipranavir.
- The range of ritonavir and tipranavir trough concentrations was similar to those reported previously for subjects who received boosted tipranavir.

A Study to Investigate the Effect of Selected Antiretroviral Combinations on The Pharmacokinetics of a Single Oral Dose of UK-427,857 300mg in HIV-Infected Subjects (Study A4001017)

Objectives: To investigate the effect of antiretroviral combinations on the pharmacokinetics of a single oral dose of UK-427,857 300mg.

Study Population: 29 male HIV-1 infected subjects aged 18 to 55 years inclusive who were stable for at least three months before study start on one of the four identified antiretroviral regimens and whose weight was between 60 and 100kg and with a Quetelet's index (Body Mass Index, BMI) between 18–28.

Study Design: This was an open, single period, single centre study to investigate the pharmacokinetics, safety and toleration of a single oral dose of UK-427,857 300mg when co-administered with one of four selected antiretroviral combination therapies:

Cohort 1: Efavirenz 600mg once daily (QD), Combivir® (lamivudine 150mg + zidovudine 300mg) twice daily (BID) (n=8)
Cohort 2: Efavirenz 600mg QD, didanosine 250mg enteric coated QD, tenofovir 300mg QD (n=8)
Cohort 3: Nevirapine 200mg BID, lamivudine 150mg BID, tenofovir 300mg QD (n=8)
Cohort 4: Kaletra® (lopinavir + ritonavir) 400mg BID, stavudine 40mg BID, lamivudine 150mg BID (n=8).

The data generated in this study were compared with historical data from Study A4001007, in which asymptomatic HIV-infected subjects not taking ART received 300mg UK-427,857.

Formulations: UK-427,857 100mg tablets, FID No. 9255-190, Lot No. S01165AA

Pharmacokinetic Measurement: Blood samples (4ml) for UK-427,857 were collected at pre-dose, and at 1, 2, 4, 6, 8 and 12 hours post UK-427,857 dose. Urine for UK-427,857 assay was collected before UK-427,857 dose and 0-12 hours post-dose.

Analytical methods: Plasma and urine concentrations of maraviroc (UK-427,857) were determined by validated LC/MS/MS methods. All samples were analyzed within the demonstrated matrix and storage stability period. As shown in the following table, the analytical methods are acceptable.

Analytical methods for maraviroc

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
maraviroc (plasma)	0.5 – 500 (R^2 >0.998)	≤4.0	0.7 to 3.0	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.
maraviroc (urine)	5 – 5000 (R^2 >0.997	≤5.8	-5.2 to 8.7	• Stable at 37°C for 9 days • Stable at -20°C for 3 months, • Stable for 5 freeze/thaw cycles at -20°C.

Pharmacokinetic Results: The following table shows the adjusted means for AUC12, Cmax and Tmax by treatment group:

Mean UK-427,857 plasma pharmacokinetic parameters

Treatment group	AUC_{12}[a] (ng.h/ml)	CV (%)	C_{max}[a] (ng/ml)	CV (%)	T_{max}[b] (h)	CV (%)
Cohort 1 (N=8)	1060	39.4	389	44.6	2.1	39.3
Cohort 2 (N=8)	1093	84.9	447	89.4	1.9	18.9
Cohort 3 (N=8)	2273	50.9	900	68.0	2.0	0.0
Cohort 4 (N=5)	5987	30.4	1050	48.4	2.2	49.8
A4001007 (N=8)	2262	30.8	585	23.0	2.9	43.4

Source: **Tables** 5.1, 5.2.1 to 5.2.3, and 5.4.
CV: coefficient of variation; N: number of subjects.
[a] geometric mean; [b] arithmetic mean.

As compared to historical data from Study A4001007, in which asymptomatic HIV-infected subjects not taking ART received 300mg UK-427,857, exposure to 300mg UK-427,857 was approximately 50% lower and Cmax was approximately 25 to 40% lower in subjects who received efavirenz (Cohorts 1 and 2). Exposure to 300mg UK-427,857 was similar and Cmax was 1.5-fold higher in subjects who received nevirapine (Cohort 3) compared with subjects who did not receive ART. Exposure to 300mg UK-427,857 was 2.6-fold higher and Cmax was approximately 1.8-fold higher in subjects who received Kaletra® (Cohort 4) compared with subjects who did not receive ART. Mean values for Tmax were similar for all treatment groups. The results for Cohort 1, 2 and 4 are comparable to the magnitude from drug-drug interaction studies in healthy subjects.

Treatment group	AUC_{12}[a] (ng.h/ml) Ratio of Means (%) [90% CI]	C_{max}[a] (ng/ml) Ratio of Means (%) [90% CI]	T_{max}[b] (h) Difference Between Means [90% CI]
Cohort 1 CBV + EFV	46.9 [30.3, 72.4]	66.5 [40.8, 109]	-0.750 [-1.44, -0.057]
Cohort 2 DdI+EFV+ TFV	48.3 [31.3, 74.6]	76.4 [46.8, 125]	-1.000 [-1.69, -0.31]
Cohort 3 3TC+NVP+ TFV	101 [65.1, 155]	154 [94.3, 251]	-0.875 [-1.57, -0.18]
Cohort 4 KAL+3TC+ d4T	265 [161, 435]	180 [103, 314]	-0.675 [-1.47, 0.115]

CI: Confidence Interval; CBV: Combivir®; EFV: efavirenz; DdI: didanosine; TFV: tenofovir; 3TC: lamivudine; NVP: nevirapine; KAL: Kaletra® (lopinavir + ritonavir); d4T: stavudine.
[a] Log transformed parameters; [b] Untransformed parameters.

The following table shows the mean urine pharmacokinetic parameters:

Mean UK-427,857 urine pharmacokinetic parameters

Treatment group	Ae_{12}[a] (mg)	Ae_{12}[a] (%)	CL_r[a] (L/h)
Cohort 1 (N=8) CBV + EFV	12.45	4.15	12.03
Cohort 2 (N=8) DdI + EFV + TFV	11.79	3.91	8.23
Cohort 3 (N=8) 3TC + NVP + TFV	22.28	7.43	9.71
Cohort 4 (N=5) KAL + 3TC + d4T	80.80	26.94	13.22

Source: Tables 5.1, 5.3.1 to 5.3.3.
Urine pharmacokinetic data was not collected in Study A4001007.
SD: Standard Deviation; N: number of subjects; CBV: Combivir®; EFV: efavirenz; DdI: didanosine; TFV: tenofovir; 3TC: lamivudine; NVP: nevirapine; KAL: Kaletra® (lopinavir + ritonavir); d4T: stavudine.
[a] arithmetic mean.

No comparison between the urine pharmacokinetic parameters in this study and Study A4001007 was possible because urine was not collected in Study A4001007. The mean values of unchanged UK-427,857 excreted in the urine appeared to correlate with the altered exposures (AUC12) seen in the different cohorts *ie* higher AUC12 and higher Ae12 in Cohort 4, lower AUC12 and lower Ae12 in Cohorts 1 and 2.

Conclusion:

- Co-administration of efavirenz-containing regimens resulted in approximately 50% reduction in systemic exposure to UK-427,857.
- The regimen containing Kaletra® resulted in an approximate doubling of exposure (2.6-fold higher).

- The nevirapine-containing regimen resulted in a small increase in Cmax, but no effect on overall systemic exposure.

4.2.4 Population Pharmacokinetics

Clearance and Mass Balance Model for Maraviroc

Executive Summery: This analysis estimated that the absolute bioavailabilty is approximately 33% at a 300 mg dose and the renal clearance accounts for 25% of the total clearance.

Objectives: To produce a model for the clearance and mass balance of maraviroc after single dose oral administration of 300mg solution in healthy male volunteers.

Study Design: Study A4001010 investigated the absorption, metabolism and excretion following a single oral solution 300 mg dose of [14C]-maraviroc in 3 healthy male subjects. Blood, urine and feces were collected for measurement of maraviroc, metabolites and total radioactivity.

Data: The main data used in the current analysis were mean values from Study A4001010 and is listed in Table 1 (mean as % of administered 300 mg dose). Total metabolites in urine and feces was calculated as the difference between radioactivity and maraviroc. The final column in the table scales values that are used in the following analysis to 100% to account for the [redacted] recovery from the study. Values in bold type will be directly transferred to the final balance diagram.

Table 1 Study A4001010 Data

	Reported (%)	Scaled to 100%
Radioactivity in Urine		
Maraviroc in Urine		**8.33**
Metabolites in Urine (calculated by difference)		**12.08**
Radioactivity in Faeces		
Maraviroc in Faeces		**26.4**
Metabolites in Faeces (calculated by difference)		**53.2**
Total Radioactivity		**100**

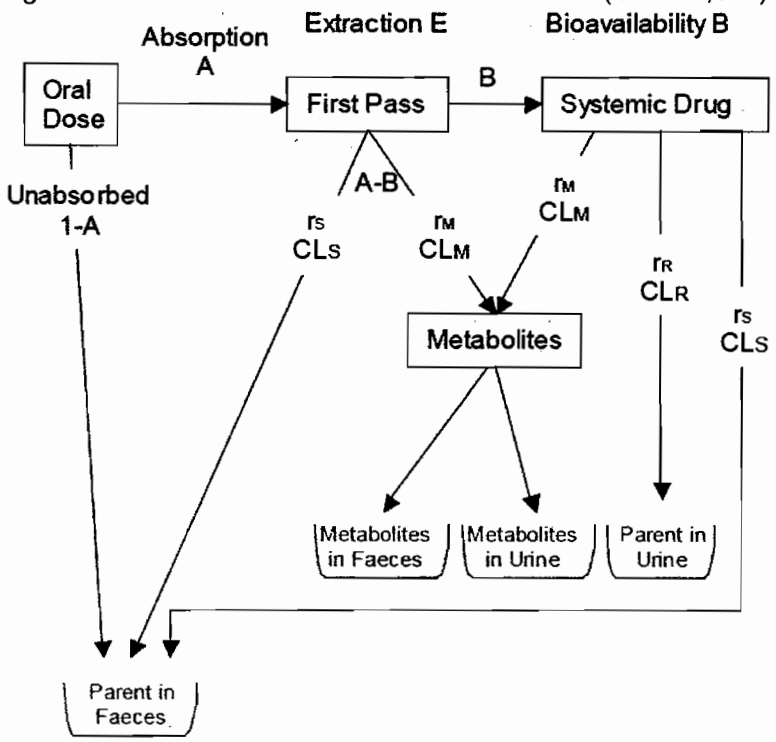
The parameters listed in Table 2 are obtained from other Phase 1 studies.

Table 2 Parameters from Other Studies

Parameters	Values	Source
Total plasma clearance (CL)	48 L/h	Study A4001009 (PPK)
Absorption at 300 mg (solution)	83.8%	Phase 1 Non-comp PPK
Absorption at 100 mg (tablet)	57.45%	Phase 1 Non-comp PPK
Renal Clearance (CL_R)	12 L/h	Phase 1 studies
blood:plasma partition ratio (r_B)	0.59	In vitro

Method and Results: The main assumption is that after the non-linear absorption, all further disposition (including all clearance terms) of maraviroc and metabolites is strictly linear, including first pass metabolism/clearance. A general diagram of the absorption and elimination pathways and terms described below are shown in Figure 1.

Figure 1 General Model of Balance for Maraviroc (UK-427,857)



Equations based on mass balance considerations are shown below, where no entero-hepatic recycling is assumed to occur (*this assumption may not be true, because dual peaks did occur in concentration-time profiles of some patients*). All of the calculations have been made using an Splus (Insightful, Co) script.

It is assumed that total systemic plasma clearance (CL) consists only of a renal component (CLR) and a hepatic component (CLH) that has a metabolic component (CL_M) and a non-metabolic component (CL_S). These individual clearance components can be expressed as fractions of the total clearance as follows:

Renal Fraction $r_R = \frac{CL_R}{CL}$, Hepatic Fraction , $r_H = \frac{CL_H}{CL}$

Metabolic Fraction $r_M = \frac{CL_M}{CL}$, Non-Metabolic Fraction $r_S = \frac{CL_S}{CL}$,

and $CL_H = CL_M + CL_S$ or $r_H = r_M + r_S$

Consideration of an IV dose with linear pharmacokinetics leads to:

Equation 1 $CL = CL_R + CL_M + CL_S = CL_R + CL_H$

Equation 11

Therefore unabsorbed parent (in faeces) = parent in faeces - total parent secreted in faeces =

$$26.4 - 10.2 = \mathbf{16.2\%}$$

Clearly, as a check, absorbed parent is $100 - 16.2 = 83.8\%$, the value of absorption used.

From equation 5, the separate metabolite contributions are calculated:

Equation 12

$$\text{First Pass Metabolite} = (\text{A} - \text{B}) \times \frac{r_M}{r_B} = (83.8 - 33.3) \times \frac{0.649}{0.75} = \mathbf{43.7\%}$$

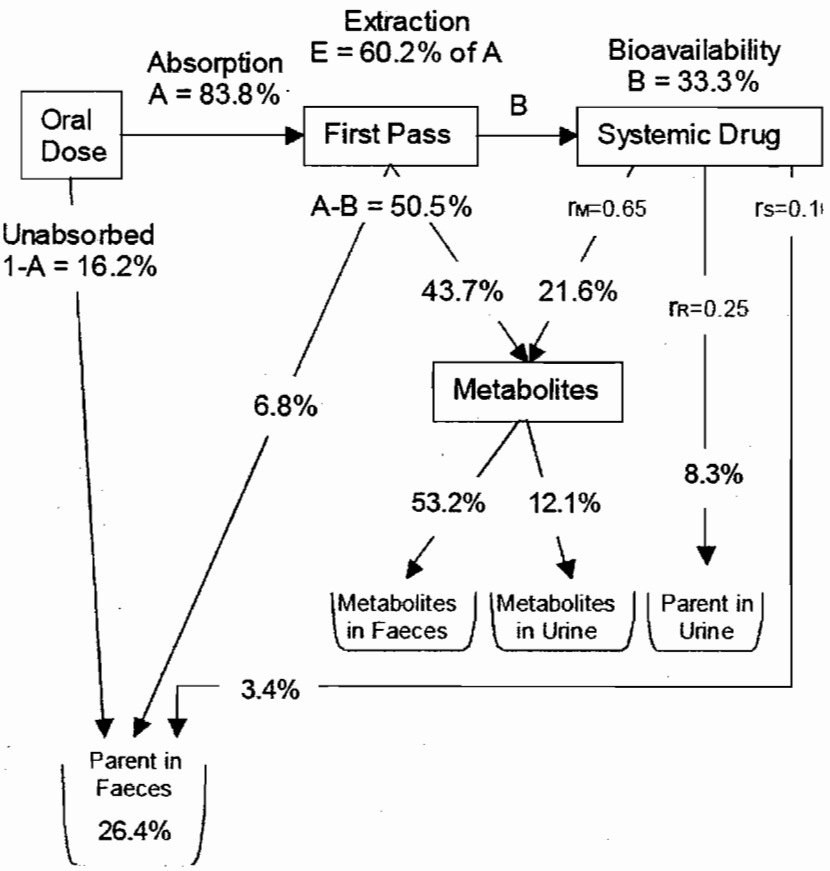
The extraction ratio (E) can be calculated:

Equation 13

$$\text{E} = 1 - \frac{B}{A} = 1 - \frac{33.3}{83.8} = \mathbf{60.2\%};$$

The values obtained above (in bold type in the text) are shown on the 300 mg balance diagram in Figure 2.

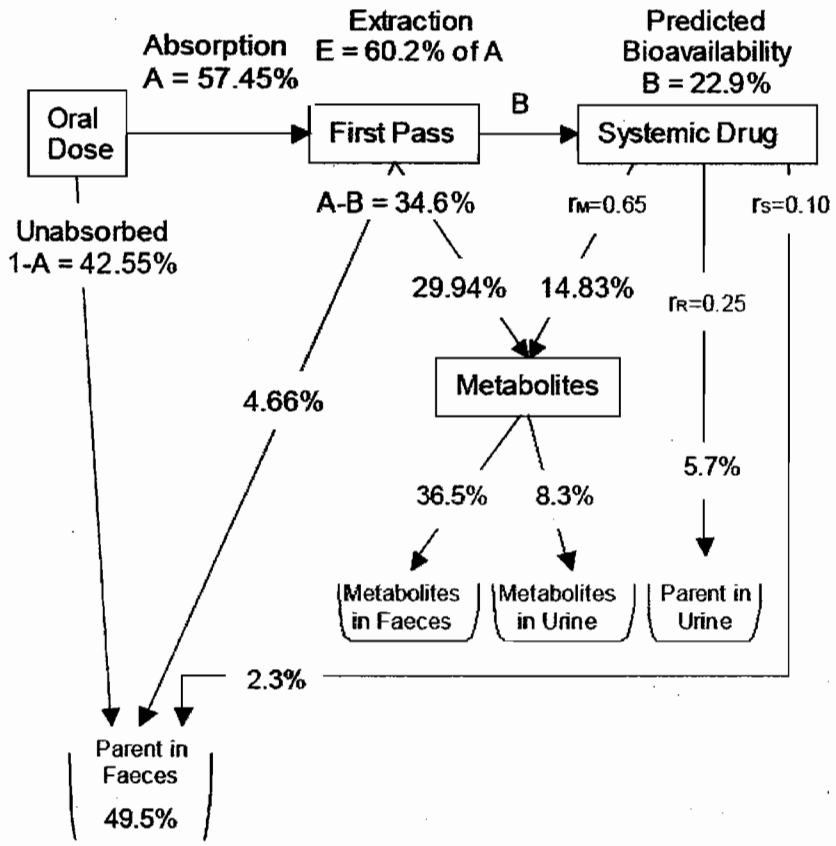
Figure 2 Model of Balance for 300 mg Solution Dose of Maraviroc (UK-427,857)



Mass balance predictions for 100 mg dose:

The mass balance was predicted for 100 mg dose using the same method as for 300 mg with predicted absorption of 57.45% (A) from noncompartmental analysis. Because, after absorption, the pharmacokinetics of both parent and metabolites are assumed to be linear, r_M, r_R, r_S, E, and the ratio of urinary metabolite (sourced from systemic parent and first pass metabolite) to urinary parent will be the same as that for 300 mg dose. The mass balance for 100 mg dose is shown in Figure 3.

Figure 3 Model of Predicted Balance for 100 mg Tablet Dose of Maraviroc (UK-427,857)



The bioavailability estimated from the model shows good agreement with the 23.1% (95% CIs: 19.2%, 27.8%) absolute bioavailability determined from the IV/PO crossover Cohort of study A1001009, comparing 30 mg IV with 100 mg PO tablet.

Using CLR values of 11, 12 and 13 L/h with CL of 48 L/h led to corresponding changes in the clearance ratios, E and bioavailability at 300 mg and 100 mg (Bio300 and Bio100, respectively). A further exploration of the sensitivity was made by assuming the maximum possible absorption (at infinite dose) from the noncompartmental analysis results was only 90% rather than 100%, leading to new estimates of solution absorption at 300 mg (75.42%) and tablet absorption 100 mg (51.71%).

Sensitivity of Balance Values on Changes in Assumed Clearances and Absorption

A_{300} (%)	A_{100} (%)	CL (L/h)	CL_R (L/h)	r_R (%)	r_H (%)	r_M (%)	r_S (%)	E (%)	Bio_{300} (%)	Bio_{100} (%)	Q_B[1] (L/h)
83.8	57.45	48	13	27.1	72.9	63.1	9.8	63.3	30.8	21.1	94
83.8	57.45	48	12	25.0	75.0	64.9	10.1	60.2	33.3	22.9	101
83.8	57.45	48	11	22.9	77.1	66.7	10.4	56.6	36.4	24.9	111
83.8	57.45	44	11	25.0	75.0	64.9	10.1	60.2	33.3	22.9	93
75.4	51.7	48	12	25.0	75.0	73.0	2.0	55.8	33.3	22.9	109

[1] Q_B is liver blood flow calculated from blood:plasma ratio of 0.59, E, CL_R and CL

The use of 90% absorption values, last row of the table, compared to the reference row (underlined), gave identical Bio300 and Bio100. Most parameters changed by approximately 10%, with the exception of r_S, the fraction secreted directly, which was reduced to only 2% from its original 10.1%. Further reduction in absorption would make this an impossible negative value. Under the 90% absorption scenario, this predicted value of Q_B (109 L/h) is a little higher than the quoted physiological reference range of 80-105 L/h and so makes the possibility of only 90% maximum absorption unlikely relative to the more likely scenario of 100% maximum absorption.

Conclusion:

- Estimated absolute bioavailabilty is 33.3% at 300 mg dose.
- Renal clearance accounts for 25% of the total clearance.
- Prediction of hypothetical balance for a 100 mg oral tablet dose of maraviroc produced an absolute bioavailability of 22.9% that was very close to the measured value of 23.1% from the formal IV/PO crossover study A4001009.
- First pass extraction of maraviroc was found to be approximately 60%, predicting maximum possible bioavailability of about 40%.
- Using a reported blood:plasma partition of 0.59, the model prediction of hepatic blood flow was 101 L/h, within the physiological acceptance range, showing overall model assumptions are reasonable.

Population Pharmacokinetics of Maraviroc (UK427,857) After Oral Tablet Administration – A Pooled Analysis of Phase 1/2a Data

Executive Summary: This analysis evaluated the effect of several intrinsic factors (HIV status, gender, race, age, and weight) on maraviroc pharmacokinetics. The analysis indicated HIV status (i.e. whether a subject was infected with HIV-1 or not) age, gender and weight do not affect maraviroc pharmacokinetic parameters. However, no subjects

over the age of 65 years were enrolled. Exposure was 26.5% higher in Asians (N=95, total N in the analysis =362).

Objectives:

- To develop a compartmental structural pharmacokinetic (PK) model to describe rich maraviroc PK data after single and multiple oral dosing with tablet in healthy volunteers and HIV-infected subjects.
- 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 PK of maraviroc.

Study Design and Data: Plasma maraviroc concentration-time data collected from 15 studies in healthy subjects and 2 studies in HIV-infected subjects (A4001007, A4001015) were pooled for the population analysis. Only data obtained following oral administration of tablet doses (at least 100 mg) under fasted (overnight fast and meals at least 4 hours post-dose) or fed (taken with food) conditions were included for the current analysis. For drug interaction studies, only observations with maraviroc alone or maraviroc with placebo were included. A summary of the studies and selected data is shown in Table 1.

Table 1. Maraviroc Phase 1/2a Studies Constituting the Analysis Data Set

Study #	Design	Dose (mg)	Single or Multiple Dosing?	Fed/Fasted	Assay	Subjects	Data to be Used
A4001003	(Oral solution and tablet) open label, randomized, 5-way crossover, relative bioavailability, dose proportionality, food effect	50, 100, 600	Single	Fed/Fasted	LC/MS/MS [redacted]	Healthy Volunteers	Only tablet data with dose>=100mg
A4001004	(Tablet) open label, randomized, 5-way crossover, incomplete block, effect of timing of food	100	Single	Fed/Fasted	LC/MS/MS [redacted]	Healthy Volunteers	Only completely fed/fasted data
A4001005	(Tablet) double-blind, placebo-controlled, randomized, 2-way crossover, oral contraceptive pill interaction	100	Multiple	Fasted	LC/MS/MS [redacted]	Healthy Volunteers (females only)	Only maraviroc with placebo; Day 1 only
A4001006	(Tablet) open label, randomized, placebo-controlled, 2-way crossover, ketoconazole and saquinavir interaction	100	Multiple	Fasted	LC/MS/MS [redacted]	Healthy Volunteers	Only maraviroc with placebo
A4001007	(Tablet) double-blind, parallel group, randomized, placebo-controlled, multicenter, HIV positive subjects	25, 50, 100, 300	Multiple	Fasted	LC/MS/MS [redacted]	HIV-infected Subjects	Only dose>=100mg
A4001011	(Tablet) open label, randomized, placebo-controlled, parallel group, efavirenz and rifampicin interaction with dose-adjustment of maraviroc	100, 200	Multiple	Fasted	LC/MS/MS [redacted]	Healthy Volunteers	Only maraviroc alone or with placebo
A4001013	(Tablet) open label, randomized, placebo-controlled, parallel group, drug interaction with dose adjustment of maraviroc (ritonavir, boosted saquinavir, lopinavir plus ritonavir)	25, 50, 100	Multiple	Fasted	LC/MS/MS [redacted]	Healthy Volunteers	Only maraviroc alone or with placebo; dose >=100mg
A4001015	(Tablet) double-blind, randomized, placebo-controlled,	100, 150, 300	Multiple	Fed/Fasted	LC/MS/MS [redacted]	HIV-infected Subjects	Only maraviroc

	parallel group, multicenter, HIV positive subjects				[redacted]		
A4001016	(Tablet) double-blind, placebo-controlled, randomized, 5-way crossover, QTc	100, 300, 900	Single	Fasted	LC/MS/MS [redacted]	Healthy Volunteers	Only maraviroc alone
A4001018	(Tablet) open label, placebo-controlled, 2-way crossover, randomized, cotrimoxazole interaction	300	Multiple	Fasted	LC/MS/MS [redacted]	Healthy Volunteers	Only maraviroc alone or with placebo
A4001019	(Tablet) double-blind, placebo-controlled, 3rd party open, randomized, parallel group, dose escalation	300-600, 600-900, 900-1200	Multiple	Fasted	LC/MS/MS [redacted]	Healthy Volunteers	Only maraviroc
A4001021	(Tablet) open label, 2-way crossover, randomized, drug interaction (Kaletra, boosted saquinavir, with or without efavirenz	100, 300	Multiple	Fasted	LC/MS/MS [redacted]	Healthy Volunteers	Only maraviroc alone or with placebo
A4001022	(Tablet) open label, placebo-controlled, 2-way crossover, randomized, tenofovir interaction	300	Multiple	Fasted	LC/MS/MS [redacted]	Healthy Volunteers	Only maraviroc alone or with placebo
A4001025	(Tablet) open label, placebo-controlled, 2-way crossover, randomized, atazanavir and ritonavir interaction	300	Multiple	Fasted	LC/MS/MS [redacted]	Healthy Volunteers	Only maraviroc alone or with placebo
A4001038	(Tablet) open label, parallel group, Asian and Caucasian subjects study, 2 centre	300	Single	Fasted	LC/MS/MS [redacted]	Healthy Volunteers	All
A4001040	(Tablet) open label, randomized, 2-way crossover, research & commercial formulation bioequivalence study	300	Single	Fasted	LC/MS/MS [redacted]	Healthy Volunteers	All
A4001043	(Tablet) open label, randomized, 2-way crossover, food effect with commercial formulation	300	Single	Fed/Fasted	LC/MS/MS [redacted]	Healthy Volunteers	All

LLOQ was 0.5 ng/mL for all studies.

