Pharmacokinetic Effects of Coadministration of Lersivirine with Raltegravir or Maraviroc in Healthy Subjects

Manoli Vourvahis,^a Grant Langdon,^{b*} Robert R. LaBadie,^a Gary Layton,^b Marie-Noella Ndongo,^c Subhashis Banerjee,^{d*} and John Davis^{b*}

Pfizer Global Research and Development, New York, New York, USA^a; Pfizer Global Research and Development, Sandwich, Kent, United Kingdom^b; Pfizer Clinical Research Unit, Erasme, Brussels, Belgium^c; and Pfizer Clinical Research Unit, New Haven, Connecticut, USA^d

Lersivirine (UK-453,061) is a new nonnucleoside reverse transcriptase inhibitor currently being developed as a treatment for human immunodeficiency virus type 1 infection. Lersivirine shows potent activity against wild-type and clinically relevant drug-resistant strains. Previous studies have demonstrated that lersivirine is metabolized by glucuronidation via UGT2B7 and by cytochrome P450 3A4 (CYP3A4). Lersivirine is also a weak inducer of the CYP3A4 enzyme. Therefore, coadministered lersivirine could potentially affect the pharmacokinetics of maraviroc, a CCR5 antagonist metabolized by CYP3A4, and raltegravir, an integrase inhibitor metabolized by glucuronidation. Two open-label studies assessed the pharmacokinetics of raltegravir and of maraviroc when they were coadministered with lersivirine and the pharmacokinetics of lersivirine when it was coadministered with raltegravir. Minor, clinically nonsignificant effects on the pharmacokinetics of raltegravir coadministered with lersivirine were observed at steady state for raltegravir, with estimated mean changes of -15% , -29% , and $+25\%$ in the area under the concentration-time profile from time zero to the end of the dosing interval (AUC_{tau}), maximum plasma concentration (C_{max}), and concentration observed 12 h postdose (C_{12}), respectively. There were no clinically relevant effects of steady-state raltegravir on lersivirine AUC_{tau} , C_{max} , or concentration observed 24 h postdose (C_{24}) (estimated mean changes of -2 to $+5\%$). Coadministration of lersivirine at steady state with maraviroc resulted in no clinically relevant effects on maraviroc AUC_{tau} , C_{max} , or C_{12} (estimated mean changes of $+3.4$ to $+8.6\%$). Lersivirine appeared to be generally well tolerated in these studies and appears to be suitable for coadministration with raltegravir or maraviroc without the need for dose modification.

Human immunodeficiency virus (HIV)-infected patients are frequently prescribed combination antiretroviral therapy (cART) regimens, which typically consist of at least three different drugs from at least two different classes. Currently approved antiretroviral drugs include nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, integrase strand transfer inhibitors (INSTIs), entry inhibitors, and chemokine receptor (CCR5) antagonists (11). The emergence of drug-resistant virus in patients treated with antiretroviral therapy, and the increasing prevalence of resistance mutations in transmitted virus, necessitates the continued development of novel antiretroviral agents (5).

Lersivirine (UK-453,061; ViiV Healthcare) is an investigational NNRTI with a unique binding interaction within the NNRTI binding pocket (16). Lersivirine has *in vitro* antiretroviral activity against wild-type virus as well as clinically relevant NNRTI-resistant strains, including viruses with transmitted resistance to NNRTI (15).

In HIV-1-infected NNRTI-naïve subjects, treatment with lersivirine monotherapy for 7 days achieved mean viral RNA reductions of $1.7 \log_{10}$ copies/ml and $1.8 \log_{10}$ copies/ml after administration of 500 and 750 mg once daily (QD), respectively, and $1.6 \log_{10}$ copies/ml after administration of 500 mg twice daily (BID). Lersivirine was generally safe and well tolerated, with the most commonly reported treatment-emergent adverse events (AEs) being headache, fatigue, and nausea (8). Synergy between lersivirine and other classes of compounds, most notably the NRTI class, has been demonstrated *in vitro* (4). Lersivirine has been assessed at doses up to 1,800 mg QD and is currently undergoing phase IIb studies in combination with tenofovir and emtricitabine in treatment-naïve patients with HIV (lersivirine doses of 500 mg

BID and 750 mg QD) and in combination with darunavir and ritonavir plus an optimized NRTI in treatment-experienced patients with HIV (lersivirine doses of 750 mg QD and 1000 mg QD; the higher dose in the experienced-patient study was to compensate for a reduced lersivirine exposure due to coadministration with ritonavir-boosted protease inhibitor).

Data from an *in vivo* mass balance study and *in vitro* metabolism studies suggest that lersivirine is predominantly cleared by metabolism, with glucuronidation (UGT2B7) and oxidation via cytochrome P450 3A4 (CYP3A4) being the major metabolic pathways (17). Recombinant CYP3A4 metabolizes lersivirine, with an intrinsic clearance rate of $0.9 \mu\text{l}/\text{pmol CYP}/\text{min}$ (17). The only other enzyme shown to metabolize lersivirine based upon a substrate depletion approach was CYP3A5, with a rate of metabolism ($<0.08 \mu\text{l}/\text{pmol CYP}/\text{min}$) more than 10-fold lower than that of CYP3A4 (17). Lersivirine is a weak inducer of CYP3A4 (6, 7) and, based on *in vitro* data, is an inhibitor and substrate for P-glycoprotein (P-gp) (Pfizer Inc., data on file).

