

A Novel Probe Drug Interaction Study to Investigate the Effect of Selected ARV Combinations on the Pharmacokinetics of a Single Oral Dose of Maraviroc (UK-427,857) in HIV +ve Subjects

Gary Muirhead¹, Anton Pozniak², Brian Gazzard², Mark Nelson², Graeme Moyle², C Ridgway¹, Richard Taylor-Worth¹, Deborah Russell¹,

¹Pfizer Global Research and Development, Sandwich Laboratories, Kent, United Kingdom. ²Chelsea and Westminster Hospital, London, UK.

Contact Information:
Mr G Muirhead
Clinical R&D
Pfizer Global Research & Development
Sandwich Laboratories
Ramsgate Road, Sandwich, Kent CT13 9NJ, UK.
gary.muirhead@pfizer.com



Introduction

- Maraviroc (MVC) is a CCR5 antagonist with potent anti-HIV activity *in vitro*, which is being developed for the treatment of HIV infection.
- MVC is a CYP3A4 substrate, however, it does not inhibit any of the major P450 isozymes *in vitro*; IC_{50} >30 μ M for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4; confirmed by specific clinical studies.^{1,2}
- Specific drug interaction studies showing the effects of inhibitors and inducers on MVC have been conducted in healthy volunteers.^{3, 4, 5, 6, 7}
- This study investigates the effect of selected ARV combinations on the pharmacokinetics of a single oral dose of MVC in HIV +ve subjects (A4001007).
- The data generated in this study were compared to the historical PK data generated in study A4001007, which investigated the effect of short-term monotherapy with MVC conducted in HIV +ve patients.⁸

Objectives

- To investigate the effect of antiretroviral combinations on the single dose pharmacokinetics of a single oral dose of MVC in HIV +ve patients.
- To assess the safety and toleration of MVC when administered in combination with 4 selected antiretroviral therapies.

Methodology

- The protocol was reviewed and approved by an independent ethics committee and all subjects gave written informed consent.
- HIV +ve subjects who had been stable for at least 3 months on the following antiretroviral regimens were recruited into one of 4 cohorts:
 - cohort 1:** Efavirenz 600 mg QD + Combivir (Lamivudine 150 mg + Zidovudine 300 mg) BID (n=8)
 - cohort 2:** Efavirenz 600 mg QD + Didanosine 250 mg QD + Tenofovir 300 mg QD (n=8)
 - cohort 3:** Nevirapine 200 mg BID + Lamivudine 150 mg BID + Tenofovir 300 mg QD (n=8)
 - cohort 4:** Kaletra (Lopinavir + Ritonavir) 400 mg BID + Stavudine 40 mg BID + Lamivudine 150 mg BID (n=5).
- For each subject the study consisted of:
 - a screening visit up to 3 weeks before dosing
 - study day from pre-dose to 12 h post-dose
 - a follow-up visit between 7-10 days after study drug dose.
- Subjects received a single 300 mg oral dose of MVC on the study day in addition to their background antiretroviral therapy.
- Safety and toleration data were collected throughout the study.
- Plasma and urine samples for MVC assay were collected at selected times from 0-12 h post-dose (same time points as for A4001007).
- MVC plasma and urine concentrations were measured by a pre-validated LC-MS-MS method.
- The following pharmacokinetic parameters were calculated for MVC: C_{max} , T_{max} , AUC_{0-12} , Ae_{0-12} , Ae_{0-12} (% dose excreted), CL_r .
- All data from the study were statistically analysed using an analysis of variance (ANOVA) appropriate for the study design and compared to the historical control, data from the monotherapy study A4001007.

Results

- Exposure to a single oral dose of 300 mg MVC was approximately 50% lower and C_{max} was approximately 25-40% lower in subjects who received efavirenz (cohorts 1 and 2) compared to those who did not receive ART.
- Exposure to a single oral dose of 300 mg MVC was similar and C_{max} was 1.5 fold higher in subjects who received nevirapine (cohort 3) compared with subjects who did not receive ART.
- Exposure to a single oral dose of 300 mg MVC was 2.6 fold higher and C_{max} was approximately 1.8 fold higher in subjects who received Kaletra[®] (cohort 4) compared with subjects who did not receive ART.
- Mean values for T_{max} were similar for all treatment groups.
- As urine was not collected in study A4001007, no comparison of urine PK was performed. However, CL_r appeared similar for all cohorts.
- All adverse events (headache, herpes simplex, sweating) were of mild or moderate severity.
- There were no clinically significant changes in laboratory safety data, 12-Lead ECGs, vital signs or physical examinations.