Methods: Plasma concentration versus time data were analyzed using a nonlinear mixed-effects modeling approach with the NONMEM software system, version V level 1.1 (GloboMax LLC, Hanover, MD with compiler GNU Fortran (GCC 3.2.3 20030502 (Red Hat Linux 3.2.3-53)) 3.2.3 20030502 (Red Hat Linux 3.2.3-53)) and the NM-TRAN subroutines version III level 1.1, and the PREDPP model library, version IV level 1.1 to estimate the population parameters (mean and inter-subject variability) and identify covariates to explain inter-subject variability in the parameters.

Parent maraviroc concentrations were modeled with a 2-compartment disposition model, with first-order absorption and a lag time on the absorption. Two forms of the 2-compartment model were developed in the course of the analysis:
a) Non-partition model: This is an exploratory model used as the basis for a relatively standard 2-compartment disposition PK model (referred to as the non-partition model) and its base and final covariate model structures were developed accordingly using data from 15 studies that were available in February 2006.
b) Partition model: The non-partition model was then reparameterized to separate absorption and clearance components on bioavailability. This was done to accommodate the needs of future work looking at the effect of interacting drugs on maraviroc PK. A new data set, which incorporates two additional studies that became available in May 2006 (17 studies), was used.

This review focuses on the partition model.

Partition Model Assumptions

- Interacting antiretroviral drugs have an effect on the GI absorption of maraviroc by inhibiting or inducing GI transporters such as P-glycoprotein (P-gp) directly.
- Non-renal clearance was entirely hepatic (CLH). Fixed value of hepatic plasma flow (FQ, 59.59 L/h) was used based on blood:plasma partition ratio R=0.59 and constant hepatic blood flow=101 L/h derived from a previous mass balance analysis of maraviroc.
- The fraction of any absorbed dose that escapes first-pass clearance (maximum oral bioavailability), F_{HEP}, is dependent only on CLH and FQ
- It was assumed that any interacting antiretroviral would have no effect on renal clearance (CLR) and so a fixed value of 12L/h was used for renal clearance (taken from a previous mass balance analysis of maraviroc). Total body clearance was the sum of CLH and CLR. (*Note: Several drug-drug interaction studies showed that CLR tended to increase with CYP3A inhibitors*)

Model Building (CLL) Parameterization **Equation 1**

$$CL_H = FQ \bullet \frac{CLL}{(1+CLL)}$$

Final (E_H) Parameterization

$$CL_H = FQ \bullet E_H$$

$$F_{HEP} = 1 - E_H = 1 - \frac{CL_H}{FQ}$$

$$CL = CL_H + CL_R$$

where CLL is clearance-like parameter for computing hepatic clearance.

- All dose nonproportionality was related to absorption effects (obeying a sigmoid Emax model) and all subsequent maraviroc disposition was entirely linear (i.e. constant clearance and first-pass).
- A limiting high dose would give complete absorption. Therefore the pure absorption component, F_{ABS}, was given as in Equation 2, with the population value of maximum absolute bioavailability $\theta_{F_{ABS-E\max}}$ fixed to 1.

$$F_{ABS} = \frac{\theta_{F_{ABS-E\max}} \bullet GRP^{\theta_{F_{ABS-Hill}}}}{\left(\theta_{F_{ABS-ED50}}{}^{\theta_{F_{ABS-Hill}}} + GRP^{\theta_{F_{ABS-Hill}}}\right)}$$

$$ka = \theta_{ka} \bullet GRP^{\theta_{Dose-ka}}$$ **Equation 2**

where GRP is dose in mg, $\theta_{F_{ABS-Hill}}$ is population value of sigmoidity parameter that describes the steepness of the dose-bioavailability curve, $\theta_{F_{ABS-ED50}}$ is population value of dose at which 50% of absolute bioavailability was achieved, and $\theta_{Dose-ka}$ is power to describe Ka increased as dose increases in a power model.

- The overall absolute bioavailability, F, is given by the product of the amount absorbed (F_{ABS}) and the fraction that escapes first-pass (F_{HEP}) (Equation 3).

$$F = F_{ABS} \bullet F_{HEP}$$ **Equation 3**

Model Development

The previous described 2-compartment model was expanded. Effects of dose and food on bioavailability (F) and absorption rate constant (ka) were considered as part of the base model based on previous modeling work. The effect of dose was shown in Equation 2. For absorption, the food effect was modeled using a multiplicative exponential function on the maximum absolute bioavailability (FABS-Emax) and dose at reach 50% of absolute bioavailability (FABS-ED50), making the assumption that food could reduce the absorption to below 1 even at very high doses as well as produce a right shift in the sigmoid Emax model for FABS (Equation 4).

IF (x.EQ.1) THEN

$$\theta_{F_{ABS\text{-}Emax}} = \theta_{0_{F_{ABS\text{-}Emax}}} \bullet e^{\theta_{xF_{ABS\text{-}Emax}}}$$

$$\theta_{F_{ABS\text{-}EE50}} = \theta_{0_{F_{ABS\text{-}ED50}}} \bullet e^{\theta_{xF_{ABS\text{-}ED50}}}$$

ENDIF

where $\theta_{0FABS\text{-}Emax}$ and $\theta_{0FABS\text{-}ED50}$ denote the population values of the parameters for the null value of fed/fasted status x (i.e. fasted, x = 0). The parameters $\theta x_{FABS\text{-}Emax}$ and $\theta x_{FABS\text{-}ED50}$ denote the fractional (approximate through the exponential) change in $\theta_{0FABS\text{-}Emax}$ and $\theta_{0FABS\text{-}ED50}$, respectively, when x =1.

Inter-subject variability was examined after the inclusion of the dose and food effects on ka and F. Inter-subject variability in the pharmacokinetic parameters was modeled using multiplicative exponential random effects. Residual variability was modeled by a continuous time after the dose (TAD) dependent error variance on the log transformed concentrations. Diagonal variance/covariance matrices for the inter-subject random effects were utilized.

Additional covariates were then added to appropriate parameters in the base model. Dichotomous covariates examined were sex, race and HIV status (HIV positive or HIV negative). Continuous covariates examined were age and weight.

A forward selection/backward elimination algorithm was performed to select a predictive, parsimonious (final) model ($p<0.001$, $\Delta OFV=10.83$). A deviation from the population modeling analysis plan (PMAP) was that a smaller α level (e.g. $\alpha = 0.001$, $\Delta OFV=10.83$ instead of $\alpha = 0.05$, $\Delta OFV=3.84$) was used for the forward selection algorithm because of the few covariates being tested on almost all major pharmacokinetic parameters.

The necessity for interoccasion variability (IOV) was addressed by an indirect method. If inclusion of inter-subject variability for residual error produced no obvious deviation in any estimated parameters and if it did not substantially differ between subjects with one and more than one occasion, it could be concluded that IOV is relatively unimportant in the current analysis and does not need to be addressed further.

Validation

The predictive performance of the final pharmacokinetic models was assessed by the similarity of the 95% degenerative tolerance intervals of 100 simulated data sets with the observed data. Precision of the final model parameter estimates was assessed by the 95% confidence intervals of 1000 non-parametric bootstrapping of the original data set. At all stages of model development, diagnostic plots were examined for model adequacy, possible lack of fit, or violation of assumptions.

Results: The study designs of the 17 Phase 1/2a trials are adequate for the population PK/PD analysis. The data integrity and model building process are acceptable.

Data

Number of subjects and number of observations from 17 studies are summarized in Table 2. The demographics of the subjects included in the dataset are showed in Table 3. Black subjects accounted for 3.9% of the subjects in the analysis.

Table 2. Number of Subjects and Number of Observations in the Data Set for Non-Partition Model Analysis, by Study

Study	Number of Subjects	Number of Observations
A4001003	15	660
A4001004	15	511
A4001005	15	298
A4001006	24	598
A4001007	16	387
A4001011	36	910
A4001013	32	558
A4001015	33	543
A4001016	61	1061
A4001018	13	194
A4001019	27	861
A4001021	28	722
A4001022	11	132
A4001025	12	300
A4001038	24	288
Total	362 (49)	8023 (930)
Shaded values = data from HIV positive subjects; Values in parenthesis = number of HIV positive subjects/observations		

Table 3. Demographics for Non-Partition Model Analysis

Gender	N	%
Female	83 (2)	22.9
Male	279 (47)	77.1
Race	N	%
Caucasian	307 (47)	84.8
Black	14 (1)	3.9
Asian	39	10.8
Others	2 (1)	0.6
HIV Status	N	%
Healthy volunteers	313	86.5
Subjects with HIV	49	13.5
	Median	Range
Age (Years)	31	18-53
Weight (kg)	72	50-109
Values in parenthesis = number of HIV positive subjects		

Final Partition Model Results

A NONMEM control stream for the final models is shown in Appendix 1. The results of identification of covariates based on the forward selection/backward elimination algorithms are shown in Appendix 2. The final parsimonious model selected by the forward selection/backward deletion procedure included covariate effects for race on CLL(clearance-like parameter for computing hepatic clearance), V3, Q and age on Q.

The following table shows the parameters from the final model and bootstrap. The means and medians of the bootstrap values are in good agreement with the final model parameters.

	Final Model (Run 262)		1000 Bootstrap Run Statistics					
	Parameter	%SE	Mean	SD	%CV	Median	Lower2.5%	Upper97.5%
CL (L/h)	51.46[a]							
E_H (θ_1)	0.662	(1.5)	0.66	0.01	1.52	0.66	0.64	0.68
Race (θ_{20})	-0.0948	(15.0)	-0.09	0.01	13.77	-0.09	-0.12	-0.07
V_2 (L) (θ_2)	132	(2.7)	131.6	3.08	2.34	132	125	137
Q (L/h) (θ_3)	16.4	(3.9)	16.27	0.57	3.52	16.3	15.1	17.3
Race (θ_{21})	-0.298	(17.7)	-0.29	0.05	15.82	-0.30	-0.39	-0.20
Age (θ_{19})	0.349	(28.3)	0.35	0.09	26.21	0.35	0.16	0.54
V_3 (L) (θ_4)	277	(4.2)	276.07	10.13	3.67	277	258	296
Race (θ_{22})	-0.637	(8.5)	-0.63	0.05	7.35	-0.64	-0.72	-0.53
ka (h^{-1}) (θ_5)	0.277	(21.0)	0.28	0.06	20.64	0.28	0.18	0.40
Dose (θ_{15})	0.173	(22.9)	0.18	0.04	22.82	0.17	0.11	0.26
Food (θ_{18})	0.547	(18.6)	0.56	0.10	17.95	0.56	0.36	0.75
$F_{ABS\text{-}Emax}$ (θ_{11})	1 FIX							
Food (θ_{16})	-0.258	(27.3)	-0.24	0.09	36.23	-0.24	-0.38	0.00
$F_{ABS\text{-}ED50}$ (θ_{12})	51.2	(12.8)	50.82	8.06	15.87	51.5	31.1	64.7
Food (θ_{17})	0.594	(34.5)	0.66	0.41	62.46	0.59	0.23	2.19
$F_{ABS\text{-}Hill}$ (θ_{13})	1.39	(15.3)	1.38	0.30	21.9	1.39	0.69	1.99
Tlag (θ_6)	0.198	(4.1)	0.20	0.01	4.13	0.20	0.18	0.21
FQ (L/h) (θ_{14})	59.59 FIX							
σ_{Prop} (θ_7)	74.2	(3.9)	74.59	2.43	3.26	74.4	69.9	79.7
σ_{Tmax} (θ_8) (h)	0.950	(8.8)	0.95	0.08	8.35	0.95	0.80	1.12
σ_{EK} (θ_9)	0.403	(6.4)	0.40	0.02	5.99	0.40	0.35	0.45
σ_{Base} (θ_{10}) (%)	20.2	(3.3)	20.0	0.66	3.28	20.0	18.7	21.4
$\omega_1[F_{ABS\text{-}ED50}]$ (%)	58.9	(32.6)[b]	61.17	15.03	24.57	58.91	38.15	102.96
$\omega_2[E_H]$ (%)	8.3[c]	(11.0)[b]	8.27	0.43	5.22	8.27	7.41	9.11
$\omega_3[V_2]$ (%)	11.5	(77.3)[b]	8.92	5.64	63.21	10.3	0.00	17.41
$\omega_4[Q]$ (%)	30.5	(22.7)[b]	29.8	3.41	11.45	30.36	22.36	35.78
$\omega_5[ka]$ (%)	40.0	(13.9)[b]	39.92	2.59	6.48	40.0	34.35	44.72
$\omega_6[V_3]$ (%)	27.8	(21.2)[b]	27.23	2.89	10.63	27.36	21.66	34.06

[a] Refer to Equation 1
[b] % standard error on ω^2
[c] $(1\text{-}E_H)*SQRT(\omega^2)$

Effects of dose, food, and race on F (FHEP and FABS), AUC and ka are summarized in Table 12. The overall race effect on clearance and volume resulted in a 26.5% increase in AUC for Asian subjects. The overall food effect on FABS resulted in a decrease in AUC. The effect of food was largest at 100 mg (43% reduction) reaching a plateau (approximately 25% reduction) at about 600 mg.

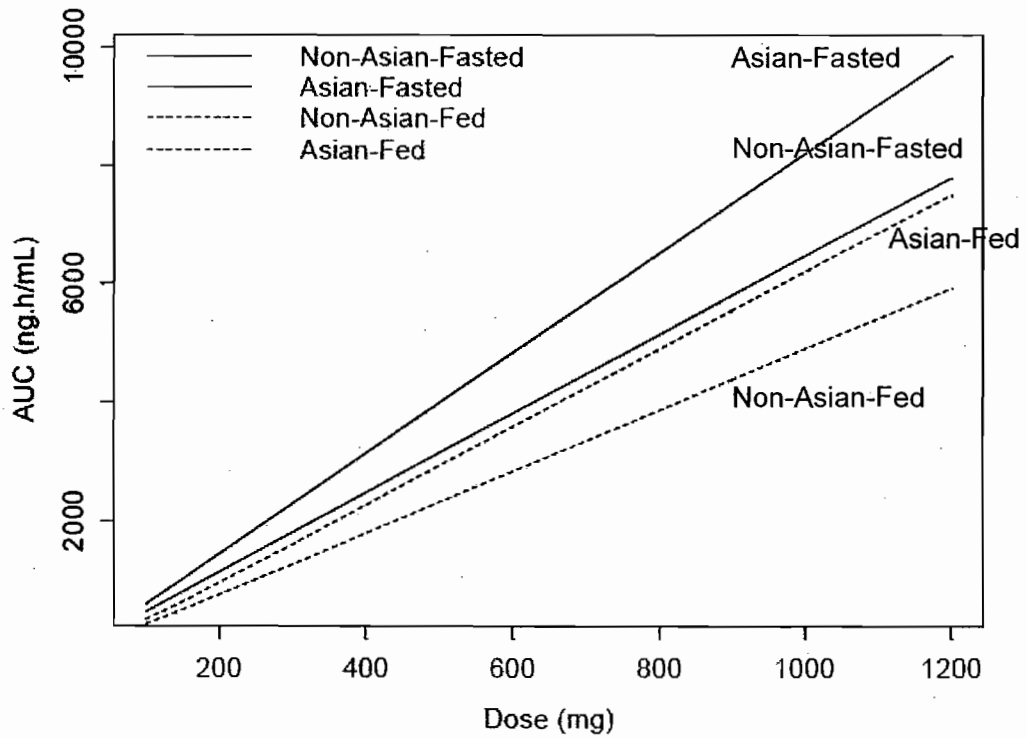
Table 12. Dose, Food and Race Effects on Clearance, AUC and Absorption Rate Constant Based on Population Parameter Estimates of the Final Partition Model

Fasted		Non-Asian					Asian					AUC Ratio	
Dose (mg)	ka (1/h)	CL (L/h)[a]	F_{HEP}	F_{ABS}	F	AUC (ng.h/ml)	CL (L/h)[a]	F_{HEP}	F_{ABS}	F	AUC (ng.h/ml)	Asian/ Non-Asian	Fed/ Fasted
100	0.614	51.45	0.338	0.717	0.242	471	47.88	0.398	0.717	0.285	596	1.265	0.567
150	0.659	51.45	0.338	0.817	0.276	805	47.88	0.398	0.817	0.325	1018	1.265	0.625
300	0.743	51.45	0.338	0.921	0.311	1815	47.88	0.398	0.921	0.366	2296	1.265	0.702
600	0.838	51.45	0.338	0.968	0.327	3817	47.88	0.398	0.968	0.385	4828	1.265	0.742
900	0.899	51.45	0.338	0.982	0.332	5805	47.88	0.398	0.982	0.391	7342	1.265	0.755
1200	0.944	51.45	0.338	0.988	0.334	7787	47.88	0.398	0.988	0.393	9849	1.265	0.76
Fed													
100	0.336	51.45	0.338	0.407	0.137	267	47.88	0.398	0.407	0.162	338	1.265	-
150	0.361	51.45	0.338	0.511	0.173	503	47.88	0.398	0.511	0.203	637	1.265	-
300	0.406	51.45	0.338	0.646	0.218	1274	47.88	0.398	0.646	0.257	1611	1.265	-
600	0.458	51.45	0.338	0.719	0.243	2834	47.88	0.398	0.719	0.286	3585	1.265	-
900	0.492	51.45	0.338	0.741	0.250	4382	47.88	0.398	0.741	0.295	5543	1.265	-
1200	0.517	51.45	0.338	0.751	0.254	5922	47.88	0.398	0.751	0.299	7491	1.265	-

[a] $CL=FQ*E_H+CL_R$ (FQ fixed to 59.59 L/h and CL_R fixed to 12 L/h)

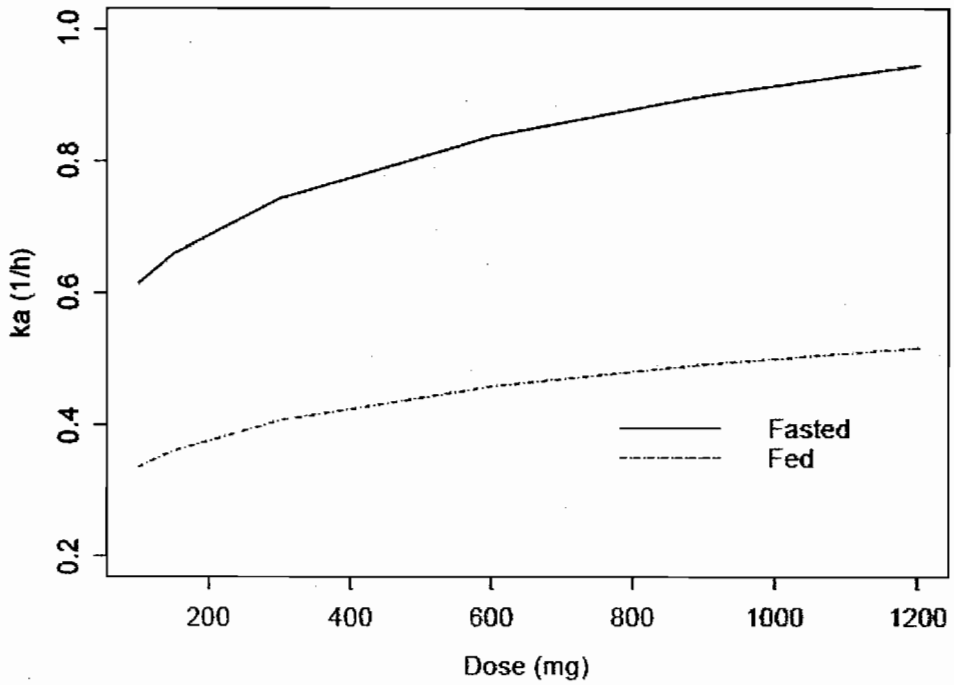
The relationship of dose and AUC for Non-Asians and Asians under fed and fasted Conditions are presented in Figure 6. The dose-AUC relationship appears almost linear because all the doses included in the analysis were above the estimated FABS-ED50 of 58 mg.

Figure 6. Relationship of Dose and AUC for Non-Asians and Asians Under Fed and Fasted Conditions



The relationship of dose and absorption rate constant (ka) under fed and fasted Conditions are presented in Figure 7.

Figure 7. Relationship of Dose and Absorption Rate Constant (ka) under Fed and Fasted Conditions



Evaluation of AUC Predictions

The *post hoc* AUCs (geometric means) showed a systematic difference (median 13% underprediction across studies with a range of 34% underprediction to 38% overprediction) when compared with the non-compartment analysis of AUCs in the clinical study reports (Table 16). The difference occurs, in part, because *post hoc* AUCs do not include the residual variability component. While the residual error (ε) is assumed to be normally distributed around the log-transformed concentration, AUCs are calculated based on untransformed concentrations.

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Table 16 Comparisons of *Post Hoc* and Clinical Study Reports AUCs

Dose (mg)	Fed/Fasted Status	Study	Non-Asian Study Report		*Post Hoc*[a]		Asian Study Report		*Post Hoc*[a]	
			AUC	(n)	AUC	Ratio	AUC	(n)	AUC	Ratio
100	Fasted	1003	576	(15)	522	0.91	--		--	--
		1004	491	(14)	426	0.87	--		--	--
		1005	466	(15)	483	1.04	--		--	--
		1006	487	(12)	458	0.94	487[c]		448[d]	0.92
			619[b]			0.74	619[c]			
		1007	425	(8)	450	1.06	--		--	--
			454[b]							
		1011	550[b]	(12)	520	0.95	550[c]		511[d]	0.93
		1013	597[b]	(8)	515	0.86	--		--	--
		1015	571[b]	(9)	499	0.87	--		--	--
		1016	396	(60)	435	1.10	396[c]		548[d]	1.38
		1021	486[b]	(11)	443	0.91	--		--	--
			543[b]			0.82				
	Fed	1004	230	(11)	244	1.06	--		--	--
300	Fasted	1007	2260	(8)	1768	0.78	--		--	--
			2550[b]							
		1015	2264[b]	(8)	1967	0.87	--		--	--
		1016	1840	(59)	1772	0.96	1840[c]		1873[d]	1.02
		1018	3020[b]	(13)	2184	0.72	--		--	--
		1019	1896	(9)	1452	0.77	--		--	--
			2120[b]			0.68				
		1021[e]	2570[b]	(11)	1703	0.66	2570[c]		2545[d]	0.99
			2450[b]			0.70	2450[c]			1.04
		1022	--		--	--	3490[b]	(11)	2549	0.73
		1025[e]	2790[b]	(12)	2234[d]	0.80	2790[c]		2157	0.77
			2610[b]			0.86	2610[c]			
		1038	2680	(12)	2214	0.83	2640	(12)	2335	0.88
		1040[e]	--		--	--	2720	(42)	2291	0.84
							2760			0.83
		1043	--		--	--	3117	(12)	2467	0.79
	Fed	1043	--		--	--	2084	(12)	1714	0.82

[a] *Post hoc* of 413 subjects
[b] Obtained from steady state profile
[c] AUC not stratified by race
[d] Only 1 subject
[e] Multiple reference arms
n = number of subjects

Conclusion:

- The pharmacokinetics of maraviroc after oral tablet administration is described by a 2-compartment model with first-order absorption and a lag time on absorption. A semi-physiological model was used to partition bioavailability into extent of absorption (FABS) and first-pass elimination effect (FHEP). Dose effect on FABS was modeled with a sigmoid Emax function and a power function for ka.
- Population pharmacokinetic parameters for the typical individual (a non-Asian 30-year old subject) from the partition model using EH parameterization are as follows: CL=51.45 L/h, hepatic extraction ratio (E_H) =0.662, Volume (central) =132 L and Volume (peripheral) =277 L
- Statistically significant covariate effects that have an influence on exposure are:

- Dose: Bioavailability increases asymptotically as dose increases from 0.24 at 100 mg to 0.31 at 300 mg and to a constant 0.33 at 600 mg and above in the fasted state.
- Food: A high fat meal taken with a maraviroc dose reduces the exposure (AUC) by 43% for a dose of 100 mg through effects on bioavailability. This reduces to a constant food effect of approximately 25% reduction in AUC at doses of 600 mg and above.
- Race effect: The typical Asian subject has a 26.5% higher AUC than the typical non-Asian subject irrespective of dose.

- In the final model a statistically significant age effect was found on apparent inter-compartmental clearance (Q) but this has no impact on exposure. Weight and HIV status were not found to influence any of the pharmacokinetic parameters on which they were tested.

3 Page(s) Withheld

b Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

Appendix 2: Model Forward Selection and Backward Elimination Algorithm Results

Model/Base	Covariate	ΔOFV (p-value) Forward Step 1	ΔOFV (p-value) Forward Step 2	ΔOFV (p-value) Forward Step 3	ΔOFV (p-value) Forward Step 4	ΔOFV (p-value) Forward Step 5	ΔOFV (p-value) Forward Step 6	ΔOFV (p-value) Backward Step 7	ΔOFV (p-value) Backward Final
CLL	Weight	-2.918 (0.088)	-4.228 (0.040)	-1.475 (0.225)	-2.142 (0.143)	-2.290 (0.130)	-0.970 (0.325)	Not Included	
	Age	-0.046 (0.830)	-0.051 (0.821)	-0.418 (0.518)	-0.310 (0.578)	-0.228 (0.633)	-0.096 (0.757)	Not Included	
	Sex	-0.729 (0.393)	-0.258 (0.611)	-0.085 (0.771)	-0.114 (0.736)	-0.179 (0.672)	-0.009 (0.924)	Not Included	
	Race	0.197 (0.657)	-30.606 (<0.001)	-4.945 (0.026)	-14.238 (<0.001)	-13.966* (<0.001)	Included	13.966 (<0.001)	45.987 (<0.001)
	HIV Status	-0.023 (0.879)	-0.211 (0.646)	-0.383 (0.536)	-0.062 (0.803)	-0.012 (0.913)	-0.058 (0.810)	Not Included	
V_2	Weight	-0.102 (0.749)	-0.017 (0.896)	-0.049 (0.825)	-0.043 (0.836)	-0.028 (0.867)	-0.051 (0.821)	Not Included	
	Age	-3.787 (0.052)	-4.646 (0.031)	-4.385 (0.036)	-4.238 (0.040)	-2.585 (0.108)	-3.264 (0.071)	Not Included	
	Sex	-0.258 (0.611)	-0.051 (0.821)	-0.015 (0.903)	-0.051 (0.821)	-0.108 (0.742)	-0.045 (0.832)	Not Included	
	Race	-0.993 (0.319)	-3.383 (0.066)	-3.692 (0.055)	-2.006 (0.157)	-2.015 (0.156)	-10.670 (0.001)	Not Included	
	HIV Status	-9.011 (0.003)	-8.294 (0.004)	-9.022 (0.003)	-8.050 (0.005)	-7.541 (0.006)	-9.002 (0.003)	Not Included	
Q	Weight	-11.264 (<0.001)	-13.642 (<0.001)	-13.889 (<0.001)	-6.864 (0.009)	-5.188 (0.023)	-4.797 (0.029)	Not Included	
	Age	-16.583 (<0.001)	-20.069 (<0.001)	-20.171 (<0.001)	-14.801* (<0.001)	Included	Included	14.530 (<0.001)	14.499 (<0.001)
	Sex	-5.532 (0.019)	-4.975 (0.026)	-5.003 (0.025)	-5.646 (0.017)	-6.365 (0.012)	-5.890 (0.015)	Not Included	
	Race	-7.634 (0.006)	-19.788 (<0.001)	-20.777* (<0.001)	Included	Included	Included	23.814 (<0.001)	28.709 (<0.001)
	HIV Status	-0.433 (0.511)	-0.061 (0.805)	-0.019 (0.890)	-1.438 (0.230)	-6.081 (0.014)	-6.239 (0.012)	Not Included	
V_3	Weight	-16.372 (<0.001)	-0.289 (0.591)	-0.379 (0.538)	-0.159 (0.690)	-0.213 (0.644)	-0.264 (0.607)	Not Included	
	Age	-7.210 (0.007)	-0.393 (0.531)	-0.496 (0.481)	-0.330 (0.566)	-2.425 (0.119)	-2.449 (0.118)	Not Included	
	Sex	-4.816 (0.028)	-0.691 (0.406)	-0.992 (0.319)	-0.503 (0.478)	-0.427 (0.513)	-0.548 (0.459)	Not Included	
	Race	-88.033* (<0.001)	Included	Included	Included	Included	Included	106.135 (<0.001)	111.978 (<0.001)
	HIV Status	-4.452 (0.035)	-0.463 (0.496)	-0.253 (0.615)	-0.320 (0.577)	-0.091 (0.763)	-0.033 (0.856)	Not Included	
$F_{ABS-HIR}$	Weight	-0.001 (0.975)	-0.004 (0.950)	-0.002 (0.964)	0.000 (>0.999)	0.000 (>0.999)	0.000 (>0.999)	Not Included	
	Age	-0.001 (0.975)	-0.004 (0.950)	-0.002 (0.964)	0.000 (>0.999)	0.000 (>0.999)	0.000 (>0.999)	Not Included	
	Sex	-1.911 (0.167)	-1.691 (0.193)	-0.953 (0.329)	-0.905 (0.341)	-0.921 (0.337)	-0.961 (0.327)	Not Included	
	Race	-39.213 (<0.001)	-35.534* (<0.001)	Included	Included	Included	Included	4.463 (0.035)	Not Included
	HIV Status	-0.415 (0.519)	-0.612 (0.434)	-0.039 (0.843)	-0.010 (0.920)	-0.001 (0.975)	-0.008 (0.929)	Not Included	
$F_{ABS-ED50}$	Weight	-0.001 (0.975)	-0.004 (0.950)	-0.002 (0.964)	0.000 (>0.999)	0.000 (>0.999)	0.000 (>0.999)	Not Included	
	Age	-0.001 (0.975)	-0.004 (0.950)	-0.002 (0.964)	0.000 (>0.999)	0.000 (>0.999)	0.001 (0.975)	Not Included	
	Sex	-0.008 (0.929)	-0.008 (0.929)	-0.034 (0.854)	-0.013 (0.909)	-0.013 (0.909)	-0.014 (0.906)	Not Included	
	Race	-30.328 (<0.001)	-26.750 (<0.001)	-0.387 (0.534)	-0.446 (0.504)	-0.452 (0.501)	-0.073 (0.787)	Not Included	
	HIV Status	-1.142 (0.285)	-1.403 (0.236)	-0.051 (0.821)	-0.089 (0.765)	-0.199 (0.656)	-0.106 (0.745)	Not Included	

* Parameter included in the model for the next step
Selection criterion: ΔOFV > 10.83 (p-value < 0.001)

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4.2.5 Exposure-Response Relationship

A Randomised, Double Blind, Placebo-Controlled, Multicentre Study Of UK-427,857 25mg QD, 50mg Bid, 100mg BID and 300mg BID in Asymptomatic HIV Infected Patients to Investigate Pharmacodynamics, Pharmacokinetics, Safety and Toleration (Study A4001007)

Objectives:

- To demonstrate that short-term UK-427,857 monotherapy decreased plasma viral load in HIV infected subjects;
- To assess the pharmacokinetic/ pharmacodynamic relationship by determining the correlation of plasma viral load decline with plasma drug concentration, CC chemokine receptor 5 (CCR5) saturation and *in vitro* antiviral IC50/90;
- To assess the safety and tolerability of UK-427,857 in HIV infected subjects.

Study Design: This was a randomized, double blind, placebo controlled 10 day monotherapy study to compare placebo with UK-427,857 25mg QD and 100mg BID. Following a pre-planned interim analysis UK-427,857 50mg BID and 300mg BID and an additional placebo were added to define more complete dose response curve. Only water was permitted for one hour after the morning dose and a large meal was not allowed in the two hours before and one hour after the evening dose.

Population: Asymptomatic HIV-infected males or surgically sterilized females aged 18 to 55 years inclusive with a weight between 50 and 90kg and a Quetelet's index (Body Mass Index, BMI) -weight (kg)/height² (m) between 18-28 were enrolled.

	UK-427,857				Placebo
	25mg QD	50mg BID	100mg BID	300mg BID	
Subjects screened 77					
Entered study.....45	9	8	8	8	12
Completed study	8	8	8	8	12
Evaluated for pharmacokinetics	9	8	8	8	0
Evaluated for efficacy	8	8	8	8	12
Assessed for safety					
Adverse events	9	8	8	8	12
Laboratory tests	9	8	8	8	12

QD=once daily; BID=twice daily

Formulation: UK-427,857 was supplied as 25mg tablets [formulation identification (FID) No. S01229AA; Lot No. 354 (9255-070)] and matching placebo tablets [FID No. S01232AA; Lot No. 400 (9255-073)], 50mg tablets [FID No. S01163AA; Lot No. 41 (8625-171)] and matching placebo tablets [FID No. S01169AA; Lot No. 167 (9255-003)], 100mg tablets [FID No. S01165AA; Lot No. 43 (8625-172)] and matching placebo tablets [FID No. S01173AA; Lot No. 480 (9522-004)] and 150mg tablets [FID No. S01167AA; Lot No. 33 (8625-173)] and matching placebo tablets [FID No. S01186AA; Lot No. 166 (8625-193)]. Doses were allocated by the double dummy method.

Pharmacokinetic Measurement: Blood samples were collected for plasma UK-427,857 concentration assay at pre-morning dose and 1, 2, 4, 6, 8 and 12 hours post-dose on Day 1, pre-morning dose on Days 2 to 9 and pre-morning dose and 1, 2, 4, 6, 8, 12, 48, 72 and 120 hours post-dose on Day 10.

Pharmacodynamic Measurement: Blood samples were taken pre-dose and at specified times post-dose to measure viral load, viral tropism, susceptibility and CCR5 saturation. Blood

samples were taken at specified times to evaluate the effect of UK-427,857 on immune effector cells. A blood sample was collected for CCR5 delta 32 (CCR5Δ32) mutation genotyping.

Analytical methods: Plasma concentrations of maraviroc (UK-427,857) were determined by a validated LC/MS/MS method. All samples were analyzed within the demonstrated matrix and storage stability period. As shown in the following table, the analytical methods are acceptable.

Analytical methods for maraviroc

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
maraviroc (plasma)	0.5 – 200 (R^2 >0.9)	≤5.7	-5.6 to 9.3	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.

Results:

The following table summarizes the pharmacokinetic data for the four UK-427,857 doses.

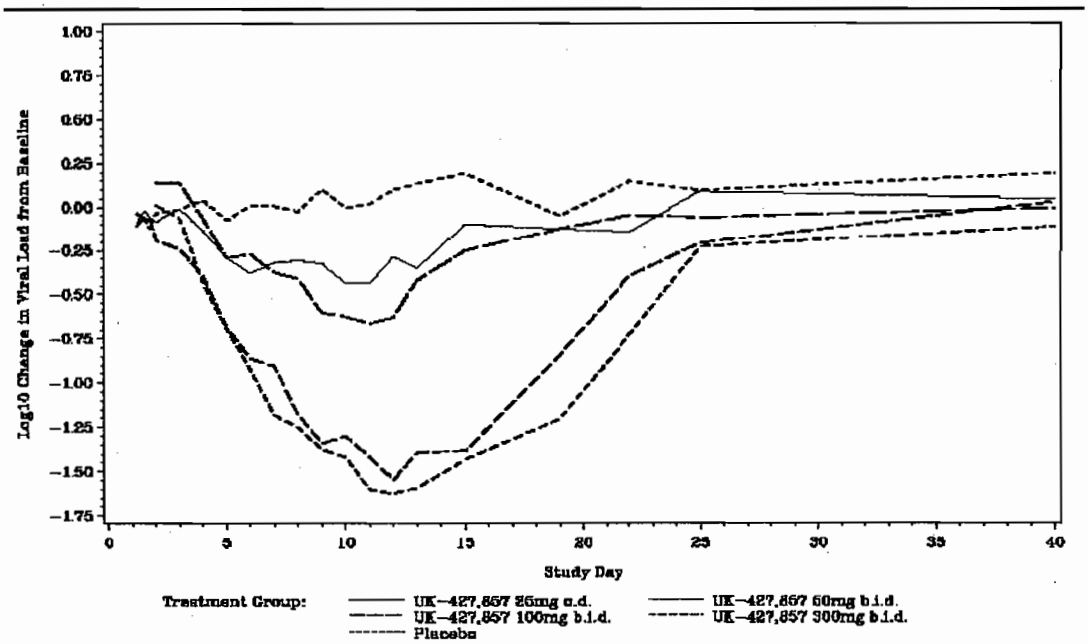
Parameter	UK-427,857			
	25mg QD N=9	50mg BID N=8	100mg BID N=8	300mg BID N=8
Day 1				
AUC_{0-12} (ng.h/ml)[a]	47.2	173	425	2260
C_{max} (ng/ml)[a]	9.65	42.2	112	585
T_{max} (h)[b]	2.78	3.38	3.25	2.88
Day 10				
AUC_{0-12} (ng.h/ml)[a]	44.1	142	454	2550
C_{max} (ng/ml)[a]	6.87	27.7	104	618
C_{min} (ng/ml)[a]	0.748	3.83	10.5	33.6
T_{max} (h)[b]	4.25	2.88	3.25	3.13
$t_{1/2}$(h)[b]	-	15.9	16.2	22.9

[a]unadjusted geometric mean; [b]unadjusted arithmetic mean.

There was no apparent UK-427,857 accumulation at any dose. Steady state was reached after approximately four days. All subjects who received 100 and 300mg BID had trough plasma UK-427,857 concentrations above the mean antiviral IC90 of primary isolates in peripheral blood mononuclear cells at steady state.

Figure 1 shows the mean Log10 viral load change from Days 1 to 40 for each UK-427,857 dose and placebo for evaluable subjects (excluding Subject 10021112 who was R5/X4 tropism at baseline in 100 mg BID arm). The figure shows that UK-427,857 100 and 300mg BID produced a large and similar decrease in viral load and that 25mg QD and 50mg BID doses produced a sub-optimal decrease. The data show it took longer for viral load to return to baseline concentrations after UK-427,857 100 and 300mg BID than after 25mg QD and 50mg BID and rebound took longer after all UK-427,857 doses than after placebo.

Figure 1 Mean plot of Log10 viral load change from Days 1 to 40



The following table shows the mean change in viral load for each UK-427,857 dose compared to placebo and the 90% CIs for the comparison with Subject 10021112 data excluded and included. No adjustment was made for multiple comparisons.

	Subject 10021112 included		Subject 10021112 excluded	
	Difference	90% CI	Difference	90% CI
25mg QD v Placebo	-0.455	-0.831, -0.079	-0.455	-0.776, -0.133
50mg BID v Placebo	-0.684	-1.061, -0.308	-0.684	-1.006, -0.363
100mg BID v Placebo	-1.220	-1.596, -0.844	-1.439	-1.774, -1.104
300mg BID v Placebo	-1.624	-2.001, -1.248	-1.624	-1.946, -1.303

Figure 2 shows the scatter plot of change in Log 10 viral load at Day 11 versus Day 10 trough plasma concentration. The data indicated greater viral load reduction with higher trough plasma concentrations.

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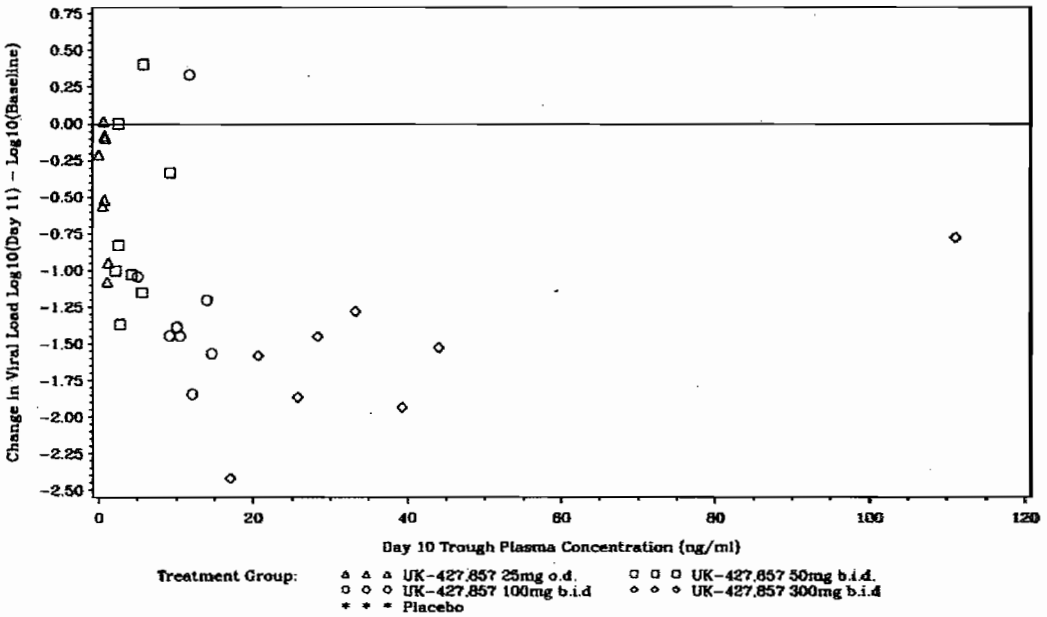
Figure 2 Scatter Plot of Change in Log 10 Viral Load at Day 11 versus Day 10 Trough Plasma Concentration

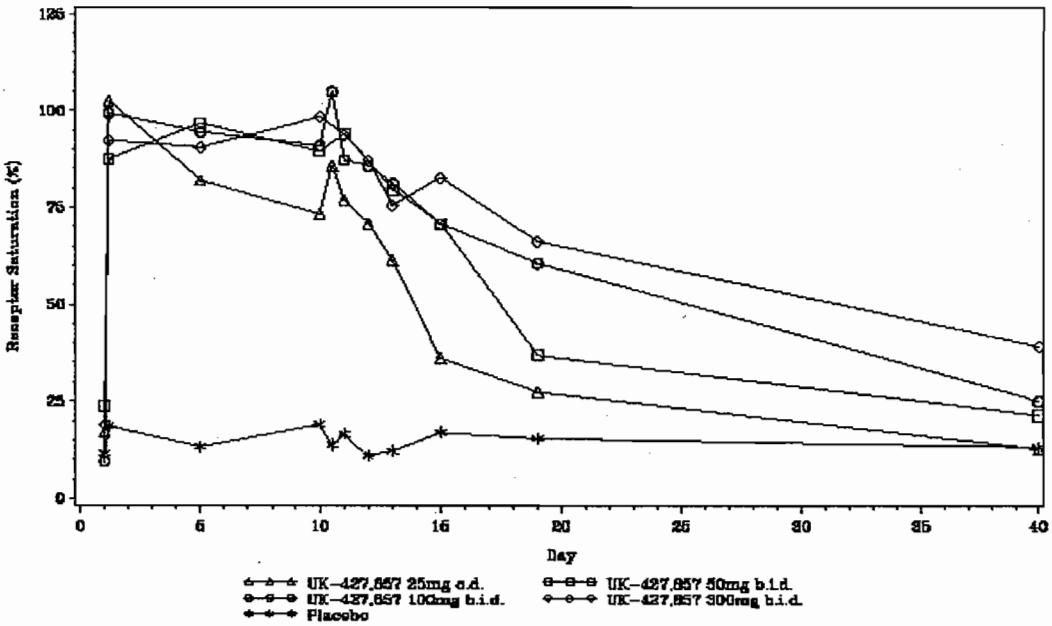


No subjects had a change in virus tropism from baseline. Evaluation of the viral tropism data from Subject 10021112 on Days 1, 11 and 40 indicated that a significant decrease in the CCR5 tropic component of the virus on Day 11. However, by Day 40, the CCR5/CXCR4 virus ratio was similar to what it was pre-dose on Day 1 indicating reversible of CCR5 tropic component after stopping UK-427,857.

Evaluating data obtained from the recombinant entry assay, there were no apparent changes in susceptibility to UK-427,857 over time using the currently available assay methodology.

Mean CCR5 saturation was >90% pre-dose on Days 5 and 10 after UK-427,857 50, 100 and 300mg BID and was approximately 80% pre-dose on Day 10 after UK-427,857 25mg QD. Figure 2 shows the mean % CCR5 saturation for each UK-427,857 dose and placebo.

Figure 2 Mean CCR5 receptor saturation by treatment group



The most common treatment related adverse events were headache, dizziness and asthenia. Most adverse events were mild and none were severe. There was no clear relationship between adverse event incidence and UK-427,857 dose. UK-427,857 did not have any clinically significant effect on blood pressure or pulse rate in the studied dose range.

Conclusion:

- All doses of UK-427,857 produced a viral load decrease that was statistically significantly superior to placebo at the two-sided 10% level, specified in the protocol. The 100 and 300mg BID doses produced a large decrease in viral load and 25mg QD and 50mg BID doses produced a sub-optimal decrease. Viral load took longer to return to baseline concentrations after 100 and 300mg BID than after 25mg QD and 50mg BID and took longer after all UK-427,857 doses than after placebo.
- UK-427,857 absorption was rapid but variable after single and multiple dosing. There was no evidence of UK-427,857 accumulation at any dose. Steady state was reached after approximately four days. All subjects who received 100 and 300mg BID had trough plasma UK-427,857 concentrations above the mean antiviral IC90 of primary isolates in peripheral blood mononuclear cells at steady state.
- There were no discontinuations, no dose related adverse events and no clinically significant laboratory test result abnormalities after UK-427,857 administration up to and including 300mg BID.

An Investigation into the Effects of Food and Dose Regimen on Viral Load Response in HIV Infected Patients on Short-Term Monotherapy with UK-427,857 (Study A4001015)

Objectives: 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 (PK-PD) relationships in HIV infected subjects on short-term UK-427,857 monotherapy, and to assess the safety and tolerability.

Study Design: This is a randomized, double blind, placebo controlled, multicenter, five treatment, parallel group study. Subjects were randomized to receive UK-427,857 150mg BID fasted, 150 mg BID fed, 100mg QD fasted or 300mg QD fasted or matching placebo for 10 days.

Formulation: UK-427,857 was supplied as 50mg tablets [formulation identification (FID) No. S01163AA; Lot No. 9255-189] and matching placebo tablets (FID No. S01169AA; Lot No. 9255-003); as well as 100mg tablets (FID No. S01165AA; Lot No. 9255-190) and matching placebo tablets (FID No. S01173AA; Lot No. 9255-004).

Pharmacokinetic and Pharmacodynamic Measurement: Blood samples (4ml) for UK-427,857 were collected at pre-morning dose on Days 1 to 11 and also at 1, 2, 3, 4, 6, 8, 12 and 24 hours post-dose on Day 10.

Parameters comprised viral tropism, susceptibility and CCR5 saturation. Blood samples were taken at specified times to evaluate the effect of UK-427,857 on immune effector cells.

Analytical methods: Plasma concentrations of maraviroc (UK-427,857) were determined by a validated LC/MS/MS method. All samples were analyzed within the demonstrated matrix and storage stability period. As shown in the following table, the analytical methods are acceptable.

Analytical methods for maraviroc

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
maraviroc (plasma)	0.5 – 200 (R^2 >0.98)	≤5.0	-3.7 to 2.0	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.

Pharmacokinetic Results: UK-427,857 showed rapid and variable absorption, with Tmax generally occurring between one and four hours post-dose. The increase in Cmax between 100mg and 300mg QD appeared to be approximately proportional, with a slightly supraproportional increase in AUCτ (approximately a four fold increase in exposure, for a three fold dose increase). Comparison of the 150mg BID fed and fasted data suggested that food reduced the Cmax and AUCτ by approximately 60% and 50%, respectively. Visual inspection of individual trough profiles, suggested that most subjects had reached steady state by Day 4.

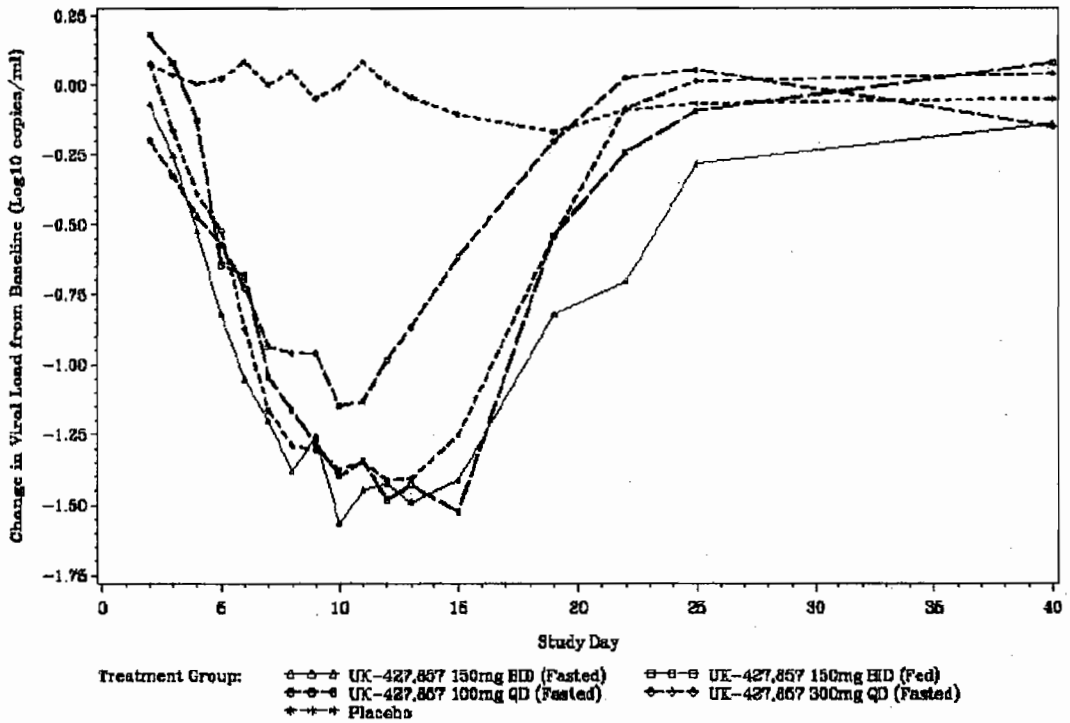
No of subjects	UK-427,857			
	150mg BID (fasted) N=8	150mg BID (fed) N=8	100mg QD (fasted) N=9	300mg QD (fasted) N=8
AUC_τ (ng.h/ml)[a]	933	474	571	2264
C_{max} (ng/ml)[a]	273	110	161	484
T_{max} (h)[b]	3.0	2.3	3.3	3.3

[a]unadjusted geometric mean; [b]unadjusted arithmetic mean

Efficacy Results: The mean viral load decreased from baseline to Day 11. After dosing was stopped, viral load increased and had returned to baseline for all groups by Day 40.
The following table shows the mean viral load at baseline and Day 11 and the mean change (Day 11 minus baseline) for each UK-427,857 dose and placebo.

Dose	Mean viral load (Log_{10} copies/ml)		Mean change (Log_{10} copies/ml)
	Baseline	Day 11	
150mg BID (fasted)	4.567	3.121	-1.446
150mg BID (fed)	4.584	3.241	-1.343
100mg QD (fasted)	4.619	3.488	-1.131
300mg QD (fasted)	4.759	3.413	-1.346
Placebo	4.857	4.942	0.085

The following figure plots the log10 change in viral load from Days 1 to 40 for evaluable subjects.



The changes in viral load were similar for the UK-427,857 150mg BID fed and fasted groups and the changes were similar for the UK-427,857 150mg BID (fasted) and 300mg QD (fasted) groups.

The following table shows the mean change in viral load for the primary and secondary comparisons and the 90% CIs.

Comparison	Difference	90% CI
Primary		
UK-427,857 150mg BID (fasted) v UK-427,857 150mg BID (fed)	-0.103	-0.390, 0.185
UK-427,857 150mg BID (fasted) v UK-427,857 300mg QD (fasted)	-0.099	-0.387, 0.188
Secondary		
UK-427,857 300mg QD (fasted) v UK-427,857 100mg QD (fasted)	-0.215	-0.502, 0.072

Conclusion: Although food reduced the Cmax and AUC of maraviroc by approximately 60% and 50% at 150 mg BID, respectively, there was little effect of food on the short-term antiviral activity (change from baseline in viral load log10 copies/mL) of maraviroc, with a -0.103 (90% CI -0.390, 0.185) difference between maraviroc 150 mg fasted and fed treatment groups on Day 11. In consequence, no food restrictions were required in Phase III studies.

A Phase 1 Study to Investigate the Haemodynamic Effects of Oral Maraviroc (Study A4001033)

Objectives: To investigate the effect of maraviroc on the cardiovascular function of healthy male subjects.

Subjects: 16 healthy male subjects aged 19 to 45 with a Body Mass Index of approximately 18 to 27g/m2; and a body weight between 50 and 90kg were enrolled.

Study Design: The study includes two parts.

Part 1: This was 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). There was at least 24 hours between periods 1 and 2.

Part 2: This was a double blind, randomized, placebo-controlled, two period (periods 3 and 4) crossover assessment of a single oral dose of maraviroc 900mg vs. placebo. There were at least five days between periods 3 and 4 and between Parts 1 and 2 of the study.

Formulation: Maraviroc was supplied as 150mg tablets for oral administration [Formulation identification (FID) No. D0401103; Lot No. 10082-193] and matching placebo was supplied as film-coated tablet (FID No. S01186AA; Lot No. 8625-193). GTN was supplied as a 0.4mg sublingual spray (Lot No. 05B14).

Pharmacokinetic Evaluation: During Part 2 of the study, blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 4 hours post-dose

Pharmacodynamic Evaluation: Subjects had impedance cardiography (ICG), to measure stroke index, cardiac index and systemic vascular resistance, and supine blood pressure and pulse rate measurements conducted pre-dose and every three minutes up to one hour post-

dose in Part 1 of the study and pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 4 hours post-dose in Part 2 of the study.