Mean MVC plasma concentrations in cohorts 1-4 compared to monotherapy control data (A4001007)

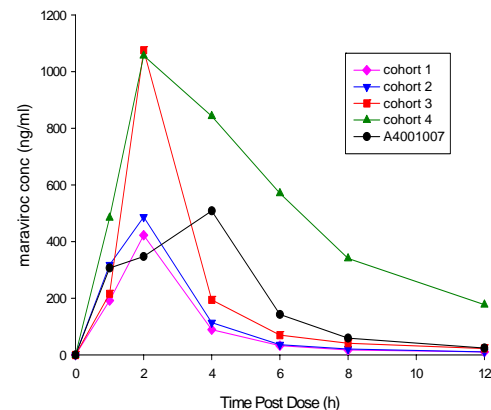


Table 1 – Pharmacokinetic results

Treatment	Mean [Range]			
	T_{max} (h) [*]	C_{max} (ng/ml) ^{**}	AUC_{0-12} (ng.h/mL) ^{**}	CL_r (L/h)
C1 – MVC+Efavirenz+ Combivir	2.1	389 [142-625]	1060 [523-1800]	12.0 [7.94-17.6]
C2 – MVC+Efavirenz+ Didanosine+ Tenofovir	1.9	447 [144-1810]	1090 [405-4140]	8.2 [6.28-14.1]
C3 – MVC+Nevirapine+ Lamivudine+ Tenofovir	2.0	900 [384-2610]	2270 [1160-5110]	9.7 [6.22-15.2]
C4 – MVC+Kaletra+ Stavudine+Lamivudine	2.2	1050 [493-2040]	5990 [3250-8430]	13.2 [5.71-17.7]
A4001007 MVC 300 mg Day 1	2.9	585 [425-829]	2262 [1460-3720]	NA

^{*}Arithmetic mean ^{**}Geometric mean

Table 2 – Statistical analysis

Comparison	%Ratio of Difference _a between Means [90% CI]		
	$AUC_{12,a}$	$C_{max,a}$	$T_{max,b}$
Cohort 1/MVC 300 mg	46.9 [30.3, 72.4]	66.5 [40.8, 109]	-0.75 [-1.44, -0.06]
Cohort 2/MVC 300 mg	48.3 [31.3, 74.6]	76.4 [46.8, 125]	-1.00 [-1.69, -0.31]
Cohort 3/MVC 300 mg	100.5 [65.1, 155]	154 [94.3, 251]	-0.88 [-1.57, -0.18]
Cohort 4/MVC 300 mg	265 [161, 435]	180 [103, 314]	0.68 [-1.47, 0.12]

Conclusions

- Efavirenz-containing regimens resulted in approximately 50% reduction in systemic exposure to MVC while the regimen containing Kaletra resulted in an approximate doubling of exposure.
- The nevirapine-containing regimen resulted in a small increase in C_{max} but no effect on AUC_{12} .
- The results of this study confirmed the results previously seen in healthy volunteer studies and support the proposed dose adjustment recommendations for MVC.
- A single oral dose of 300 mg MVC was tolerated in HIV +ve subjects when co-administered with each of four different ART regimens.

References

- Abel, D, Russell, C, Ridgway, C, Medhurst, L, Whitlock, G, Weissgerber and G Muirhead. The effect of CCR5 antagonist UK-427,857, on the pharmacokinetics of CYP3A4 substrates in healthy volunteers. 5th International Workshop on Clinical Pharmacology of HIV Therapy, 1-3 April, 2004 Rome.
- Abel, L, Whitlock, C, Ridgway, A, Saifunwar, A, Bakhtyari and D Russell. Effect of UK-427,857 on the pharmacokinetics of oral contraceptive steroids, and the pharmacokinetics of UK-427,857 in healthy young women (CAAC, Chicago 14-17 September, 2003).
- Jenkins, S, Abel, D, Russell, M, Boucher, L, Whitlock, G, Weissgerber and G Muirhead. The effect of P450 inducers on the pharmacokinetics of CCR5 antagonist, UK-427,857, in healthy volunteers. 5th International Workshop on Clinical Pharmacology of HIV Therapy, 1-3 April, 2004 Rome.
- Abel, D, Russell, C, Ridgway, C, Medhurst, G, Weissgerber and G Muirhead. Effect of CYP3A4 inhibitors on the pharmacokinetics of CCR5 antagonist UK-427,857 in healthy volunteers. 5th International Workshop on Clinical Pharmacology of HIV Therapy, 1-3 April, 2004 Rome.
- D Russell, C, Ridgway, C, Mills, R, van der Merwe and G Muirhead. A Study to Investigate the Combined Co-administration of P450 CYP3A4 inhibitors and inducers on the pharmacokinetics of the novel CCR5 inhibitor UK-427,857. Seventh International Congress on Drug Therapy in HIV Infection, Glasgow, UK 14-18 November 2004.
- Muirhead, D, Russell, S, Abel, K, Turner, R, Taylor-Worth, L, H Tan and M Toh. An investigation of the effects of tenofovir on the pharmacokinetics of the novel CCR5 inhibitor UK-427,857. Seventh International Congress on Drug Therapy in HIV Infection, Glasgow, UK 14-18 November 2004.
- Muirhead, S, Abel, D, Russell, F, Hackman, R, Taylor-Worth, M Toh and L H Tan. An investigation of the effects of atazanavir and ritonavir boosted atazanavir on the pharmacokinetics of the novel CCR5 inhibitor UK-427,857. Seventh International Congress on Drug Therapy in HIV Infection, Glasgow, UK 14-18 November 2004.
- Pozniak, G, Fatkenheuer, M, Johnson, J, Hopelman, J, Rockstroh, F, Goebel, S, Abel, I, James, M, Youle and Van der Ryst. Effect of short-term monotherapy with UK-427,857 on viral load in asymptomatic HIV-infected patients. CAAC, Chicago 14-17 September, 2003.