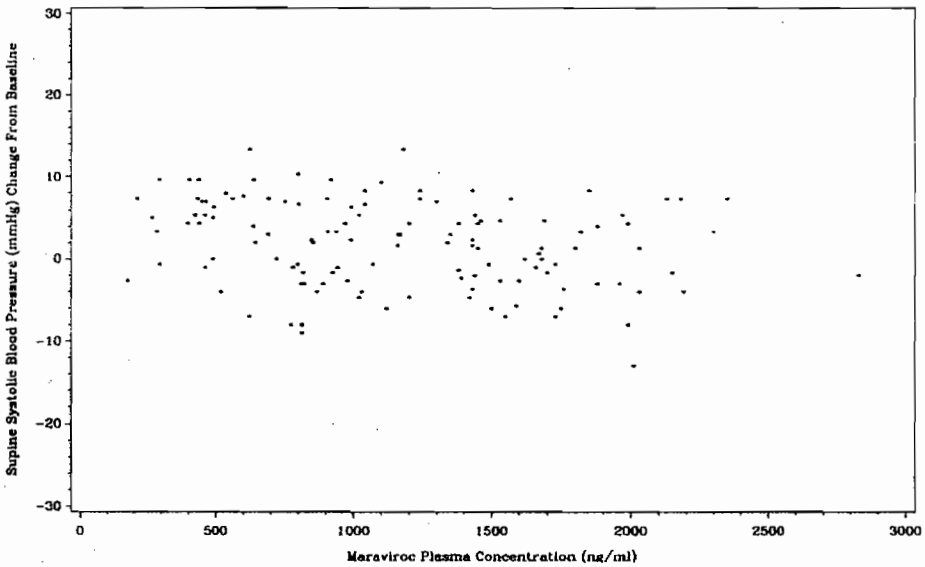
Analytical methods: Plasma concentrations of maraviroc (UK-427,857) were determined by a validated LC/MS/MS method. All samples were analyzed within the demonstrated matrix and storage stability period. As shown in the following table, the analytical methods are acceptable.

Analytical methods for maraviroc

Analyte	Standard Curve Range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Dev.)	Validation and sample for stability and conditions
maraviroc (plasma)	0.5 – 500 (R^2 >0.98)	≤2.0	0.4 to 6.7	• Stable in human plasma at temp up to 50°C for five days; • Stable at -20°C for up to 24 months; • Stable for three freeze/thaw cycles at -20°C.

Results:

Blood samples were collected to measure plasma maraviroc concentration but no pharmacokinetic parameters were calculated for this study. The relationship between plasma maraviroc concentration and pharmacodynamics was investigated. There was no apparent relationship between % change from baseline in ICG parameters or change from baseline in supine blood pressure and pulse rate and maraviroc plasma concentration.



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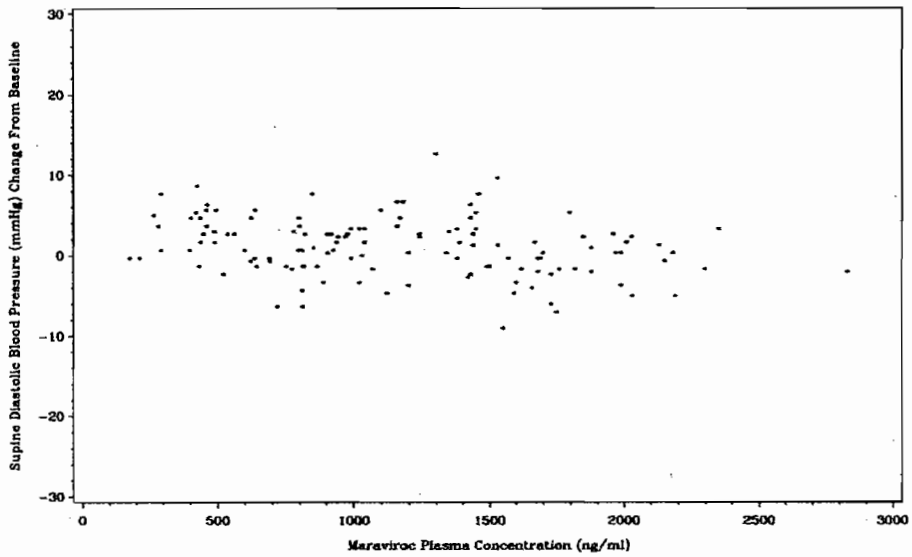

The results show that, GTN decreased systemic vascular resistance (largest mean decrease –9.2%), stroke index (largest mean decrease –8.6%) and supine diastolic blood pressure and increased cardiac index (largest mean increase 6.2%) and pulse rate and that these effects peaked approximately six to nine minutes post-dose.

The following table shows the statistical analysis of the comparison between maraviroc 900mg and maraviroc placebo (mean difference and 95% CI) in the change from baseline or % change from baseline in haemodynamic parameters at each time point.

Table 10. Statistical Analysis of Haemodynamic Changes (Maraviroc 900mg v Maraviroc placebo)

Parameter	Maraviroc 900mg v Maraviroc placebo comparison							
	Time post-dose (h)							
	0.5	1	1.5	2	2.5	3	3.5	4
Stroke index (ml/m²)[a]	-0.1	-4.2	-3.2	-3.6	-4.4	-2.5	-4.1	-3.3
95%CI	-1.9,1.7	-7.2,-1.2	-6.9,0.4	-8.1,1.0	-9.0,0.2	-7.0,2.1	-7.0,-1.2	-6.1,-0.6
Cardiac index (L/min/m²)[a]	2.4	4.7	1.0	4.4	3.3	0.8	3.1	1.0
95%CI	-3.2,8.0	0.4,8.9	-4.8,6.7	-1.3,10.0	-6.9,13.6	-6.6,8.2	-4.4,10.7	-3.5,5.4
Systemic vascular resistance (dyne s/cm⁵)[a]	-3.2	-4.4	0.1	-6.4	-5.4	-1.6	-2.8	-3.2
95%CI	-10.7,4.3	-8.8,0.1	-7.2,7.4	-12.5,-0.3	-14.1,3.3	-6.2,3.1	-7.7,2.2	-7.0,0.5
Supine systolic blood pressure (mmHg)[b]	-1.0	0.4	-1.9	-1.0	-3.3	-0.8	-1.0	-1.3
95%CI	-4.6,2.6	-2.9,3.7	-5.8,1.9	-4.8,2.8	-6.8,0.2	-4.3,2.7	-4.2,2.2	-4.3,1.7
Supine diastolic blood pressure (mmHg)[b]	-1.2	0.6	0.2	-0.9	-0.3	0.1	0.8	-2.0
95%CI	-4.0,1.7	-2.1,3.2	-2.5,2.9	-3.3,1.5	-3.0,2.3	-3.3,3.5	-1.7,3.4	-4.0,0.0
Supine pulse rate (bpm)[b]	2.1	4.6	2.1	4.6	4.2	2.2	4.2	1.7
95%CI	0.3,3.9	1.5,7.7	0.1,4.1	1.0,8.2	2.0,6.5	-0.4,4.9	2.1,6.3	0.2,3.2

[a]% change from baseline; [b]change from baseline; bpm=beats per minute.

The data show that maraviroc 900mg 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%, Figure S1) and stroke index (largest mean decrease –5.6%, Figure S2) and increased cardiac index (largest mean increase 6.8%, Figure S3) and pulse rate. These effects were mostly sustained over the four hours post-dose measurement period.

Figure S1. Mean Profiles of Systemic Vascular Resistance; % Change from Baseline v Time by Treatment

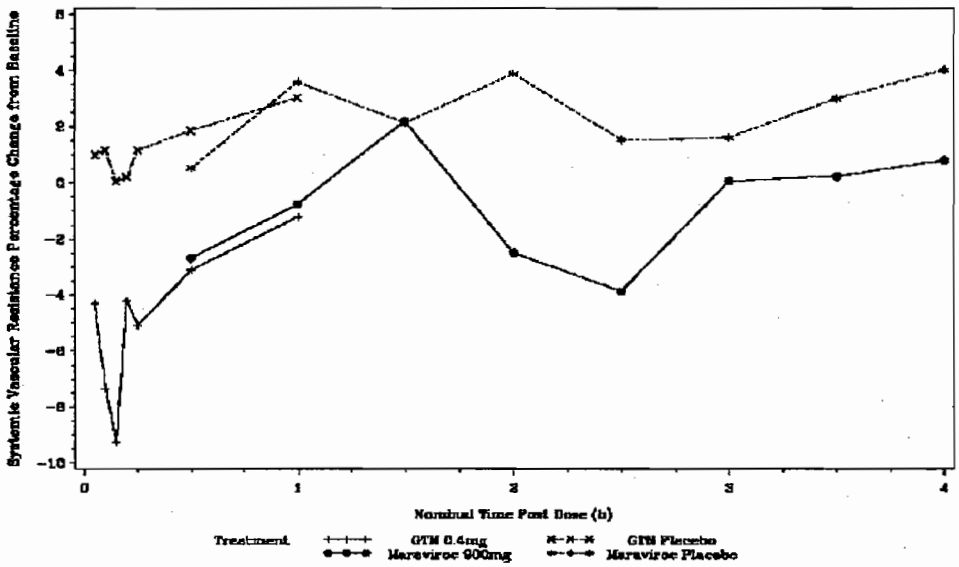

Figure S2. Mean Profiles of Stroke Index; % Change from Baseline v Time by Treatment

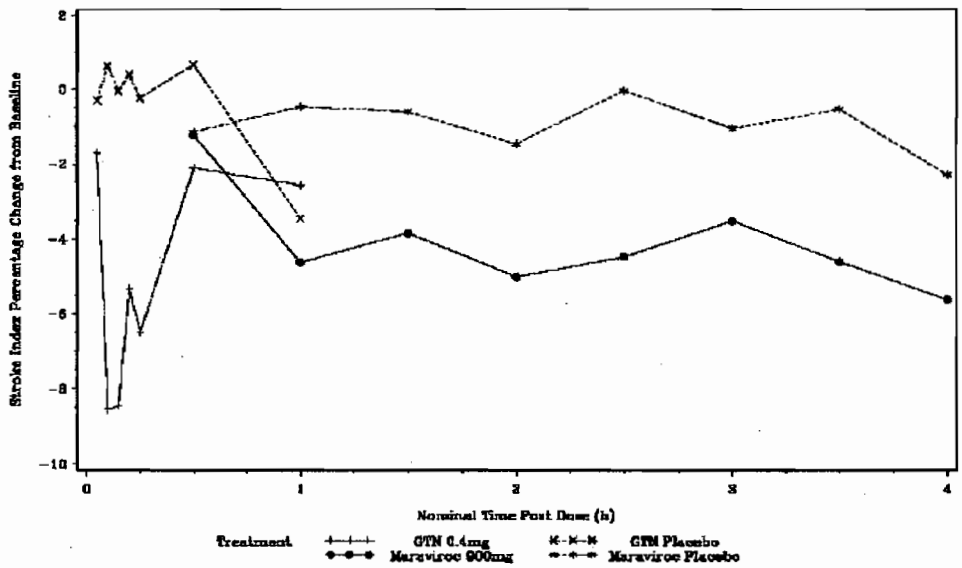

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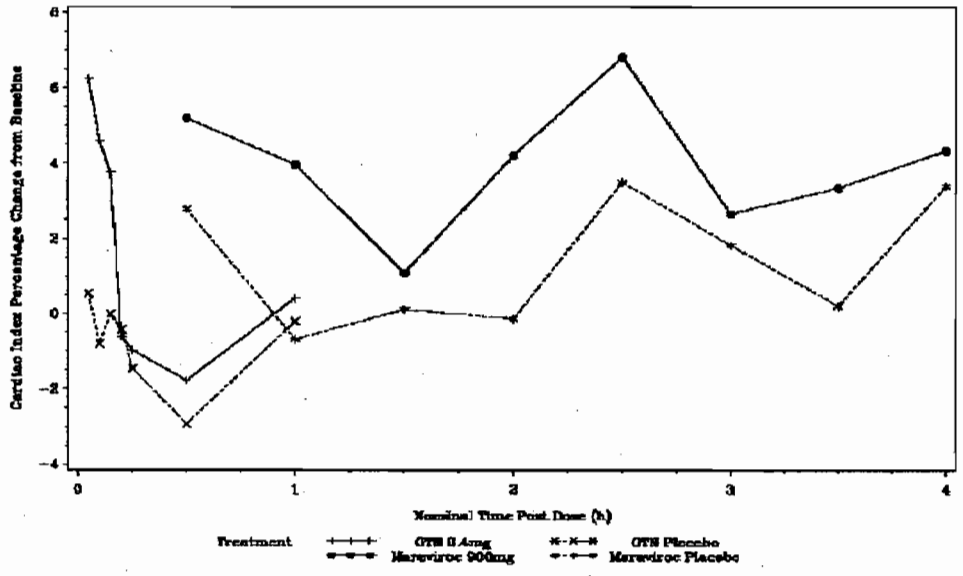
Figure S3. Mean Profiles of Cardiac Index; % Change from Baseline v Time by Treatment



The most common treatment related adverse event after maraviroc was orthostatic hypotension (3/16). There were more subjects with an adverse event after maraviroc 900mg than after maraviroc placebo.

Conclusion: There was no apparent relationship between % change from baseline in ICG parameters or change from baseline in supine blood pressure and pulse rate compared with maraviroc plasma concentration. However, the 3/16 subjects experienced postural hypotension in the maraviroc treatment group (900 mg single dose) as compared to 0/3 subjects in the placebo group.

Population Pharmacokinetic/Pharmacodynamic Analysis of Blood Pressure for A4001002 and A4001006 Data from Phase I of Maraviroc (UK427,857)

Objectives: To establish the relationship between maraviroc plasma concentrations and blood pressure data from two healthy volunteer studies A4001002 and A4001006.

Study Design: A4001002 was a parallel group multiple dose (3, 20, 25, 100, 300 mg BID, and 600 mg QD) maraviroc pharmacokinetic-toleration study and A4001006 was a drug-drug interaction crossover study determining the effect of ketoconazole (400 mg QD) and saquinavir (1200 mg TID) on maraviroc pharmacokinetics.

Data: This analysis focused on the underlying concentration effect relationship in subjects who did not experience postural hypotension. The combined population of 96 subjects (A4001002: n=72; A4001006: n=24) provided on average 60 blood pressure observations and 28 quantifiable maraviroc (100 mg BID) plasma concentrations.

Pharmacokinetic Modeling

No pharmacokinetic modelling was carried out on pharmacokinetic data. Concentrations were used directly in the PK/PD modelling.

Pharmacodynamic Modeling

Baseline Data Analysis
The presence of diurnal variation was modelled. The baseline structural model was assessed using only data collected the day before the first day of treatment in study (Baseline dataset).

The model for baseline consisted of a parameter for the rhythm-adjusted 24-hour mean and two cosine functions that modify the mean blood pressure as a function of clock time. The model can be described by the following equation:

$$BSL(TIMED) = RYTH \cdot \left[1 + AMP1 \cdot COS\left(\frac{2 \cdot \pi \cdot TIMED}{24} - SHIF1\right) + AMP2 \cdot COS\left(\frac{2 \cdot \pi \cdot TIMED}{12} - SHIF2\right)\right]$$

Where:
BSL (TIMED) is the dependant variable (Standing SBP or Standing DBP)
TIMED is the independent variable (clock time in decimal format)
The parameters to be estimated are:
RYTH, the rhythm-adjusted 24-hour mean of SBP or DBP
AMP1, the amplitude of the first cosine term
SHIF1, the phase shift of the first cosine term
AMP2, the amplitude of the second cosine term
SHIF2, the phase shift of the second cosine term
The period of 24 and 12 hours was used for the two cosine terms, respectively.

Placebo effect
A placebo effect (PL) was investigated as an additive term to the baseline model (Y=BSL(TIMED) + PL). This model used baseline and placebo data only.

Two forms of the placebo model were investigated:
- A simple theta (step model) (set to zero for non placebo events)
- A discrete time placebo effect (different placebo theta for each of days 1, 7 and 12)
- An exponential model such that *PL=(PLA(1)*EXP(-KPT*DAY))*

Drug effect
The full dataset (baseline, placebo and active treatment) was then used for the full model. Concentration effects of maraviroc were explored using the following model:
Y=BSL(TIMED) + PL + DRUG - effect additive to the baseline/placebo model.

where:
Y is the dependent variable (standing systolic or diastolic blood pressure),
BSL(TIMED) is the baseline (or baseline/placebo) model, and

$$DRUG = SLOPE \cdot CONC \quad \text{- for the linear model}$$

$$DRUG = \frac{E\max \cdot CONC}{D50^{\gamma} + CONC} \quad \text{- for the } E_{max} \text{ model}$$

Error Structure

Inter-individual variability (IIV) in the baseline model parameters was modeled using additive random effects for TMED and multiplicative exponential random effects for RYTH. Inter-occasion variability (IOV) was modeled for BSL and TMED. This was used to account for the 2 periods of baseline run-in data for crossover study A4001006. A proportional and an additive residual error model were both tested.

Model Diagnostics

The models were evaluated based on the following criteria:

- A 'successful termination' statement by the NONMEM program
- Number of significant digits ≥ 3 for all θ's (also a criterion for 'successful termination').
- Successful covariance step
- Estimates of θ's not close to a boundary (where boundaries were specified).
- Basic goodness of fit plots
- Reduction of inter-and/or intra-subject variance estimates

Results

Plots of the measured plasma levels of maraviroc versus standing systolic/diastolic blood pressure split by study (1002 and 1006) are presented in Figure 1 below. These plots show a small decrease in blood pressure relative to increases in maraviroc plasma concentration.

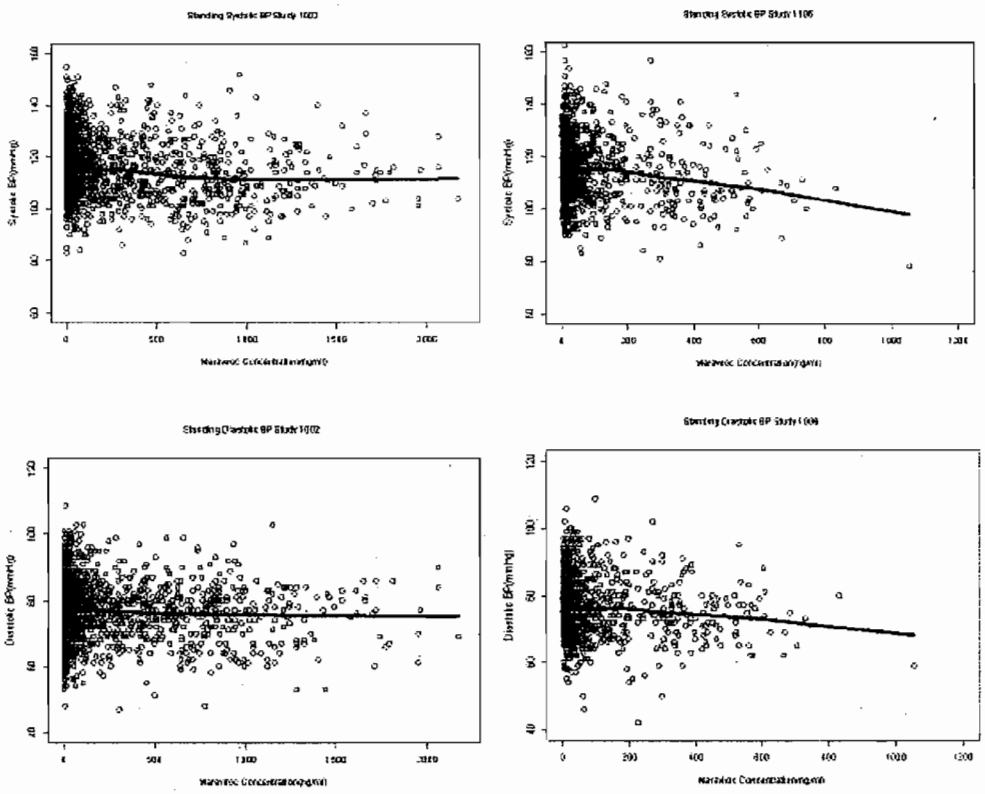


Figure 1: Measured plasma concentration versus standing systolic/diastolic blood pressure for maraviroc from studies A4001002 and A4001006. The solid line is a smooth line.

A single cosine model was sufficient for standing systolic blood pressure and standing diastolic blood pressure. No significant placebo effect was found. The linear model was found to significantly improve the fit. The parameter estimates and precision are shown below.

Parameter Estimates from Final Models with Standard Errors

	Standing Systolic Blood Pressure (Run 13)		Standing Diastolic Blood Pressure (Run 14)	
Parameter	Estimate	S.E.	Estimate	S.E.
RYTH	117	0.862	76.3	0.691
AMP1	-0.0111	0.00306	0.0194	0.00208
SHIF1	3.47	0.218	-39.2	0.107
Slope	**-0.00387**	0.000626	**-0.00179**	0.000436
IIV_{ADD} on TMED	13.8	12.0	2.93	0.839
IIV_{EXP} on RYTH	0.00434	0.000622	0.00725	0.000891
IOV_{ADD} on BSL	11.4	2.52	7.22	1.54
Residual (ADD)	68.7	2.93	29.6	1.61

Conclusion: Based on the slope estimate for standing systolic blood pressure, a decrease of 3.87 mmHg was associated with an increase of 1000ng/mL in maraviroc plasma concentration (corresponding to Cmax values following doses of >300mg). Based on the slope estimate for standing diastolic blood pressure, the decrease in blood pressure per 1000ng/mL increase in plasma concentration was 1.79 mmHg. However, the data need to be interpreted carefully because subjects with higher maraviroc exposure who developed postural hypotension were not included in the analysis.

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4.2.6 *In vitro* Studies

UK-427,857 metabolism

Study DM5: In vitro metabolism of UK-427,857 in human liver microsomes and recombinant cytochrome P450 enzymes

The in vitro metabolism of UK-427,857 was studied in hepatic microsomes from 3 human livers (HM/9-2, HM/28, HM/29) with varying CYP3A4, 2C9 and 2D6 activities.

Human Liver ID	UK-427,857 half-life (min)	CYP2C9 activity (pmol/mg/min)	CYP2D6 activity (pmol/mg/min)	CYP3A4 activity (pmol/mg/min)
HM/9-2	>120	1282.0	14.5	17.3
HM/28	>120	1093.6	10.8	272.8
HM/29	80 ± 5	2720.1	38.7	219.7

Due to the small number of liver samples evaluated, it is not possible to determine a correlation between enzyme activity and in vitro metabolism rate. However, in vitro metabolic rate of UK-427,857 was slow.

The in vitro metabolism of UK-427,857 was also studied in microsomes prepared from cells expressing individual cytochrome P450 enzymes. UK-427,857 incubations were performed in microsomes from baculovirus cells engineered to individually express one of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. UK-427,857 was detectable in all samples, but metabolites were only detected in the CYP2D6 and CYP3A4 samples. Metabolites were about five-fold greater in the CYP3A4 samples, compared to the CYP2D6 samples.

Study DM24: Identification of the CYP enzymes involved in the metabolism of K-427,857 in human liver microsomes

The in vitro metabolism of UK-427,857 was studied in human liver microsomes. Incubations with UK-427,857 (1µM) were performed in human liver microsomes in the presence and absence of CYP2C9, CYP2D6 and CYP3A4 inhibitors. UK-427,857 was metabolized with a disappearance half-life of 13.1min. In the presence of the specific CYP3A4 inhibitor ketoconazole, the disappearance half-life was extended to 79min. The inhibitors sulphaphenazole (CYP2C9), and quinidine (CYP2D6) had no effect on the rate of UK-427,857 metabolism. The applicant estimated that CYP3A4 contributes to 83% of the metabolism of UK-427,857 based on these data. However, it is unclear how the value was calculated.

In incubations with recombinant CYP enzymes in the form of Supermix, the role of the polymorphic enzymes CYP2C19 and CYP2D6 was evaluated. Incubations were performed in control Supermix (containing CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4), CYP2C19PM Supermix (lacking CYP2C19) and CYP2D6PM Supermix (lacking CYP2D6) at 1µM UK-427,857. As shown in the following table, neither enzyme contributes significantly to the metabolism of UK-427,857.

	Mean T1/2 ± SD (min) (n=4)	% CYP contribution
Control Supermix	8.2 ± 2.7	-
CYP2D6PM Supermix	7.4 ± 1.2	0%
CYP2C19PM Supermix	8.1 ± 1.8	0%

In further studies with individually expressed recombinant CYPs, UK-427,857 (1µM) was incubated with individual CYP enzymes at 100pmol CYP/ml. UK-427,857 was slowly

metabolized by CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 with disappearance half-lives of >120min. Metabolism was only observed in the CYP3A4 and CYP3A5 incubations, with disappearance half-life values of 4.2min and 99min, respectively.

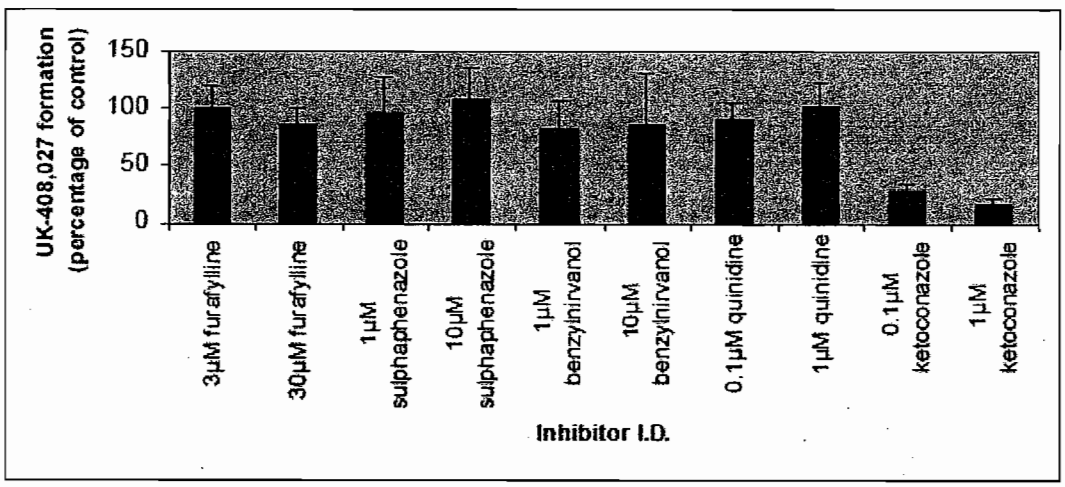
Study DM35: In vitro metabolism of UK-427,857 in human liver microsomes: enzymology of UK-408,027 formation

UK-408,027 has been identified as a metabolite of UK-427,857 in man. This study identifies the major cytochrome P450 enzymes responsible for the metabolism of UK-427,857 to this metabolite in human liver microsomes.

The rate of UK-408,027 formation in human liver microsomes was determined over a range of UK-427,857 concentrations from 1 to 1000µM. Km was determined to be 23 µM.

Further studies were performed to establish the identity of the enzymes responsible for the formation of UK-408,027. Specific CYP inhibitors were co-incubated with UK-427,857 (50µM) and their influence on metabolite formation investigated. The inhibitors used were furafylline (3 & 30µM, CYP1A2 inhibitor), sulphaphenazole (1 & 10µM, CYP2C9 inhibitor), benzylnirvanol (1µM & 10µM, CYP2C19 inhibitor), quinidine (0.1 & 1µM, CYP2D6 inhibitor) and ketoconazole (0.1 & 1µM, CYP3A4 inhibitor).
Incubations in the presence of the CYP3A4 inhibitor ketoconazole decreased the formation of UK-408,027 in human liver microsomes, while inhibitors of other CYPs had no effect.

Effect of Specific CYP Inhibitors on UK-408,027 Formation in Human Liver Microsomes



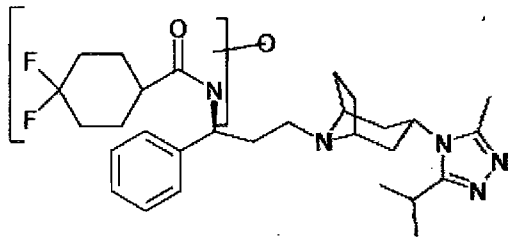
In incubations with individual CYPs, only CYP3A4 produced substantial metabolite formation. Kinetic studies carried out with this enzyme gave a Km value of 13 µM. Therefore, metabolism of UK-427,857 to UK-408,027 is mediated by CYP3A4 in man.

These data indicate an important role for CYP3A in the metabolism of UK-427,857.

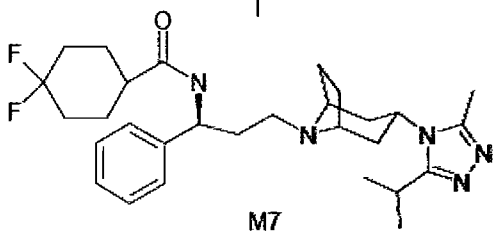
Metabolic profiling

Study DM19: Profiling and characterization of metabolites of [^{3}H]-UK-427,857 in human, dog and monkey hepatocytes

Following incubation of 5 μM [^{3}H]-UK-427,857 with human, dog and monkey hepatocytes, qualitative and quantitative metabolism was studied using 2-hour incubation samples. Unchanged drug was the major compound detected for each of the three species. Total radioactivity quantified for metabolites represented approximately 6.6% of the dose in monkey and less than 1% in dog and human hepatocyte incubate samples. The following figure shows the proposed transformation pathway for UK-427,857 in human, dog and monkey hepatocytes.

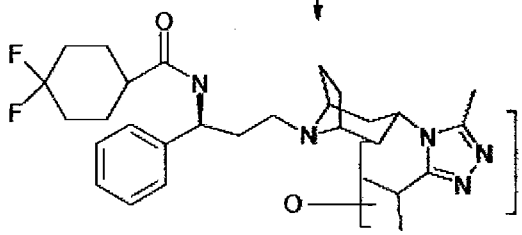


M1, M2, M4, M



M7

UK-427,857



M3, M6, M8

Transformation products were mono-hydroxylated derivatives of UK-427,857. Five metabolites (M1, M2, M4 and M5) were detected in human and monkey samples. The same four metabolites and an additional two metabolites (M3 and M6) were detected in dog samples.

Effect of UK-427,857 on metabolism

Study DM7: In vitro cytochrome P450 inhibition studies on UK-427,857 in recombinant cytochrome P450 enzymes

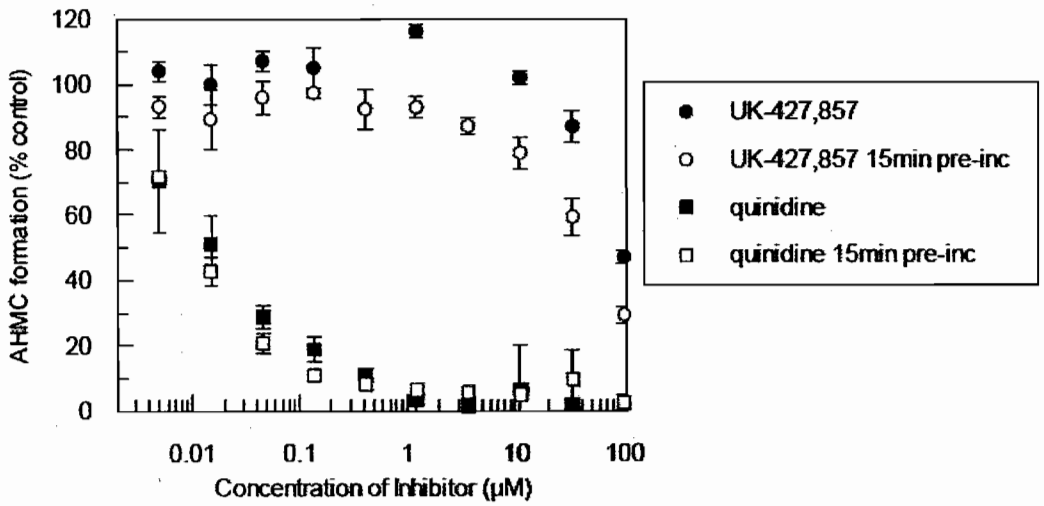
The potential for UK-427,857 to inhibit the activity of five drug metabolizing cytochrome p450 enzymes (CYP1A2, 2C9, 2C19, 2D6, 3A4) was studied in vitro in recombinant CYPs with and without preincubation. All positive control inhibitors inhibited the probe reactions. Probe enzyme activities and the fluorescent probe substrate concentrations used are listed below.

CYP1A2: 3-cyano-7-ethoxycoumarin (CEC) deethylase (1 µM CEC)
CYP2C9: 7-Methoxy-4-trifluoromethylcoumarin (7-MFC) O-demethylase (100 µM 7-MFC)
CYP2C19: 3-cyano-7-ethoxycoumarin (CEC) deethylase (40 µM CEC)
CYP2D6: 3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methoxy-4-methylcoumarin (AMMC) O-demethylase (1 µM AMMC)
CYP3A4: Dibenzylfluorescein (DBF) O-dealkylase (1 µM DBF)
CYP3A4: 7-Benzyloxy-4-(trifluoromethyl)-coumarin (7-BFC) O-dealkylase (125 µM 7-BFC)
CYP3A4: 7-Benzyloxyquinoline (7-BQ) O-dealkylase (10 µM 7-BQ)

At the concentrations used in this study (up to 100µM), UK-427,857 did not inhibit any of these enzymes (IC50 > 100 µM) except for CYP2D6. However the inhibition by UK-427,857 towards CYP2D6 was weak (IC50 = 87 µM). A slight increase in potency (<2 fold) upon pre-incubation of maraviroc with CYP2D6 was also observed (IC50=50 µM). Maraviroc is therefore unlikely to inhibit the metabolism of other cytochrome P450 substrates at clinical doses (I/KI <= 0.03).

P450 enzyme	Reaction (Substrate concentration)	Positive control	No pre-incubation IC_{50} (µM)	Plus pre-incubation IC_{50} (µM)
CYP1A2	3-cyano-7-ethoxycoumarin (CEC) deethylation (1 µM)	Furafylline	> 100	> 100
CYP2C9	7-methoxy-4-trifluoromethylcoumarin (7-MFC) O-demethylation (100 µM)	Sulphaphenazole	> 100	> 100
CYP2C19	3-cyano-7-ethoxycoumarin (CEC) deethylation (40 µM)	Fluconazole	> 100	> 100
CYP2D6	3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methoxy-4-methylcoumarin (AMMC) O-demethylation (1 µM)	Quinidine	87 ± 2	50 ± 5
CYP3A4	Dibenzylfluorescein (DBF) O-dealkylation (1 µM)	Ketoconazole	> 100	> 100
CYP3A4	7-Benzyloxy-4-(trifluoromethyl)-coumarin (7-BFC) O-dealkylation (125 µM)	Ketoconazole	> 100	> 100
CYP3A4	7-Benzyloxyquinoline (7-BQ) O-dealkylation (10 µM)	Ketoconazole	> 100	> 100

EFFECT OF UK-427,857 ON AMMC O-DEMETHYLASE ACTIVITY (CYP2D6)



Study DM22: In vitro cytochrome P450 inhibition studies on UK-427,857 in human liver microsomes

This study evaluated the in vitro inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 by UK-427,857 in human liver microsomes. Probe substrates for these enzymes were co-incubated with UK-427,857. Probe enzyme activities and the substrate concentrations used are listed below.

CYP1A2- Phenacetin O-deethylase (20 μM phenacetin)
CYP2C9- Diclofenac 4-hydroxylase (18 μM diclofenac)
CYP2C19- (S)-mephenytoin-4-hydroxylase (37 μM S-mephenytoin)
CYP2D6- Dextromethorphan O-demethylase (4 μM dextromethorphan)
CYP3A4- Testosterone 6β-hydroxylase (120 μM testosterone)
CYP3A4- Felodipine oxidase (20 μM felodipine)
CYP3A4- Midazolam 1'-hydroxylase (3 μM midazolam)

Investigations for all enzymes included known inhibitors as positive controls. The concentrations of UK-427,857 in the incubations were 0 (control), 0.3, 3.0 and 30.0 μM. Incubations were conducted without pre-incubation and with pre-incubation of UK-427,857, to investigate the possibility of mechanism-based inhibition. The IC_{50} value for all enzymes, with and without pre-incubation, was >30 μM.

Study DM33: In vitro cytochrome P450 inhibition studies on CYP2B6 and CYP2C8 by UK-427857 in human liver microsomes

The potential for UK-427,857 to inhibit the activity of the drug metabolizing cytochrome P450 enzymes CYP2B6 and CYP2C8 was studied *in vitro* in human liver microsomes. Probe substrates for these enzymes were co-incubated with UK-427,857. Probe enzyme activities and the substrate concentrations used are listed below.

CYP2B6- Bupropion 1-hydroxylase (100 μM bupropion)
CYP2C8- Rosiglitazone O-Desmethylase (9 μM rosiglitazone)

Investigations for both enzymes included known inhibitors as positive controls. The concentrations of UK-427,857 in the incubations were 0 (control), 0.3, 3.0 and 30.0 μM. Incubations were conducted without pre-incubation and with pre-incubation of UK-427,857, to investigate the possibility of mechanism-based inhibition. The IC_{50} value for both enzymes, with and without pre-incubation, was >30 μM.

The results of studies DM7, DM22, and DM33 indicate that the likelihood of UK-427,857 inhibiting the activity of seven common CYP enzymes is low.

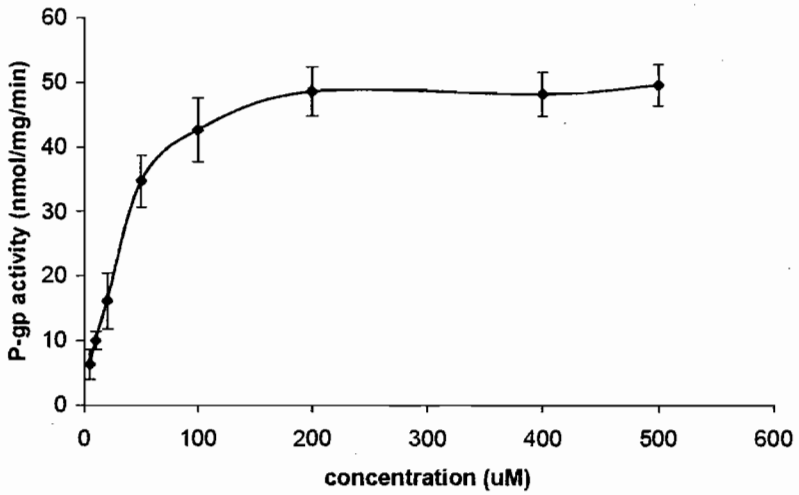
P-glycoprotein involvement

Study DM21: *In Vitro* Affinity of UK-427,857 for Recombinant Human P-glycoprotein

The ability of UK-427,857 to stimulate the release of ADP was determined in insect cell membranes containing P-glycoprotein. The release of ADP and subsequent conversion back to ATP is linked via a catalytic cycle to the oxidation of NADH to NAD+.

UK-427,857 was found to stimulate activity of P-glycoprotein contained in insect cell membranes in a concentration dependant manner. Michaelis-Menten saturation kinetics were obtained. UK-427,857 was confirmed to be a P-glycoprotein substrate with mean (n=5) apparent Km of 37 ± 6.4μM and an apparent Vmax of 55 ± 3.4 nmol/mg/min. The positive control UK-343664 was included and had the values similar to previous analyses.

Concentration dependent stimulation of P-glycoprotein by UK-427,857 (n=5)



Study DM20: In Vitro Permeability Studies with UK-427,857 in Caco-2 Cells and Effect of P-Glycoprotein and MRP Inhibitors

The permeability of UK-427,857 (25 µM) was studied across Caco-2 cell monolayers at pH7.4. Lucifer yellow and nadolol were used as markers of membrane integrity. All data quoted are from monolayers that were still intact at the end of the experiment.

UK-427,857 shows limited permeability in the apical to basolateral direction (A-B) in Caco-2 cells with Papp values of <1 x 10-6 cm/s. Higher permeability is observed in the basolateral to apical direction (B-A). UK-427,857 exhibits an efflux ratio (B-A/A-B) of >10 demonstrating polarized transport in Caco-2 cells. The P-glycoprotein inhibitors verapamil (100 µM) and CP-100,356 (10 µM) and the MRP-2 inhibitor MK-571 (50 µM) all reduced the efflux ratio of UK-427,857 in Caco-2 cells suggesting MRP-2 and P-glycoprotein are both partially involved in the efflux of UK-427,857.

Inhibition of efflux of UK-427,857 with the P-glycoprotein inhibitors verapamil (100µM) and CP-100,356 (10µM) with apical and basolateral chambers at pH 7.4. The range of data generated is in brackets.

Concentration UK-427,857 (µM)	Inhibitor	Concentration of inhibitor (µM)	Mean Papp A-B (x 10^{-6} cm/s) (n=3)	Mean Papp B-A (x 10^{-6} cm/s) (n=3)
25	None	N/A	<1 (no range)	12 (11-14)
25	Verapamil	100	1 (no range)	6 (6-7)
25	CP-100,356	10	2 (no range)	7 (6-7)

Inhibition of efflux of UK-427,857 with the MRP-2 inhibitor MK-571 with the apical chamber at pH 6.5 and basolateral chamber at pH 7.4. The range of data generated is in brackets.

Concentration UK-427,857 (µM)	Inhibitor	Concentration of inhibitor (µM)	Average Papp A-B (x 10^{-6} cm/s) (n=2)	Average Papp B-A (x 10^{-6} cm/s) (n=2)
25	None	N/A	<1 (no range)	24 (23 & 24)
25	MK-571	50	<1 (no range)	12 (12 & 13)

Study DM44: In Vitro Permeability Studies with UK-427,857 and P-gp Inhibitors in Caco-2 Cells

The efflux of UK-427,851 from Caco-2 cell monolayers was studied in the presence of a number of P-gp inhibitors. The rank order for inhibitory potency of UK-427,857 efflux was ketoconazole>ritonavir>nelfinavir>saquinavir>indinavir.

IC50 values for inhibition of UK-427,857 efflux in Caco-2 cells

Inhibitor compound	IC50 value (μM)
Nelfinavir	14.02±1.67
Saquinavir	>30
Indinavir	>100
Ritonavir	7.63±0.76
Ketoconazole	2.25±0.19

The results from Studies DM21, DM20, DM44 indicated UK-427,857 is a substrate of P-gp and MRP-2

Protein binding

Study DM12: Plasma protein binding of [^{3}H]-UK-427,857 in the plasma of mouse, rat, rabbit, dog and human at concentrations of 1, 30 and 1000ng/ml

Plasma protein binding was determined using equilibrium dialysis. The results indicate UK-427,857 is 78% bound to plasma proteins in humans. The protein binding values in mouse, rat, rabbit and dog were 66%, 46%, 50% and 52%, respectively. In all species evaluated, plasma protein binding was independent of drug concentration over the range of 1 to 1000 ng/mL.

BINDING OF [^{3}H]-UK-427,857 IN THE PLASMA OF RAT, RABBIT, MOUSE, DOG AND HUMAN AT INITIAL DRUG CONCENTRATIONS OF 1, 30 AND 1000ng/ml

Species	Mean percentage bound in plasma (n=5)			Mean
	1ng/ml	30ng/ml	1000ng/ml	
Mouse	68.2 ± 1.9	64.7 ± 2.2	66.0 ± 5.7	66.3
Rat	48.4 ± 1.6	45.3 ± 1.9	44.5 ± 2.1	46.1
Rabbit	50.8 ± 1.5	52.7 ± 4.9	47.4 ± 2.3	50.3
Dog	50.9 ± 4.5	54.3 ± 3.2	51.2 ± 1.8	52.1
Human	78.5 ± 2.7	78.9 ± 1.4	77.6 ± 3.3	78.3

Study DM23: Ex vivo plasma protein binding of [^{3}H]-UK-427,857 in mouse, rat, rabbit, dog, monkey, and human

The ex *vivo* plasma protein binding (PPB) of UK-427,857 was investigated by equilibrium dialysis. Plasma samples were obtained during toxicology studies in mouse, rat, rabbit, dog and monkey and a multiple dose clinical study in human (at Cmax). Levels of plasma protein binding were monitored by introducing a small percentage (< 10% of total drug measured) of [^{14}C]-UK-427,857 to the samples.

In the species where samples were studied from both male and female animals (mouse, dog and monkey), no sex difference was seen in the percentage binding. For all species, no

difference was observed in the percentage binding of UK-427,857 across the dose range. The mean percentage binding was 58.0% (mouse), 51.0% (rat), 66.0% (rabbit), 63.7% (dog), 48.4% (monkey) and 75.5% (human). The results are consistent with in the vitro study (Study DM12).

Study DM18: Plasma Protein Binding of [^{3}H]-UK-427,857 to Human Albumin and α-1-Acid Glycoprotein

A series of experiments was conducted in order to study the binding of [^{3}H]-UK-427,857 to the plasma constituents albumin and α-1-acid glycoprotein (AAG) at physiological concentrations of these proteins. Initial drug concentrations of 1, 30 and 1000ng/ml were used.

The results show that UK-427,857 has a moderate affinity to the plasma constituents albumin (56% bound) and AAG (69% bound). The binding to AAG is somewhat decreased with increased UK-427,857 concentrations as shown in the following table. The mean proportion of drug bound to albumin was similar across the concentration range. Under physiological conditions UK-427,857 is likely to bind to both proteins in similar proportions.

BINDING OF [^{3}H]-UK-427,857 TO ALBUMIN AND α-1-ACID GLYCOPROTEIN AT INITIAL DRUG CONCENTRATIONS OF 1, 30 AND 1000ng/ml.

Plasma constituent	Initial Drug Concentration (ng/ml) Nominal	Actual	Mean percentage bound (n=5)	Mean across initial concentration range
Albumin	1	0.95	55.0 ± 2.3	55.6 ± 1.89
	30	30.5	55.6 ± 2.3	
	1000	1090	56.2 ± 1.1	
α-1-acid glycoprotein	1	1.02	73.8 ± 1.2	69.1 ± 5.68
	30	31.3	69.6 ±2.6	
	1000	1100	63.8 ± 6.4	

Blood/Plasma Ratio

Study DM16: [^{3}H]-UK-427,857 *In Vitro* Blood : Plasma Concentration Ratio in Rat, Dog and Human Blood

The in *vitro* blood:plasma concentration ratio for [^{3}H]-UK-427,857 was determined in fresh blood from rat, dog and human at a nominal concentration of 100 ng/ml.
Mean values were 1.1, 0.9 and 0.7 for rat, dog and human respectively.
The results show that for rat and dog [^{3}H]-UK-427,857 distributes equally between the blood cells and plasma. Results in human blood indicated that [^{3}H]-UK-427,857 partitioned mainly into plasma.

BLOOD:PLASMA RATIOS OF [^{3}H]-UK-427,857 IN BLOOD FROM RAT, DOG AND HUMAN AT A NOMINAL CONCENTRATION OF 100ng/ml

Species	Mean dpm/g (n=3)		Mean ratio (n=3)
	Whole Blood	Plasma	
Rat	2718.9	2508.2	1.08
Dog	2854.2	3205.4	0.89
Human	2683.9	4083.0	0.66

Study DM32: [^{14}C]-UK-427,857 *In Vitro* Blood:Plasma Concentration Ratio in Human Blood

The *in vitro* blood: plasma concentration ratio for [14C]-UK-427,857 has been determined in fresh blood from six human volunteers at a nominal concentration of 100ng/ml. The mean value was 0.59, which is similar to the value obtained from Study DM16.

BLOOD:PLASMA RATIOS OF [^{14}C]-UK-427,857 IN BLOOD FROM HUMAN VOLUNTEERS AT A NOMINAL CONCENTRATION OF 100ng/ml

Donor	Sex	Mean initial [^{14}C]-UK-427,857 concentration (ng/ml)	Mean ratio ± SD n=3
1	Female	72.8	0.55 ± 0.13
2	Male	75.1	0.51 ± 0.09
3	Female	77.1	0.55 ± 0.13
4	Male	72.8	0.58 ± 0.05
5	Male	88.3	0.68 ± 0.02
6	Male	90.7	0.65 ± 0.01
	Mean	**79.5**	**0.59 ± 0.09**

4.3 DCP4 Division Director Concurrance on Post-Marketing Commitment

From: Lazor, John A
Sent: Tuesday, June 19, 2007 2:03 PM
To: Zheng, Jenny H.
Cc: Reynolds, Kellie S
Subject: RE: maraviroc PMC

OK... please change wording to "who require dialysis"

From: Zheng, Jenny H.
Sent: Tuesday, June 19, 2007 1:59 PM
To: Lazor, John A
Cc: Reynolds, Kellie S
Subject: RE: maraviroc PMC

I think it is a design issue. They will submit the protocol and if the design is not what we like, we can ask them to change.

Jenny

From: Lazor, John A
Sent: Tuesday, June 19, 2007 1:50 PM
To: Zheng, Jenny H.
Subject: RE: maraviroc PMC

If they do a study in patients who are on dialysis, but don't do the study during dialysis (in the inter-dialysis) period, it seems they will meet the PMC. Is this what we want?

From: Zheng, Jenny H.
Sent: Tuesday, June 19, 2007 11:22 AM
To: Lazor, John A
Cc: Reynolds, Kellie S
Subject: maraviroc PMC

John,

The following is the full maraviroc PMC after revision based on your comment. Please ESO. Thanks,

Jenny

PMC:

- Conduct a study to evaluate the effect of renal impairment on the pharmacokinetics of maraviroc

  a) at a dose of 150 mg when combined with a boosted protease inhibitor in subjects with mild and moderate renal impairment
  b) at a dose of 300 mg alone in subjects with severe renal impairment and subjects with End-Stage Renal Disease that require dialysis.

  Protocol submission: December 30, 2007
  Final report submission: December 30, 2008

- Conduct a study to evaluate the potential for maraviroc metabolite(s) to inhibit CYP2D6 enzymes. Debrisoquine urinary ratio data suggest maraviroc or its metabolite(s) may inhibit CYP2D6 at dose of 600 mg.

  Protocol submission: December 30, 2007
  Final report submission: June 30, 2008

- Conduct a study to evaluate the potential of maraviroc to inhibit P-gp.

  Protocol submission: December 30, 2007
  Final report submission: June 30, 2008

- Conduct a study to evaluate the potential of maraviroc to induce CYP1A2.

  Protocol submission: December 30, 2007
  Final report submission: June 30, 2008

4.4 Consult Review

4.4.1 Pharmacometric review

PHARMACOMETRICS REVIEW

NDA Number:	22218
Generic Name:	Maraviroc
Brand Name:	Celsentri
Proposed Indication:	Treatment experienced patients infected with CCR5-tropic HIV-1
Sponsor:	Pfizer Inc.
Type of Submission:	NME
Pharmacometrics (PM) Reviewer:	Pravin Jadhav Ph.D.
Primary Reviewer:	Jenny H. Zheng Ph.D.
Clinical Pharmacology Team Leader:	Kellie S. Reynolds Pharm.D.
PM Team Leader:	Jogarao Gobburu Ph.D.
Proposed Dosage and Administration	150 mg BID when administered with PIs (except tipranavir/ritonavir) or delavirdine (CYP3A4/P-gp inhibitors) and 300 mg BID when administered in the absence of PIs/delavirdine

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Executive summary

Is there an exposure response relationship for maraviroc to support evidence of effectiveness?

The relationship between plasma trough concentration of maraviroc (Cmin) and change from baseline viral load at week 24 in treatment-experienced HIV-1-infected patients with optimized background therapy (OBT) was established. Several binary endpoints indicating virologic success, such as, protocol defined success at week 24, viral load <50 copies/mL at 24 weeks, viral load <400 copies/mL at 24 weeks, were investigated. The Cmin, baseline viral load, baseline CD4+ count and overall sensitivity score (OSS) at baseline were found to be the important predictors of the virologic success. The relationship was consistent across all endpoints. The current report focuses on findings derived from the analyses of one clinically relevant endpoint, viral load <400 copies/mL at 24 weeks. Patients with Cmin >50-75 ng/mL have a better chance of virologic success. In addition to Cmin, the probability of success is also influenced by other patient specific factors such as baseline CD4+ count, baseline viral load and overall susceptibility score (OSS).

a. With the sponsor's proposed dosing, ~67% of patients should achieve <400 RNA copies/mL.

b. Concomitant drugs or demographic factors were not the source of lower Cmin values.

What is the advantage of dose individualization for maraviroc?

The simulations indicate that by doubling the dose the probability of virologic success (<400 RNA copies/mL) can be increased from 56% to 62% in patients with Cmin <75 ng/mL. At the overall population level the probability increases from 67% to 69%.

Is there an exposure safety relationship for maraviroc?

Toxicity (ALT/AST elevation and hypotension) was not dose or concentration dependent within the observed concentration range. There are no apparent differences between maraviroc and placebo groups with respect to proportion of patients with 3 fold elevation in ALT (1.95% vs 2.08%) and AST (0.5% vs 1.5%).

Does 300mg (w/o PI) maraviroc with optimized background offer additional benefit compared to that of a matching placebo?

Yes, 300mg (w/o PI) maraviroc with optimized background offers additional benefit compared to that of a matching placebo. There were no apparent differences among 150 mg BID/QD and 300 mg BID/QD groups on overall treatment success. All dose groups were found to be beneficial over the matching placebo group.

Recommendations

1. Exposure response analyses support effectiveness of maraviroc. The following description of exposure response relationship is recommended for the labeling.

Exposure response relationship

The relationship between maraviroc plasma trough concentration (Cmin) and virologic response was evaluated in 973 treatment-experienced HIV-1-infected subjects in studies A4001027 and A4001028. The Cmin, baseline viral load, baseline CD4+ cell count and overall sensitivity score (OSS) were found to be important predictors of virologic success (defined as viral load < 400 copies/mL at 24 weeks). The following table illustrates the proportion of patients with virologic success (%) within each Cmin quartile for 150 mg BID and 300 mg BID groups.

	150 mg BID (with CYP3A inhibitors)			300 mg BID(without CYP3A inhibitors)		
	n	Median Cmin	% patients with virologic success	n	Median Cmin	% patients with virologic success
Placebo	160	-	30.6	35	-	28.6
Q1	77	33	53.3	22	13	50.0
Q2	78	87	62.8	22	29	68.2
Q3	78	166	78.2	22	46	63.6
Q4	78	279	74.4	22	97	68.2

2. There are no exposure dependent safety concerns for maraviroc within the observed concentration range.

3. Given the predicted 2% increase in overall response rate, doubling the dose in patients with Cmin <75 ng/mL is not recommended at this time. However, there is a need to address dose individualization using different dosing strategies (as opposed to single dose doubling) for patients that could potentially fail on maraviroc due to lower exposures. It is only possible by conducting a prospective study comparing individualized dosing strategy and a fixed dose regimen. For maraviroc, such study is not practical due to 2% difference in response rates. Therefore, a concentration controlled trial or a study evaluating the benefit of concentration controlled monitoring at the overall population level is not recommended at this time.
4. A concentration controlled trial evaluating safety and efficacy of an optimized dosing strategy for patients with maraviroc Cmin <50-75 ng/mL is not recommended at this time. The need for such a study will be evaluated after review of the 48 week efficacy and safety data. The week 48 data might help to further understand long term exposure-response relationship and to determine the threshold Cmin, if any.

Exposure response analysis

Data

The data from two placebo controlled phase 2b/3 studies (A4001027 and A4001028) of maraviroc and optimized background therapy (OBT) in treatment experienced patients infected with CCR5-tropic HIV-1 were used in this analysis. These trials used 150 mg QD and 150 mg BID of maraviroc when administered with PIs (except tipranavir/ritonavir) or delavirdine (CYP3A4/P-gp inhibitors) or 300 mg QD and 300 mg BID when administered in the absence of PIs/delavirdine. A4001027 and A4001028 are identical ongoing studies of maraviroc plus optimized background therapy (OBT) in 1049 treatment experienced CCR5 tropic HIV-1 subjects, in the USA and rest of the world.

A4001027 (Phase 3 efficacy study in subjects infected with CCR5 (R5) HIV-1, North America)

This is a 48 week multi-centre, double-blind, randomized (2:2:1), placebo-controlled, phase 2b/3 superiority study to compare the safety and antiviral activity of 2 oral maraviroc treatment regimens [300mg dose equivalent once daily (QD) and 300mg dose equivalent BID] versus placebo, each in combination with OBT (3-6 ARVs, not counting low dose ritonavir). This study planned to enroll subjects infected with CCR5-tropic HIV-1, ≥16 years of age, with no evidence of infection with X4- or dual/mixed-tropic virus (as determined by the Monogram Trofile™ assay). Subjects must have had ≥6 months of prior treatment with at least 1 agent from 3 of the 4 antiretroviral drug classes (or at least 2 for PIs), or documented multi-class resistance and treatment failure to an existing regimen, defined by a plasma viral load =5,000 copies/mL.

The study is ongoing and will be fully unblinded when the last subject has completed the Week 48 visit. An interim efficacy analysis is being performed at 24 weeks. Subjects were stratified at the time of randomization by use of enfuvirtide in the OBT (yes or no) and by screening viral load (<100,000 or ≥100,000 copies/mL). Subjects were randomized in a 2:2:1 ratio (maraviroc QD: maraviroc BID: placebo), balanced within each randomization strata.

As maraviroc is a substrate for cytochrome P450 3A4 (CYP3A4), the dose of maraviroc selected required adjustment based on the concomitant antiretroviral administered in the OBT,

as many components of OBT are modulators of CYP3A4 activity. The recommended dose for subjects receiving at least 1 protease inhibitor (excluding tipranavir/ritonavir) or delavirdine was 150 mg while that for all other regimens was 300 mg. Subjects were randomised to receive their OBT in combination with maraviroc QD, maraviroc BID or placebo. They remained on their assigned treatment for a minimum of 48 weeks unless they discontinued from the study early. Administration of study drug was via the oral route and could be taken with or without food. Antiretroviral agents comprising the OBT were suggested to be taken according to the manufacturer's product labelling. For subjects randomized to QD they were to receive maraviroc + OBT in the evening with placebo + OBT in the morning to maintain the blind.

A4001028 (Phase 3 efficacy study in subjects infected with R5 HIV-1, Europe, Australia and USA)

This study is identical in most respects to study A4001027 except that it recruited subjects from Europe, Australia and North America.

See section 4.2 of sponsor's report (exposure-response-maraviroc-full-final.pdf) submitted with amendment 036 for details on data included in the analyses. The identical datasets were used in the following analyses. The final analysis datasets consisted of 973 subjects.

Table 1: Description of the database used for analyses.

	Placebo 150 mg matched	Placebo 300 mg matched	QD 150 mg	BID 150 mg	QD 300 mg	BID 300 mg
Patient Demographic information						
Number of subjects (n)	160	36	290	311	88	88
Mean age (years)	45.3	46.3	45.2	46.4	47.2	46.9
Male (%)	90.0	86.1	87.2	90.7	87.5	86.4
Race: White (n)	142	29	229	265	79	74
Black (n)	15	6	54	35	7	13
Asian (n)	1	0	3	5	0	0
Others (n)	2	1	4	6	2	1
Clinical end points in exposure response analyses (effectiveness)						
Patients with RNA copies <50 ng/mL (%)	25	27.8	49	50.2	48.9	44.3
Patients with RNA copies <400 ng/mL (%)	30.6	30.6	62.4	67.2	62.5	62.5
Patients with protocol defined failure (%)	53.8	55.6	22.1	19.9	17.0	28.4
Patients with failure at week 4 (%)	32.5	38.9	12.8	11.9	11.4	10.2
Maraviroc exposure						
Median minimum concentration (Cmin) ng/mL (see Figure 13)	0	0	38.7	127.3	16.7	34.4
Median average concentration (Cave) ng/mL	0	0	101.5	230.5	78.7	123
Patient disease information						
Median time since diagnosis (years)	14.0	16.1	13.8	12.8	15.2	14.4
Median baseline CD4 (cells/mL) (see Figure 14)	171.8	149.0	172.5	170.5	206.8	149.8
Median viral load (log10(RNA copies/mL)) (see Figure 15)	4.9	4.9	4.9	4.9	4.8	4.9
Patients with R5 tropism at baseline (%)	91.3	91.7	89.7	90.4	90.9	90.9
Patients with dual tropism at baseline (%)	7.5	8.3	7.9	7.7	8.0	9.1
Patient medication information						
Mean time since first treatment (years)	9.3	11.9	10.0	9.7	9.9	9.9
Patients with OSS=0 (%)	16.9	16.7	12.8	14.1	11.4	9.1
OSS=1 (%)	21.3	19.4	32.4	32.2	36.4	30.7
OSS=2 (%)	28.8	33.3	22.1	23.2	18.2	35.2
OSS=3 (%)	20	19.4	20.7	19.6	26.1	15.9
OSS=4 (%)	10.6	8.3	9.7	7.7	5.7	6.8
OSS=5 (%)	2.5	0	2.1	3.2	1.1	2.3
OSS=6 (%)	0	2.8	0.3	0	1.1	0
Patients with NRTIS=0 or not sensitive (%)	28.1	33.3	31.7	32.8	29.5	33
NRTIS=1 (%)	30	38.9	31.4	32.5	40.9	38.6
NRTIS=2 (%)	30.6	11.1	25.9	26	20.5	14.8
NRTIS=3 (%)	11.3	16.7	11	8.7	9.1	13.6
Patients with NNRTS=0 or not sensitive (%)	89.4	91.7	88.3	90	89.8	78.4
NNRTS=1 (%)	3.8	0	2.8	2.3	0	0
NNRTS=2 (%)	5	8.3	5.9	5.5	9.1	10.2
NNRTS=3 (%)	1.9	0	3.1	2.3	1.1	11.4
Patients with PIS=0 or not sensitive (%)	51.3	55.6	53.1	53.7	61.4	60.2
PIS=1 (%)	45	44.4	41	40.5	38.6	39.8
PIS=2 (%)	3.8	0	5.9	5.8	0	0
Patients receiving tipranavir (%)	0	61.1	0.7	1	65.9	62.5
Patients receiving ritonavir (%)	93.1	58.3	93.4	92	64.8	63.6
Patients not receiving T-20 (%)	58.8	41.7	63.1	60.8	46.6	42
Patients receiving T-20-sensitive (%)	35	44.4	26.6	30.9	40.9	42
Patients receiving T-20-not sensitive (%)	6.3	13.9	10.3	8.4	12.5	15.9
Patients with previous exposure to T-20 (%)	25.6	38.9	31	30.9	35.2	39.8

Is there an exposure response relationship for maraviroc to support evidence of effectiveness?

Generalized additive modeling

The effect of maraviroc exposure and several other predictors on the viral load was analyzed as a binary variable (success) using both logistic regression and generalized additive models (GAM). A GAM model was built using the automated step-wise search developed in S-PLUS. This automated step-wise search selects the best GAM using forward selection and backwards deletion given the range of models. A series of candidate relationships (e.g. linear, log-transformation, spline, Loess smooth) that describe how each particular predictor might enter the model was defined for every predictor and the final model was built up by evaluating all candidate forms for each predictor in a step-wise manner.

Several binary endpoints indicating virologic success, such as, protocol defined success at week 24[§], viral load <50 copies/mL at 24 weeks, viral load <400 copies/mL at 24 weeks and >1 log decrease in viral load at 4 weeks were investigated. See section 5.2 of the sponsor's report (exposure-response-maraviroc-full-final.pdf submitted with amendment 036) for details on these endpoints. In the sponsor's report, these endpoints were modeled as failures (1-success).

The population PK model predicted plasma trough concentrations (Cmin) were used as an exposure variable. The average concentration and Cmin were correlated (Figure 12), Cmin was used as the exposure variable because it may be amenable to routine monitoring in patients. The following covariates that could impact the Cmin-virologic success relationship were also evaluated in the generalized additive (logistic) regression analysis:

- Dosing information
  - Randomization group (GRP: 0=Placebo, 1=QD, 2=BID)
  - Dosing/treatment group (GRP1: 0=Placebo, 1=150mgQD, 2=150mgBID, 3=300mgQD, 4=300mgBID)
- Patient disease information
  - Time since diagnosis (TDIA)
  - Baseline viral load (BVL)
  - Baseline CD4 count (BCD4)
  - Tropism at baseline (BTRP: 1=not readable, 2=Dual/Mixed, 3=non-phenotypable, 4=X4, 5=R5)
  - Time since first treatment (TFHT)

[§] In the protocol treatment failure was defined. For analysis purposes, success=1-failure was used. Treatment failure was defined as (1) An increase to at least 3x the baseline [mean of all 3 values before start of dosing; screening, randomisation and baseline (Day 1)] viral load at the Week 2 visit or thereafter (confirmed by a second measurement taken no more than 14 days after the first measurement); (2) Viral load <0.5 log10 decrease from baseline on 2 consecutive measurements starting at Week 8 (second measurement taken no more than 14 days after the first measurement); (3) Viral load <1.0 log10 decrease from baseline on 2 consecutive measurements starting at Week 8 (second measurement taken no more than 14 days after the first measurement), in a subject who had previously achieved a ≥2.0 log10 decrease from baseline; or (4) An increase in viral load to ≥5,000 copies/mL on 2 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.

- Overall susceptibility score (OSS)**
- Number of sensitive NRTIs (NRTIS)
- Number of sensitive NNRTIs (NNRTS)
- NNRTI in the OBT (NNRTI: 1=delavirdine, 2=efavirenz, 3=nevirapine)
- Number of sensitive protease inhibitors (PIS)
- Presence and sensitivity to T20 (T20S: 0=no T20, 1=T20 and sensitive, 2=T20 but insensitive)
- Previous treatment with T20 (T20H: 0=No, 1=Yes)
- Presence of ritonavir or Kaletra(RIT: 0=No, 1=Yes)
- Presence of tipranavir (TIPpresent)

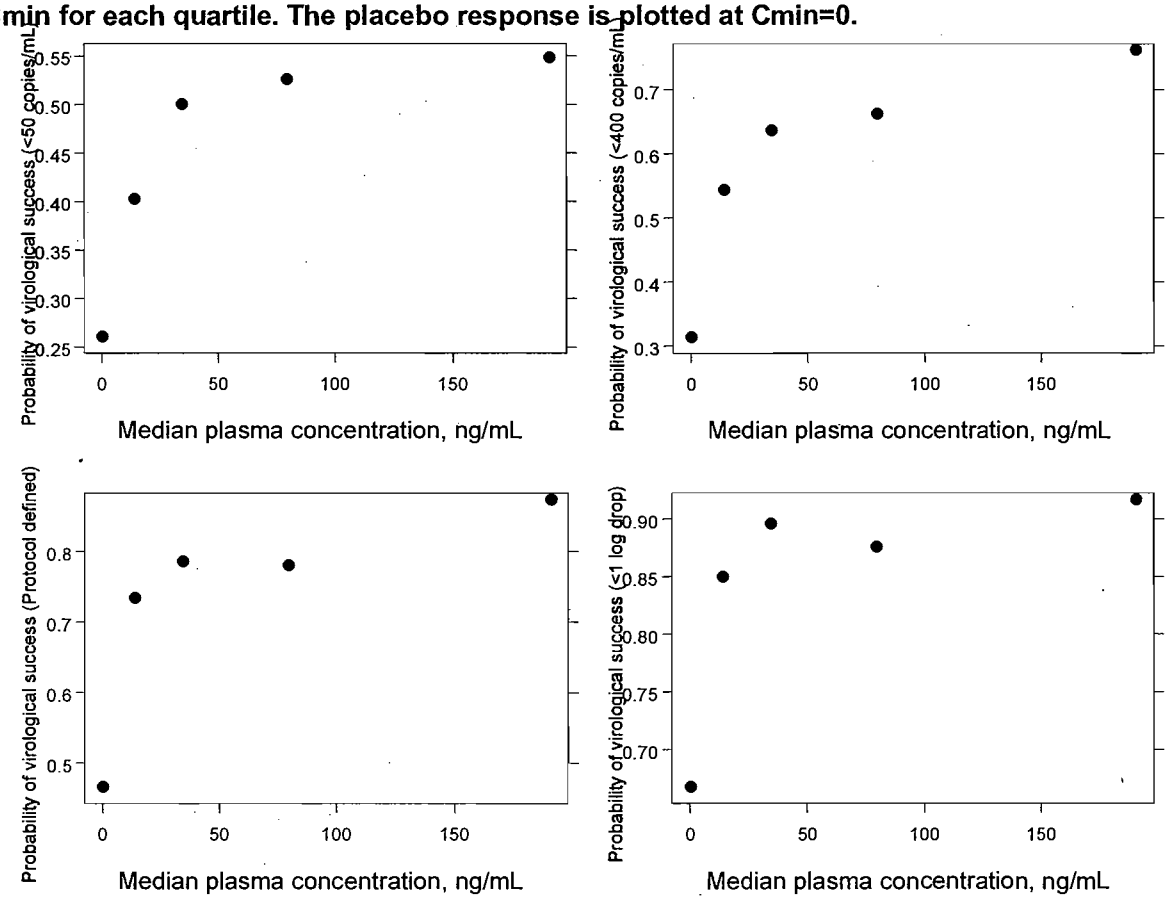
- Patient demographic information
  - Age
  - Sex (1=male, 2=female)
  - Race (1=White, 2=Black, 3=Asian, 4=other)

** OSS relates to number of treatment options available as predicted by genotype (GSS) and phenotype (PSS) susceptibility score. 0=No treatment options.

GAM modeling Results

Figure 2 illustrates the relationship between Cmin and response for all endpoints. Clearly, there is a concentration dependent increase in probability of virologic success across all endpoints. There is no additional benefit at Cmin greater than 50-75 ng/mL.

Figure 2: Cmin-response relationship. The mean response is plotted against the median Cmin for each quartile. The placebo response is plotted at Cmin=0.



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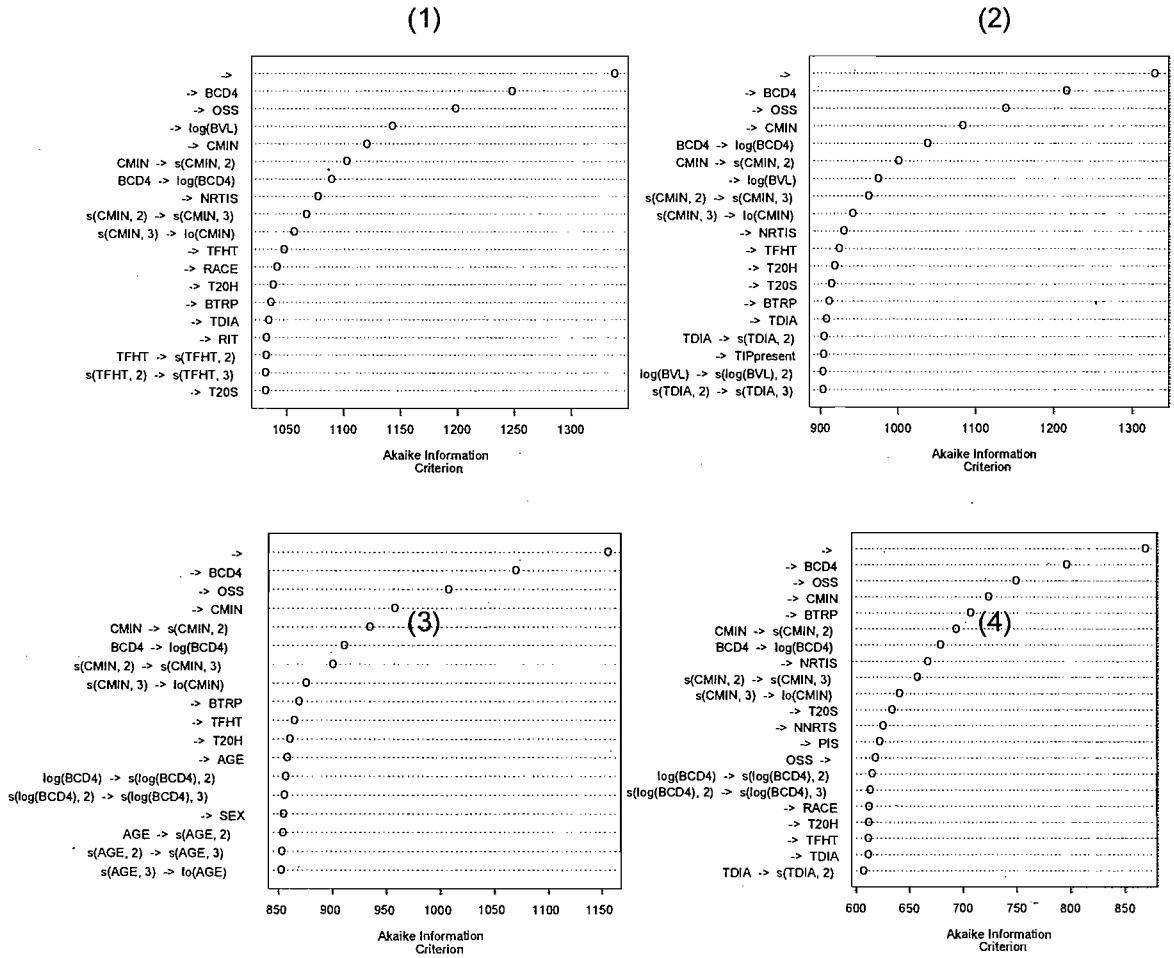
The Akaike statistic (AIC) was used to select the final model. Table 2 summarizes the final model for all endpoints and Figure 3 summarizes the change in AIC in the automated step-wise search for model predictors.

Table 2: Final GAM model for all endpoints

	Endpoint	Final model
1	Viral load <50 copies/mL at 24 weeks	HIVF5S ~ lo(CMIN) + log(BCD4) + log(BVL) + BTRP + OSS + TDIA + s(TFHT, 3) + NRTIS + T20S + T20H + RIT + RACE
2	Viral load <400 copies/mL at 24 weeks	HIVF4S ~ lo(CMIN) + log(BCD4) + s(log(BVL), 2) + BTRP + OSS + s(TDIA, 3) + TFHT + NRTIS + T20S + T20H + TIPpresent
3	Protocol defined success at week 24	HIVPS ~ lo(CMIN) + s(log(BCD4), 3) + BTRP + OSS + TFHT + T20H + lo(AGE) + SEX
4	>1 log decrease in viral load at 4 weeks	HIVFW4S ~ lo(CMIN) + s(log(BCD4), 3) + BTRP + s(TDIA, 2) + TFHT + NRTIS + NNRTS + PIS + T20S + T20H + RACE

Figure 3: Results of the automated step-wise search for predictors of virologic success. -> a indicates addition of variable a; a->b indicates the replacement of variable b with a, c->indicate removal of a variable.



Overall, baseline CD4+ count, baseline viral load, OSS and Cmin were the most important predictors of the virologic success.

Here onwards, the current report focuses on findings derived from the analyses of the clinically relevant endpoint, viral load <400 copies/mL at 24 weeks. Figure 4 illustrates distribution of residuals and qqplot for residuals in the final GAM model. The residuals exhibit reasonable normal distribution. The assumption does not seem to hold at the tail ends and the central tendency is slightly farther from zero.

Figure 4: Distribution of residuals and qqplot for residuals in the final GAM model for viral load <400 copies/mL at 24 weeks

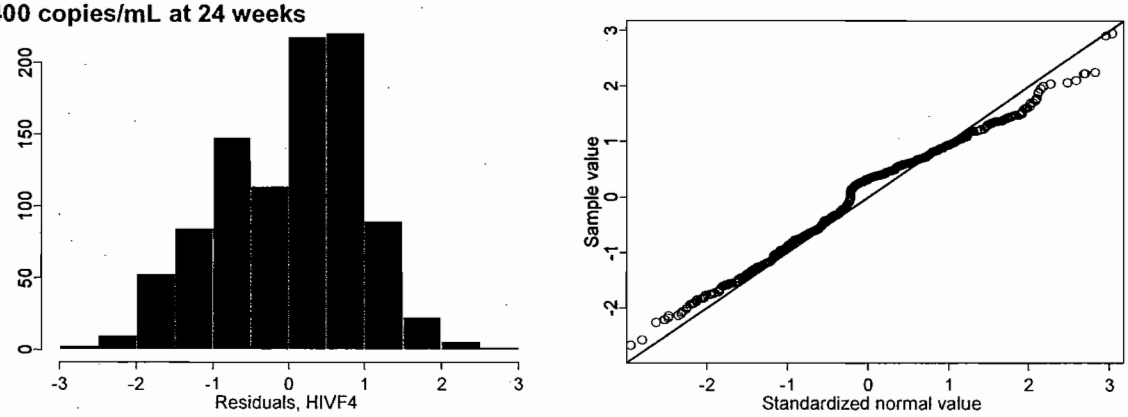
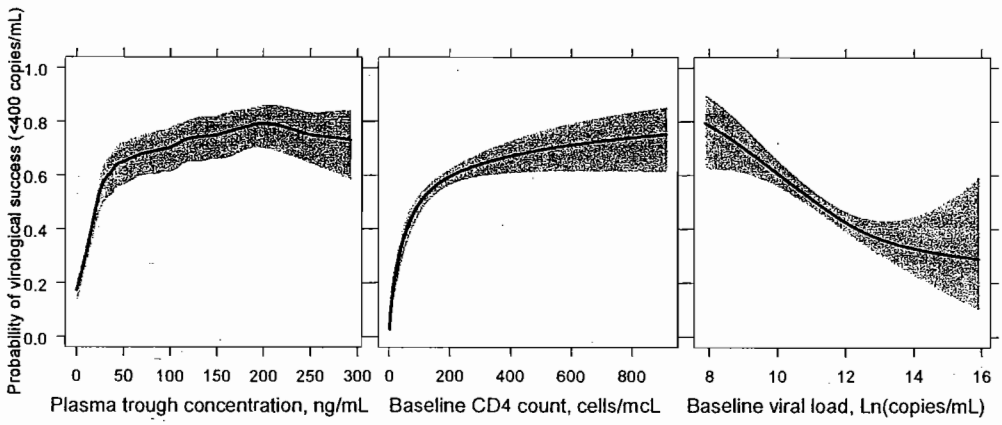


Figure 5 illustrates the relationship between the probability of virologic success (<400 copies/mL) and Cmin, baseline CD4+ count and baseline viral load. The baseline tropism, time since diagnosis, time since the first treatment, NRTIS, T20S, T20H and TIPpresent were also found to impact the virologic success. The probability of virologic success is higher at higher Cmin and/or higher baseline CD4+ count and/or lower baseline viral load.

Figure 5: Cmin (left panel), baseline CD4+ count (middle panel) and baseline viral load (right panel) are important predictors of the virologic success. The shaded area represents twice standard error region.

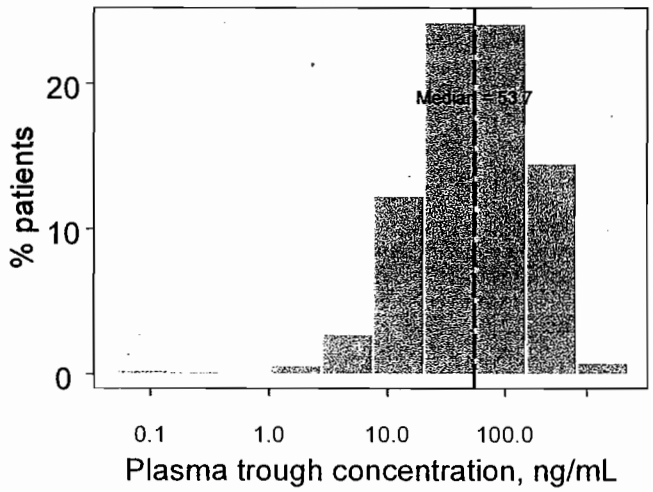


What is the advantage of dose individualization for maraviroc?

The variability in Cmin is high, with a range of 0.1 to 560 ng/mL.

Figure Q3 illustrates distribution of Cmin across all dose groups and proposed market doses in the phase 2b/3 studies. For the proposed market doses, the proportion of patients with Cmin <50 ng/mL was higher for 300 mg BID (no PIs (except tipranavir/ritonavir) or delavirdine) group than 150 mg BID (with PIs (except tipranavir/ritonavir) or delavirdine) group as shown in Table Q2.

Figure 6: Distribution of plasma trough concentrations across all dose groups (upper panel). The lower panel represents distribution across the proposed market doses.



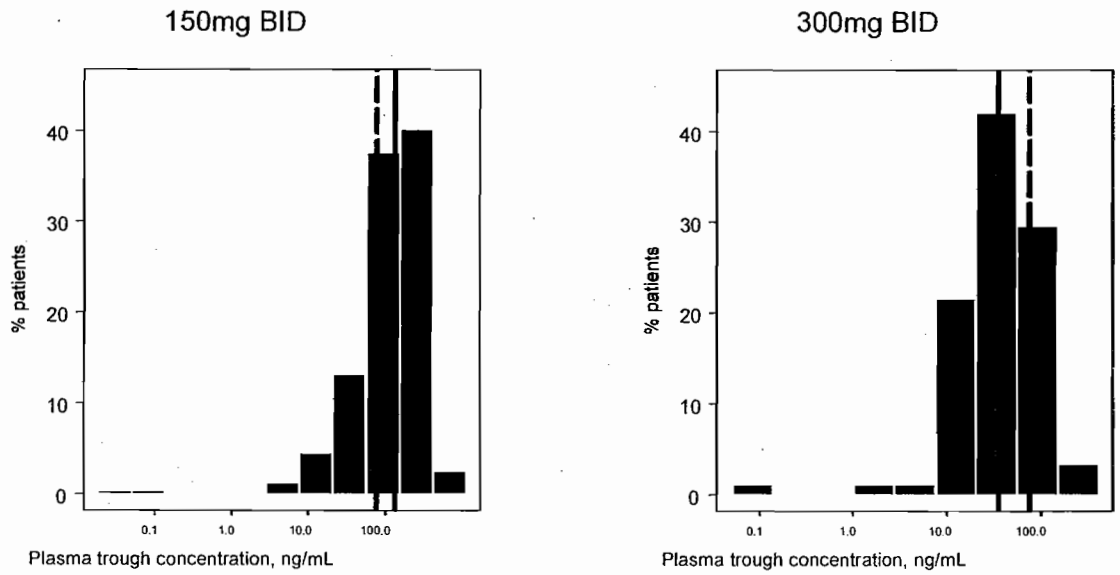
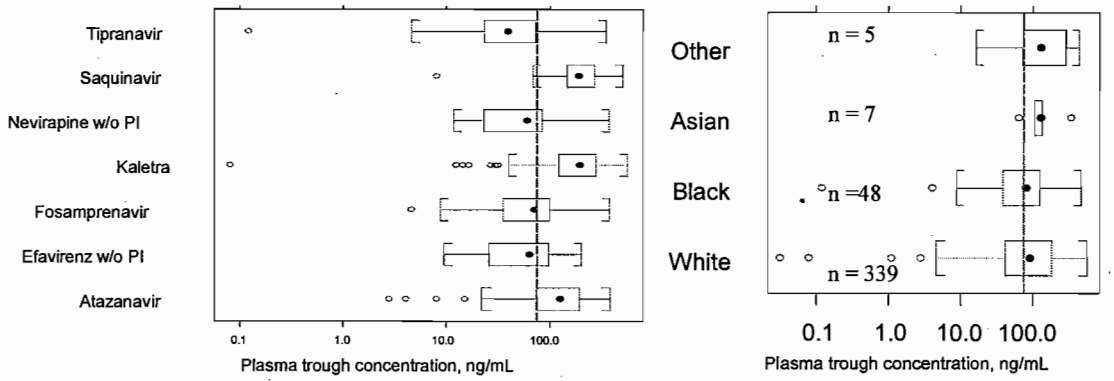


Table 3: Distribution of concentrations for 150 and 300 mg BID.

Dose group	Number of patients	Concentration range	% patients <25 ng/mL	% patients <50 ng/mL	% patients <75 ng/mL	% patients <100 ng/mL
150 mg BID	311	0.03-561.7	7.7	17.3	28.3	42.4
300 mg BID	88	0.12-204.7	33.0	65.91	77.3	89.8

An attempt was made to understand the factors leading to lower Cmin. The box plots in Figure 7 illustrate that the distribution of Cmin is not affected by concomitant drugs and race groups (see Figure 16 for the complete list). Other covariates were also investigated and were not found to be explanatory of the lower Cmin. See Figure 11 assessing collinearity between concentration and all the covariates listed above.

Figure 7: Concomitant drugs (left panel) [5] and race (right panel) do not explain lower Cmin levels (BID only).



The proposed dosing does not allow good control over pharmacokinetic variability in maraviroc concentrations. To understand the intrinsic source of variability (inter-patient vs within patient variability) in Cmin, data from treatment naïve patients were analyzed (A4001015 study, monotherapy study). In this study, daily Cmin measurements were available from day 6 to day 10. A random effect approach was used to estimate inter-patient and within patient variability. The inter-patient variability (%CV=50%) was greater than within patient variability (%CV=33%). The inter-occasion variability in the phase III trials was higher (~45%) than the above monotherapy trial. Estimates from phase III trial are usually less reliable due to difficulties in proper documentation. However, these phase III estimates could represent a situation closer to a typical clinical setting where it may be difficult to assess exact plasma levels based on single concentration. However, the factors leading to high inter-occasion/residual variability, such as, compliance, food intake, concomitant medication intake etc. may be controlled in the clinical setting allowing reliable assessment of Cmin.

Since Cmin is a major predictor of the virologic success and a single trough measurement is a good predictor of the concentrations (inter-patient variability > within patient variability), a threshold-based simulation was conducted to understand the advantage of doubling the dose for patients with 'below threshold' concentrations.

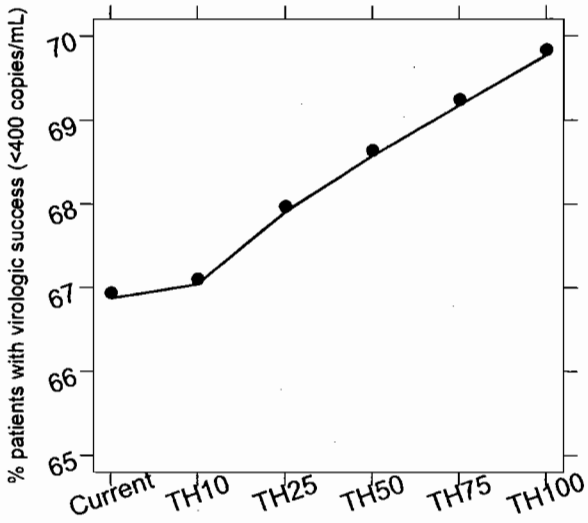
The Cmin-virologic success relationship was employed to investigate the advantage of doubling maraviroc doses in patients with Cmin lower than a certain threshold Cmin. Five different

[5] For drug interaction plot, the multiple drugs in patients' OBT were not taken into account. The aim was to highlight if any concomitant medication might stand out as a predictor of lower concentrations

threshold Cmins, 10, 25, 50, 75 and 100 ng/mL, were studied. Data from the proposed market doses (150 and 300 mg BID) were used for the simulations. A factor of 2 was applied to the original values, if the Cmin was below the defined threshold. If the Cmin was above the defined threshold, the original value was retained.

Figure 8 illustrates the predicted virologic success for threshold-based simulations.

Figure 8: The probability of virologic success can be increased up to 69% (vs. original 67%) by doubling the dose in patients with Cmin <75 ng/mL. THxx represents threshold Cmin (ng/mL) values used in simulation.



With the proposed market dosing, the virologic success on maraviroc with OBT was shown to be 67%. The probability of virologic success can be increased to 69% by doubling the dose in patients with Cmin <75 ng/mL. As seen from Table 3, 75 ng/mL as a threshold will require 28% (150mg BID group) and 77% (300 mg BID group) to have dosing adjustments post Cmin assessment. The population benefit of monitoring therapeutic concentration is 2%. In addition to Cmin, several other patient and virus specific factors are important determinants of the virologic success.

The benefit of doubling the dose in patients with Cmin <75 ng/mL could be looked at differently. In the current simulations, we evaluated 399 patients out of which 146 (37%) patients needed dose doubling due to concentrations below 75 ng/mL. The current probability of the virologic success in those 146 patients is 56%. Dose doubling could increase the probability of virologic success to 62%, an 11% relative increase in the population that actually received dose change from monitoring therapeutic concentrations.

In conclusion, patients with Cmin >50-75 ng/mL have a better chance of virologic success. In addition to Cmin, the probability of success is also influenced by other patient specific factors such as baseline CD4+ count, baseline viral load and OSS.

d. With the sponsor's proposed dosing, ~67% of patients should achieve <400 RNA copies/mL.

e. Concomitant drugs or demographic factors were not the source of lower Cmin values.

The simulations indicate that by doubling the dose the probability of virologic success (<400 RNA copies/mL) can be increased from 56% to 62% in patients with Cmin <75 ng/mL. At the overall population level the probability increases from 67% to 69%.

Is there an exposure safety relationship for maraviroc?

The exposure response relationship for QT prolongation, ALT/AST elevation, hypotension were investigated. The ALT/AST elevation was a concern for an earlier CCR-5 inhibitor and postural hypotension was observed in early phase trials at maraviroc 1200mg dosing. The following table summarizes incidences of AST/ALT elevations. There are no apparent differences between maraviroc and placebo groups. Similarly, there were very few cases of hypotension in the clinical trials and there were no differences between maraviroc and placebo groups. A separate IRT/QT report is available investigating the effect of maraviroc on QT prolongation.

Table 4: Proportion of patients with 3 fold elevation in ALT and AST

	Maraviroc (n=768)	Placebo (n=192)
% patients with 3 fold increase in ALT	1.95%	2.08%
% patients with 3 fold increase in AST	0.5%	1.5%

Toxicity (QT prolongation, ALT/AST elevation, hypotension) was not dose or concentration dependent within the observed concentration range.

Does 300mg (w/o PI) maraviroc with OBT offer additional benefit to that of a matching placebo?

Based on the preliminary analysis conducted by the sponsor (Figure 9), there seemed no difference between 300 mg BID/QD (w/o PI) and placebo group. This comparison was not found to be convincing as there was a matching placebo group available for 150 mg and 300 mg groups, based on the background treatments. Also, the sponsor's analyses was based on limited number of patients as it was done as an interim analysis. Figure 10 illustrates comparison of each dose group with that of a matching placebo in both clinical trials. Four binary endpoints, RNA <400 copies/ML, RNA <50 copies/ML, RNA <400 copies/mL or >1 log drop change in viral load and RNA <400 copies/mL or >0.5 log drop change in viral load, were investigated. There were no apparent differences between 150 mg BID/QD and 300 mg BID/QD on overall treatment success (as defined by each endpoint). Both dose groups were found to be beneficial over the corresponding placebo group.

Figure 9: Sponsor's preliminary analysis: Probability of failure (>50 copies/mL) by dose groups.

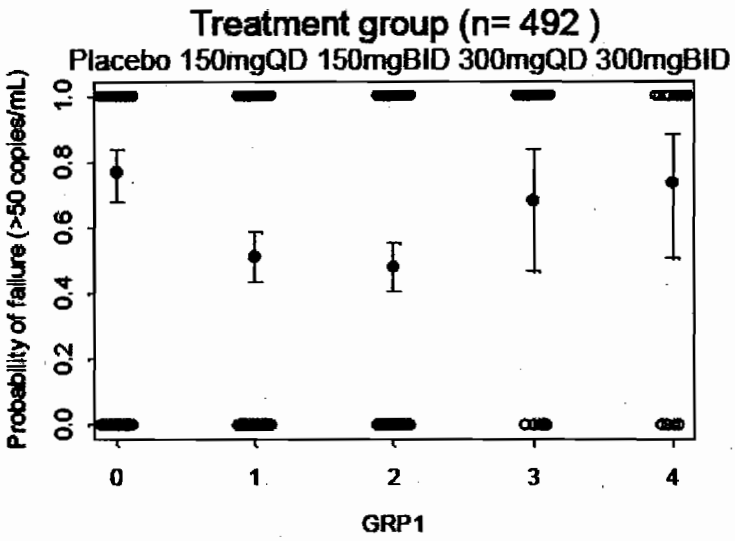
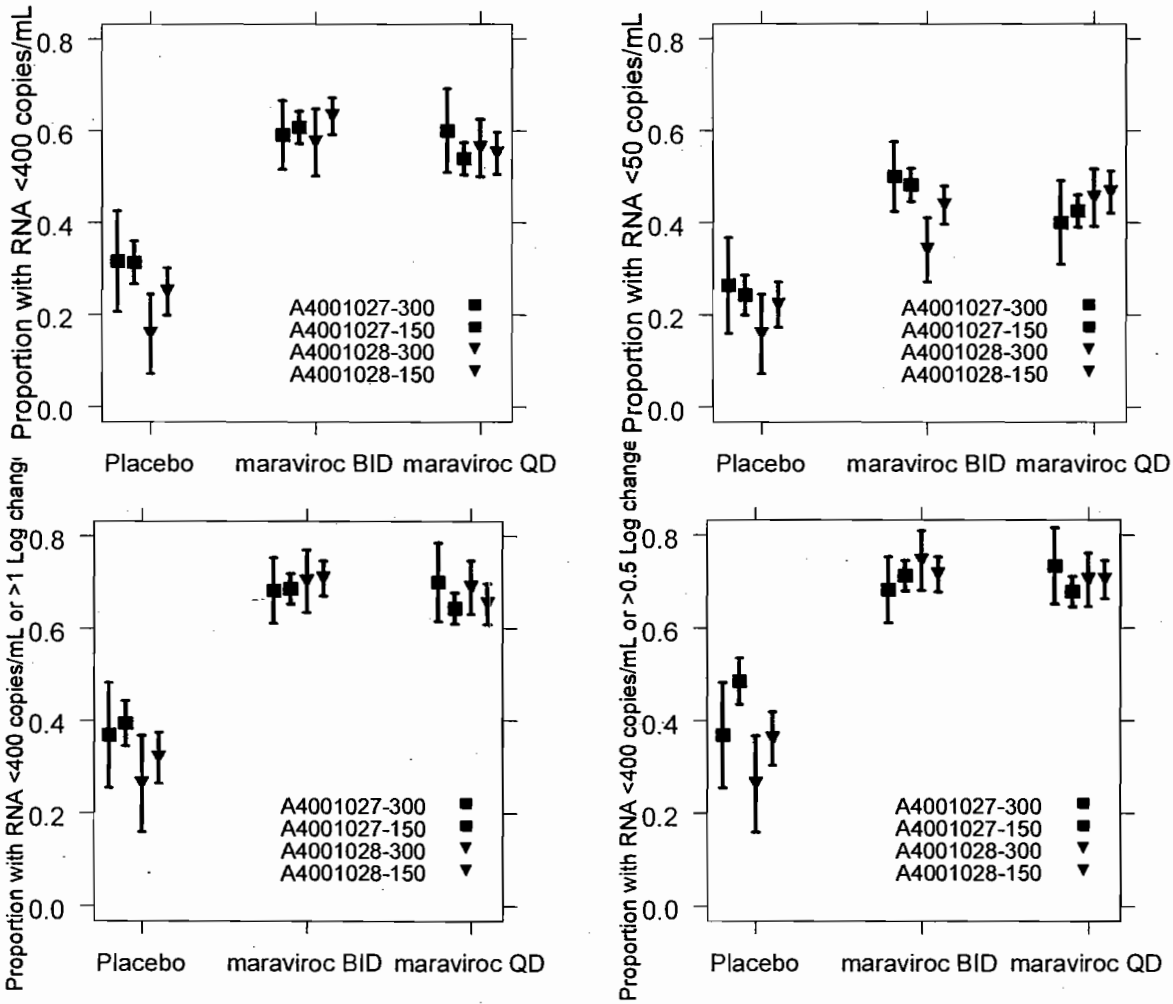
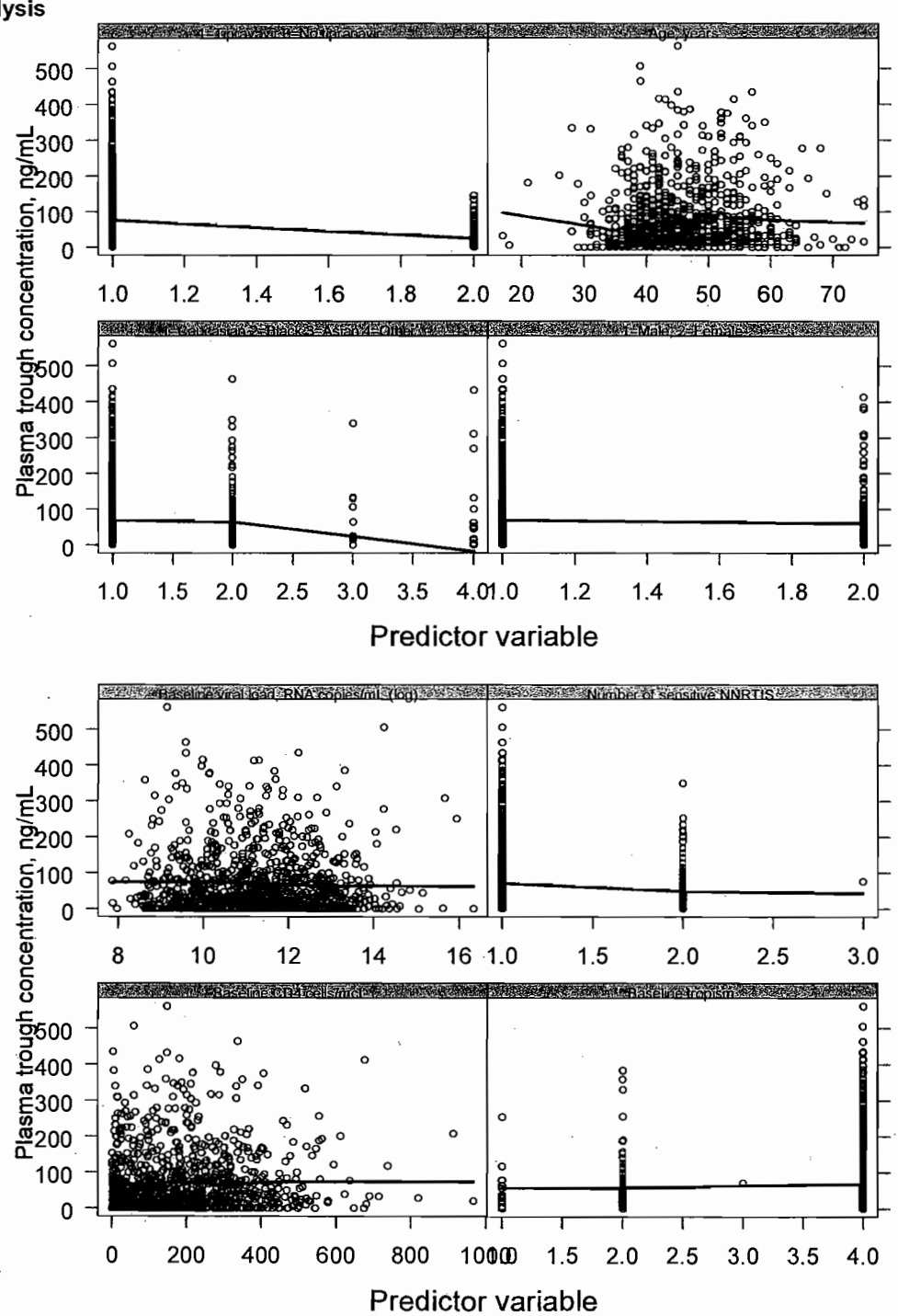


Figure 10: Reviewer's analysis on full dataset using four endpoints



Appendix

Figure 11: Collinearity between Cmin and all covariates used in the exposure response response analysis



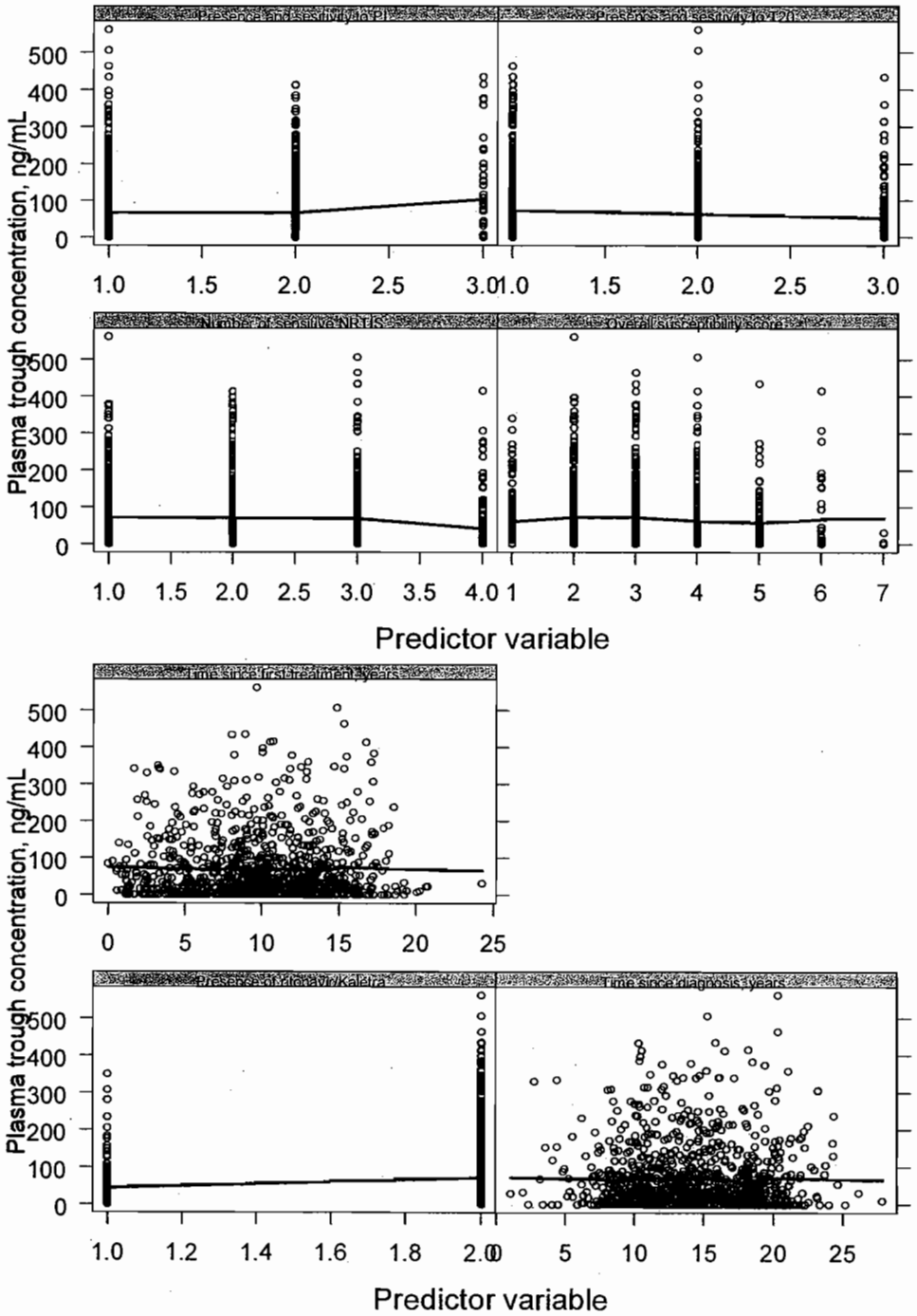

Plasma trough concentration, ng/mL
Predictor variable
Number of sensitive NRTIs
Overall susceptibility score
Time since first treatment, years
Time since diagnosis, years

Figure 12: Correlation between Cmin and average plasma concentration

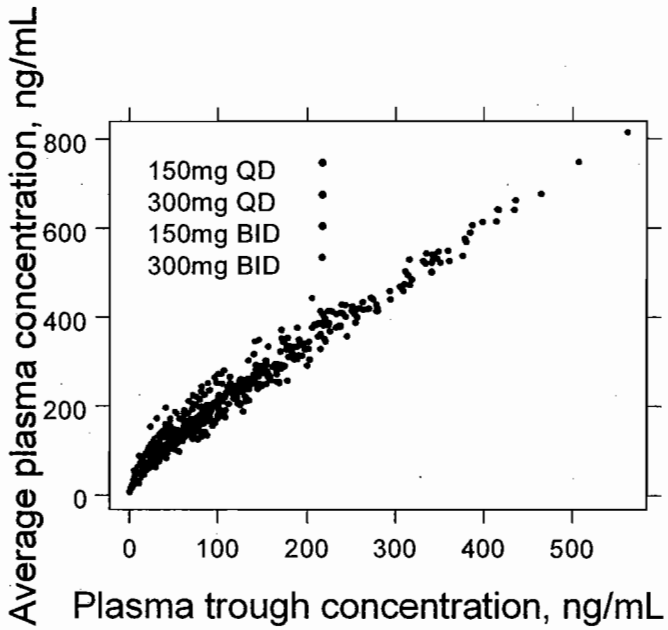


Figure 13: Distribution of Cmin across dose groups

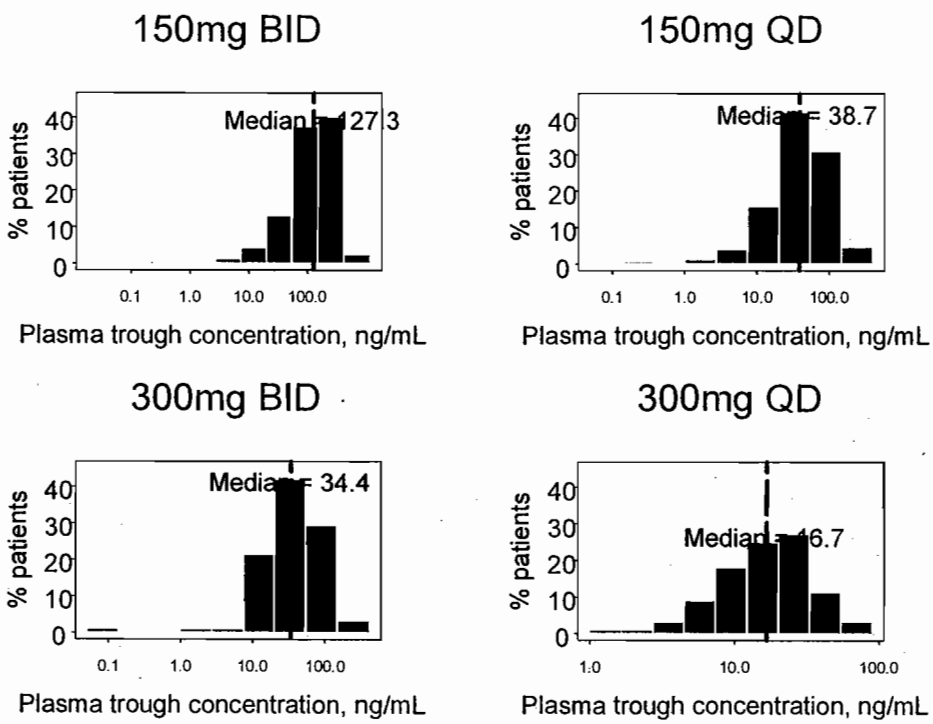


Figure 14: Distribution of baseline CD4+ across dose groups

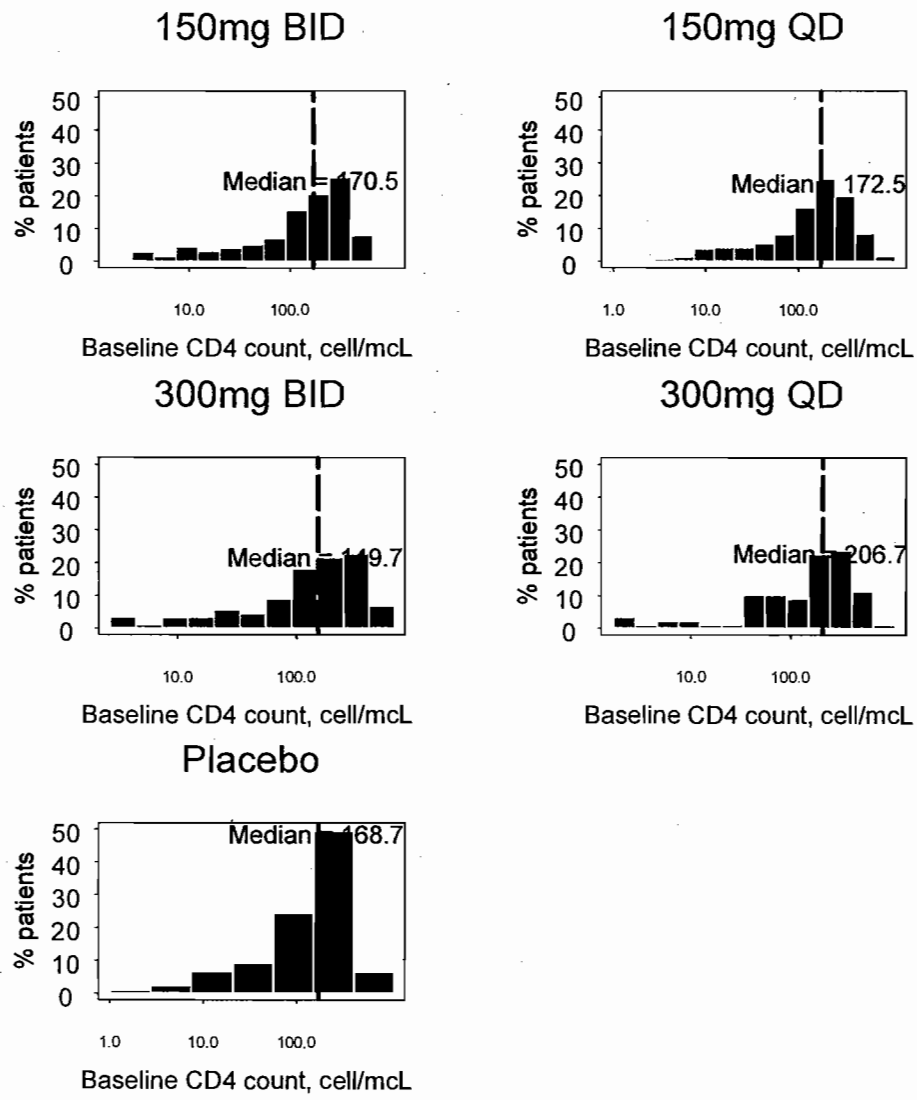


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Figure 15: Distribution of baseline viral load across dose groups

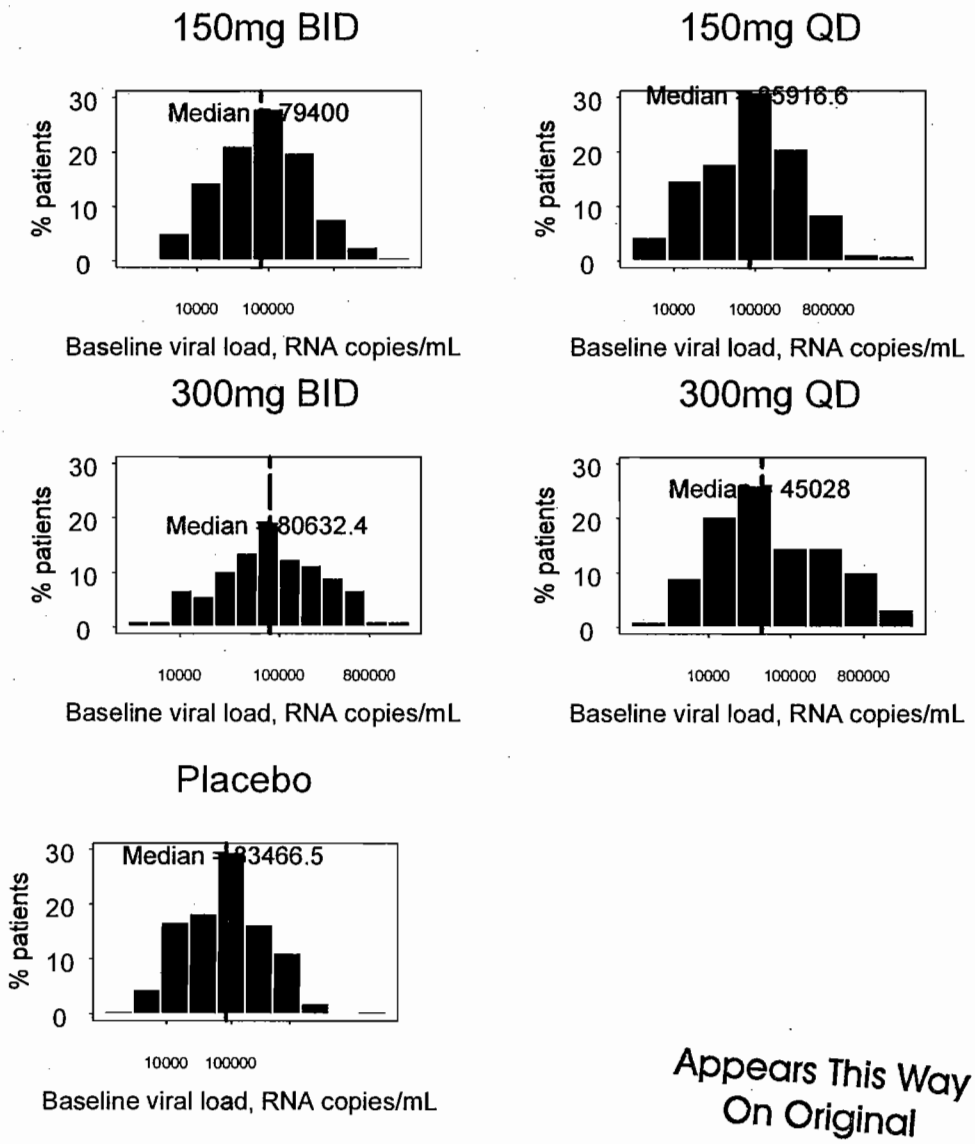

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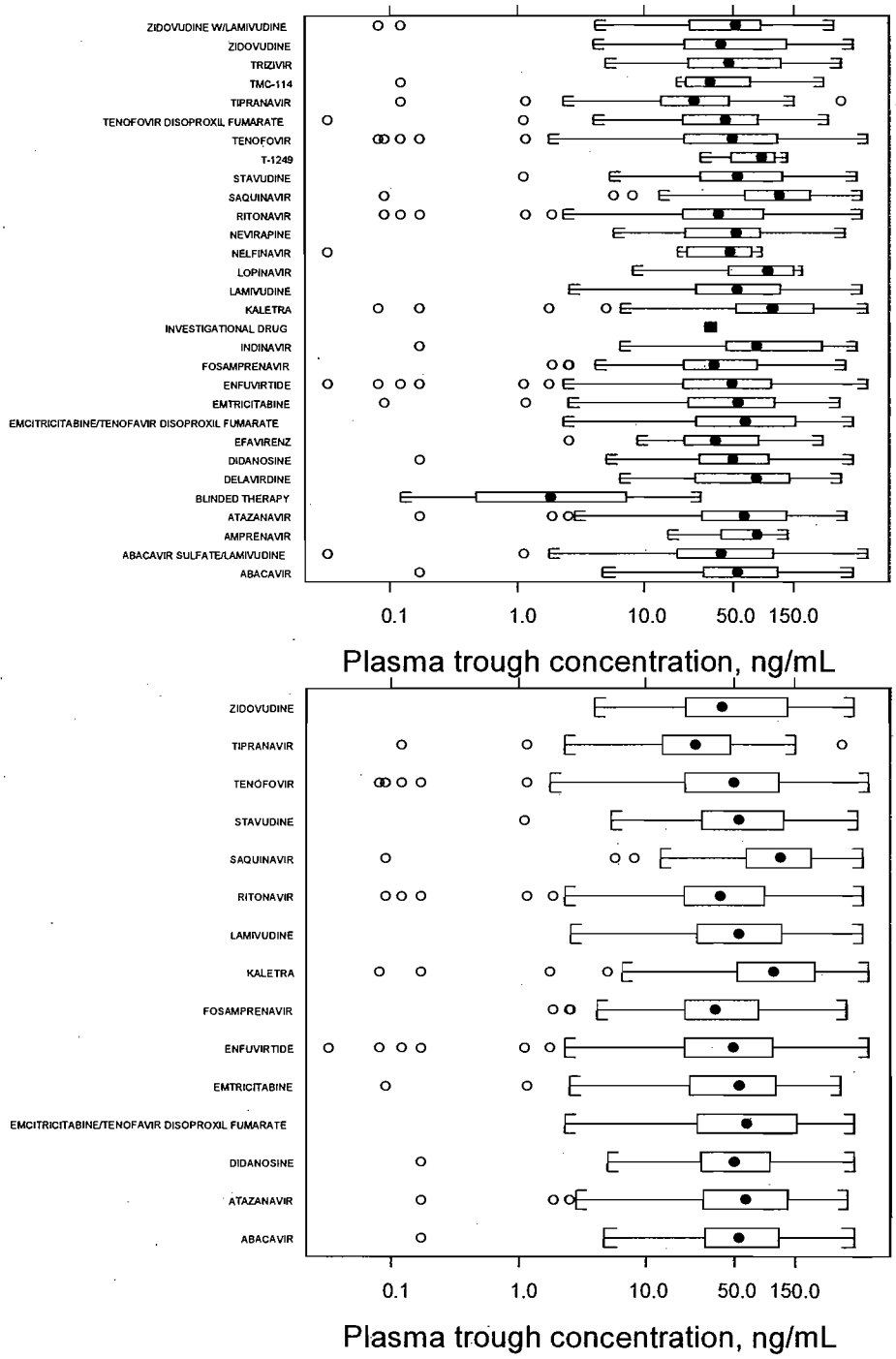
Figure 16: Distribution of Cmin by the drugs included in the OBT. The upper panel shows all drugs in OBT and the bottom panel shows the selected drugs



4.4.2 Pharmacogenomics review

PHARMACOGENOMICS REVIEW

NDA: 22128	Submission Date(s): Dec 19, 2006
Generic Name	Maraviroc
Pharmacogenomic Reviewer	Shashi Amur, Ph.D.
Applicant	Pfizer Inc.
Relevant IND(s)	IND 65229
Submission Type	Priority
Formulation; Strength(s)	150 mg and 300 mg film-coated tablets
Indication	Treatment for treatment-experienced patients infected with CCR5-tropic HIV-1, in combination with other antiretroviral agents

1. EXECUTIVE SUMMARY

In the pharmacogenomics special review report (IND 65, 229) associated with NDA 22128, the applicants have discussed the results of their exploratory studies. These include the study of the impact CCR5 and CCR2 polymorphisms on safety and toleration of maraviroc in healthy volunteers and on safety, toleration and efficacy in asymptotic-, non-CCR5 tropic- and CCR5-tropic HIV infected individuals.

The applicants have selected 16 polymorphisms for genotyping studies in the above-mentioned populations based on

- the frequency of the allele in Caucasian and/or African populations and
- on published association between the polymorphism and HIV-1 infection and/or disease progression

These polymorphisms include 2 variants in the CCR5 coding region, 13 variants in the CCR5 promoter region and 1 variant in CCR2 coding region. In addition, 12 haplotypes derived from the promoter variants have also been selected since these variants are in strong linkage disequilibrium with each other. The promoter polymorphisms are more common than the widely studied CCR5Δ32 genotype found in the coding region of CCR5. Another variant studied was the m303 (a nonsense mutation) in the CCR5 coding region that results in a truncated, non-functional receptor.

In brief, no evidence of association between genotypes and any of the major viral endpoints or adverse events was observed. Other findings are listed below:

1. As expected, an association of CCR5Δ32 genotype and CCR5 expression was observed in all the studies.
2. CCR5 WT/Δ32 individuals had a lower baseline viral load in non-CCR5 tropic-HIV infected individuals.
3. A potential haplotype/treatment interaction with viral load from baseline was observed in non-CCR5 tropic- HIV infected individuals.
4. No effect of CCR5 WT/Δ32 genotype was seen on baseline viral load in CCR5 tropic- HIV infected individuals

1.1 Recommendation

The Pharmacogenomics information provided is acceptable. Phase IV commitments section lists additional studies suggested.

1.2 Suggestions for Phase IV Commitments

Several CCR5 gene polymorphisms have been reported to be associated with susceptibility to HIV infection and progression (Navratilova Z, 2006: Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech. Repub. 150(2):191-204). In a study with a diversity of races (Caucasian, Black, Hispanic and Asian) to be carried out as part of the Phase 4 commitments, additional SNPs in CCR5 reported to be relevant in Black and Asian population(none appear to be reported in the Hispanic population) should be studied. For example, C101X variant in Black population (allele frequency, 1.4%) which results in non-functional CCR5 similar to CCR5 WT/Δ32 seen in Caucasian population and C269F variant in Asians that results in poor expression of CCR5 with impaired function. In addition, A29S variant in Blacks (allele frequency 1.5%) and R60S variant in Blacks (allele frequency, 1.3%), have been reported to affect the pharmacology of CCR5 receptor function; G106R variation in Asians has been shown to cause deficiency in binding chemokines and in allowing entry of HIV (Arenzana-Seisdedos and Parmentier, 2006: Seminars in Immunol. 18:387-403).

2. SUMMARY OF IMPORTANT PHARMACOGENOMICS FINDINGS

I. Pharmacogenomics and maraviroc in healthy volunteers: This study was undertaken with 164 healthy volunteers from four phase 1 clinical protocols, A 4001001, A 4001002, A 4001005 and A 4001008. The objective of this study was to study possible association of CCR5 genotypes with the following primary phenotypes: blood pressure, adverse events such as hypotension and dizziness and CCR5 expression. As expected, an association of CCR5Δ32 genotype and CCR5 expression was observed. No clinically significant associations of CCR5/CCR2 genotypes to safety and toleration of maraviroc were observed.

II. Pharmacogenomics and PK profile of maraviroc in Asians: This study examined the impact of CYP P450 2D6, 2C9, 2C19, 3A4, 3A5 and MDR1 polymorphisms on the PK profile of maraviroc in 24 Asians (clinical studies

A4001022 and A4001025). No significant association between the individual genotypes and Cmax/AUC for any of the SNPs studied, except a possible trend with a SNP at position 681 of the CYP2C19 locus.

III. Pharmacogenomics and PK profile of maraviroc in phase 1 and phase 2a: In this analysis, the relationship between CYP3A4/A5, CYP2B6, MDR1 and BCRP1 polymorphisms and PK profile of maraviroc was studied in 320 Caucasians (Phase 1:protocols A4001001, 1002, 1005, 1008, 1019 and 1021) and phase 2a (protocols A4001007 and 1015). No visible trends were observed among between CYP3A4/A5, CYP2B6 and BCRP1 polymorphisms and Cmax in healthy volunteers or in HIV patients treated with maraviroc. A possible trend was observed between two MDR1 polymorphisms and Cmax in both the healthy and infected groups.

IV. Pharmacogenomics and maraviroc monotherapy in asymptomatic HIV-1 infected individuals: The objective was to carry out an exploratory analysis of the possible correlation of CCR5 polymorphisms to safety, tolerance and efficacy of maraviroc monotherapy in 80 asymptomatic HIV infected individuals (protocols A4001007 and A4001015). The results showed no evidence of association of CCR5 genotypes and baseline viral load or antiretroviral activity of maraviroc. CCR5 genotype was also did not impact blood pressure changes observed in maraviroc-treated subjects. As expected and as observed previously, CCR5Δ32 variants had a lower CCR5 expression.

V. Pharmacogenomics and maraviroc in non CCR5-tropic subjects: This analysis was conducted in 163 subjects (120 Caucasian- and 43 Black subjects, protocol A4001029) to determine the impact of CCR5/CCR2 polymorphisms on the safety, toleration and efficacy of maraviroc in antiretroviral-treated, non-CCR5-tropic HIV-1 infected group. The results of the study showed that the CCR5 WT/Δ32 individuals had a lower baseline viral load. A potential haplotype/treatment interaction with viral load from baseline was observed. No correlation between genotypes and any of the major viral endpoints was observed.

VI. Pharmacogenomics and maraviroc in CCR5-tropic subjects: The aim of this study with 982 subjects (823 Caucasian and 136 Black subjects, protocols A4001027 and A4001028), was to study the influence of CCR5/CCR2 polymorphisms on the safety, toleration and efficacy of maraviroc in antiretroviral-treated, CCR5-tropic HIV-1 infected group. In contrast to the observations in the previous study, no effect of CCR5 WT/Δ32 genotype was seen on baseline viral load. As with the previous study, no evidence of association between genotypes and any of the major viral endpoints was observed.

3. QUESTION BASED REVIEW

3.1 Are host genetic factors likely to influence the response to Maraviroc?

Maraviroc is a selective antagonist of the chemokine receptor, CCR5. A 32-base deletion in the CCR5 gene (CCR5Δ 32) has been shown to influence HIV infection and progression. Other genetic variants of the

CCR5 gene that affect the function of the protein could theoretically influence the response to Maraviroc.

Maraviroc is a substrate of CYP3A4 and of the transporter P-glycoprotein (MDR1). Thus, genetic polymorphisms in these genes could have a significant effect on the response to maraviroc.

3.2 Which deletions/genetic polymorphisms in CCR5 gene are known to influence CCR5 function?

Deletions/polymorphisms in the CCR5 coding region: The most well-studied deletion in the CCR5 gene is the CCR5Δ 32 deletion, which is a 32-base pair deletion in the CCR5 gene. This deletion results in the production of a non-functional protein. The CCR5Δ 32 deletion appears to increase resistance to HIV infection and does not appear to have any deleterious consequences in individuals.

A nonsense mutation, m303, truncates the CCR5 protein that results in a non-functional receptor. These two genetic variants are known to influence CCR5 function *in vivo*. Other polymorphisms have been observed in the CCR5 gene that appear to influence the function of the CCR5 receptor *in vitro*. However, these are very rare and are not likely to have a major impact on treatment of HIV infection.

Polymorphisms in the promoter region of CCR5 gene: Many polymorphisms in the promoter region of the CCR5 gene associated with progression to AIDS are reported. These polymorphisms are in strong linkage equilibrium with each other.

3.3 Are genetic variations in CCR2 gene likely to influence response to Maraviroc?

The CCR2 gene is closely linked to the CCR5 gene on chromosome 3. A polymorphism in the CCR2 gene at position 64, changes the amino acid valine to Isoleucine (CCR2 V64I). This polymorphism appears to have a protective effect and appears to be associated with slower disease progression. However, some studies failed to confirm the disease-slowing association with this variant. One report showed that the non-responder population did not carry the CCR2 V64I variant allele (Van Vaerenbergh et al., 2002: AIDS Res Hum Retroviruses 18(6):419-426). The results of this unconfirmed study suggest that the variant could possibly serve as a biomarker for responders to HIV treatment.

3.4 Do genetic polymorphisms in CCR5/CCR2 gene influence safety or efficacy of Maraviroc?

Four studies, A 4001001, A 4001002, A 4001005 and A 4001008, with 164 healthy volunteers examined association between CCR5 genetic polymorphisms and baseline blood pressure measurement. No statistically

significant trends were observed for baseline systolic blood pressure. An association was observed for SNPs -2459 and -2135 with baseline diastolic systolic blood pressure. However, no significant associations were found between any of the CCR5 genotypes or promoter haplotypes and any of the blood pressure end points.

No significant association was found between the CCR5 promoter haplotypes and the safety endpoints studied.

Two studies, A4001007 and A4001015 with 80 asymptomatic HIV infected individuals showed no effect of the CCR5 polymorphisms on baseline viral load or antiretroviral activity. As with the A 4001001, A 4001002, A 4001005 and A 4001008 studies with 164 healthy volunteers, no statistically significant associations were observed between CCR5 genotypes or CCR5 promoter haplotypes and baseline blood pressure measurements.

Two studies, A4001027 and A4001028, with 982 CCR5-tropic subjects (823 Caucasian and 136 Black subjects) showed no evidence of association between genotypes and baseline viral load, CD4 counts or CD8 counts or HIV RNA viral load.

One study, A4001029, in 163 CCR5 non-tropic subjects (120 Caucasian- and 43 Black subjects) showed a potential haplotype/treatment interaction with viral load from baseline.

CCR5 WT/Δ32 individuals studied had a lower baseline viral load. This finding was consistent with previously published results (Hendel et al., J. Acquir. Immune Defic.Syndr.Hum.Retrovirol. 1998 19:381-386).

A significant association between genotypes and haplotypes with ethnicity was observed. Significant associations are shown below:

Splitter	P	aP(adjusted P value)	FDR (aP)	bP (Bonferoni P value)
Haplotype 2	5.76E-22	1.49E-16	1.05E-15	2.09E-15
SNP_2132	3.70E-17	3.95E-16	1.85E-15	5.54E-15
Haplotype 1	3.30E-13	1.45E-09	5.09E-09	2.03E-08
SNP_999999	5.35E-07	5.35E-07	1.50E-06	7.49E-06
SNP_2733	3.37E-07	2.23E-06	5.21E-06	3.13E-05
SNP_2086	1.31E-06	8.25E-06	1.65E-05	1.15E-04
SNP_2459	1.20E-04	6.15E-04	1.08E-03	8.61E-03
SNP_2135	4.53E-04	2.13E-03	3.32E-03	2.99E-02
SNP_1951	2.12E-02	2.12E-02	2.97E-02	2.97E-01

Haplotypes 1 and 2 are computed by EM

However, no correlation between genotypes and CD4 counts or CD8 counts or HIV RNA viral load was observed. The table below shows the lack of correlation between genotypes and CD4 counts.

Splitter	P	aP	FDR (aP)	bP
Haplotype 1	6.87E-02	2.47E-01	1.00E+00	1.00E+00
SNP_2086	1.25E-01	3.25E-01	1.00E+00	1.00E+00
SNP_2554	1.25E-01	3.25E-01	1.00E+00	1.00E+00
SNP_2733	6.36E-01	6.36E-01	1.00E+00	1.00E+00
SNP64	7.27E-01	7.27E-01	1.00E+00	1.00E+00
SNP_1835	7.27E-01	7.27E-01	1.00E+00	1.00E+00
SNP_999999	7.69E-01	7.69E-01	1.00E+00	1.00E+00
SNP_2135	2.96E-01	7.78E-01	8.64E-01	1.00E+00
SNP_2459	2.96E-01	7.78E-01	8.64E-01	1.00E+00
Haplotype 2	6.06E-01	1.00E+00	1.00E+00	1.00E+00

3.5 What is the effect of genetic polymorphisms in genes encoding metabolizing enzymes on PK profile of Maraviroc?

Eight Studies, A4001001, 1002, 1005, 1007, 1008, 1015, 1019, 1021, with 320 Caucasians, examined the influence of CYP3A4/A5, CYP2B6, MDR1 and BCRP1 polymorphisms on the PK profile of maraviroc.

Two studies, A4001022 and A4001025, with 24 Asians, studied the effect of CYP P450 2D6, 2C9, 2C19, 3A4, 3A5 and MDR1 polymorphisms on the PK profile of maraviroc.

No significant/definitive association between the individual genotypes and Cmax/AUC was observed.

4 Page(s) Withheld

5 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

4.5 OCPB Filing/Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	022128	Brand Name	Maraviroc®
OCP Division	4	Generic Name	maraviroc
Medical Division	DAVP	Drug Class	CCR5 antagonist
OCP Reviewer	Jenny H. Zheng	Indication(s)	CCR5 tropic HIV-1
OCP Team Leader	Kellie Reynolds	Dosage Form	150 and 300 mg tablets
Date of Submission	12/19/2006	Dosing Regimen	300 mg dose equivalent twice daily
Estimated Due Date of OCP Review	4/19/2006	Route of Administration	oral
PDUFA Due Date	06/19/2007	Sponsor	Pfizer
Division Due Date		Priority Classification	P1

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies being reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:	x	1	1	
Isozyme characterization:	x	3	3	
Metabolic profiling	x	2	1	
In vitro effect on metabolism	x	3	3	
P-gp	x	3	3	
Blood/plasma ratio:	x	2	2	
Plasma protein binding:	x	3	3	
Pharmacokinetics (e.g., Phase I) -	[redacted]			
Healthy Volunteers-	[redacted]			
single dose:	x	1	2	
multiple dose:	x	1	2	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -	[redacted]			
fasting / non-fasting single dose:	x			
fasting / non-fasting multiple dose:	x			
Drug-drug interaction studies -	[redacted]			
In-vivo effects on primary drug:	x	9	9	

In-vivo effects of primary drug:	x	4	4	
In-vitro:	x			
Subpopulation studies -				
ethnicity:	x	1	1	
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:	x			
Phase2/3:				
PK/PD:	x	11		
Phase 1 and/or 2, proof of concept:	x		4	
Phase 3 clinical trial:	x		1	
Population Analyses -	x			
Data rich:	x	5	2	
Data sparse:	x	1	1	
II. Biopharmaceutics				
Absolute bioavailability:	x	1	1	
Relative bioavailability -	x			
solution as reference:	x			
alternate formulation as reference:				
Bioequivalence studies -	x			
traditional design; single / multi dose:	x	1	1	
replicate design; single / multi dose:				
Food effect studies:	x	2	2	
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	x	1	1	
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		57	47	
Filability and QBR comments				

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	"X" if yes	Comments
Application filable ?	x	
Comments sent to firm ?		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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Jenny H. Zheng
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Shashi and Pravin, please check your section to make sure I do not mess up your format.
Jenny

Shashi Amur
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INTERDISCIPLINARY

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BIOPHARMACEUTICS

Jogarao Gobburu
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BIOPHARMACEUTICS

Kellie Reynolds
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