Many of the agents used in cART are known to modulate the

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Address correspondence to Manoli Vourvahis, manoli.vourvahis@pfizer.com.

* Present address: Grant Langdon, PTx Solutions Ltd., Deal, United Kingdom; Subhashis Banerjee, Eli Lilly and Company, Indianapolis, Indiana, USA; John Davis, Genentech Inc., San Francisco, California, USA.

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TABLE 1 Study design overview

Study	Coadministered drug	No. of individuals	Study design	Treatment	Period (days)	
					Treatment	Washout (minimum)
1	Raltegravir	18	3-way crossover	Lersivirine 1,000 mg QD Raltegravir 400 mg BID Lersivirine 1,000 mg QD + raltegravir 400 mg BID	10 days	3 days
2	Maraviroc	14	2-way crossover	Maraviroc 300 mg BID ^a + lersivirine 500 mg BID Maraviroc 300 mg BID + placebo BID	14 days	14 days

^a The dose was to be increased on days 11 to 14 if a $\geq 25\%$ difference was observed between placebo-adjusted comparison of day 1 and day 7 maraviroc $C_{av(2-4)}$. BID, twice daily; $C_{av(2-4)}$, geometric mean of the observed concentrations at 2, 3, and 4 h post dose; QD, once daily.

activity of important drug-metabolizing enzymes and transporters, such as CYP3A4 and P-gp (3). Because patients are likely to receive treatment for life and because of the possibility of potential drug interactions, rigorous pharmacokinetic investigation is a requisite step in the development of new HIV drugs, both to determine their suitability for introduction into existing treatment regimens and to define dose adjustments, if necessary.

Here we report the results from two open-label studies designed to assess the pharmacokinetics of raltegravir and maraviroc, both first-in-class agents, when they are coadministered with lersivirine and the pharmacokinetics of lersivirine when it is coadministered with raltegravir. Raltegravir is an HIV-1 integrase inhibitor that is metabolized predominantly through UGT1A1-mediated glucuronidation (13). Maraviroc is a CCR5 antagonist that is a substrate for both CYP3A4 and P-gp (1, 12).

MATERIALS AND METHODS

Two phase I clinical trials investigating the pharmacokinetics of coadministration of lersivirine with raltegravir (study 1) and maraviroc (study 2) were performed. Study 1 was conducted at the Pfizer Clinical Research Unit (CRU) in New Haven, CT, and study 2 was conducted at the Pfizer CRU in Brussels, Belgium. All protocols were approved by the Institutional Review Board of the investigational centers and were conducted in

accordance with the ethical principles established by the Declaration of Helsinki (18) and the International Conference on Harmonisation Good Clinical Practice guidelines (www.ich.org). All subjects provided written informed consent.

Subjects. Both studies were conducted in healthy adult subjects (HIV negative) aged 18 to 55 years inclusive. All subjects were required to be healthy and have a body mass index of 18 to 30 kg/m² and a total body weight of >50 kg. "Healthy" was defined as the absence of clinically relevant abnormalities, identified by a detailed medical history and a full physical examination, including blood pressure and heart rate measurements, a 12-lead electrocardiogram, and clinical laboratory tests. Subjects were excluded if they showed evidence or history of clinically significant diseases or disorders or were receiving any medications, with the exception of acetaminophen, within 7 days prior to the first dose of study medication. Additional exclusion criteria included history of regular alcohol consumption or chemical dependency (including use of nicotine products equivalent to >5 cigarettes per day), a positive urine drug screen, and a positive test result for HIV, hepatitis B, or hepatitis C infection.

Study design. The studies were both open-label, randomized crossover trials with screening visits occurring up to 28 days before commencement of treatment. An overview of the studies, including the dose and schedule of lersivirine and the coadministered drug, the number of subjects, study design, length of treatment, and washout periods, is shown in Table 1. In both studies, on the pharmacokinetics (PK) sampling day (final day of treatment) subjects were dosed in a fasting state (study 1, morning dose only). Food was allowed from 4 h postdose and water was allowed starting from 1 h postdose.

Pharmacokinetic sampling and analysis. Blood samples for lersivirine, raltegravir, and/or maraviroc analyses were collected on the final day of treatment in each period at 0 h (predose) and 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 h postdose. Lersivirine and maraviroc PK samples were collected into lithium heparin and raltegravir PK samples into dipotassium EDTA.

TABLE 2 Demographics and baseline characteristics

Characteristic	Study 1 (lersivirine and raltegravir; $n = 18$)	Study 2 (lersivirine and maraviroc; $n = 14$)
Age (yr)		
Mean (SD)	40.6 (8.8)	37.5 (9.8)
Range	24–53	24–53
Gender (no. [%])		
Male	17 (94.4)	14 (100)
Female	1 (5.6)	0
Wt (kg)		
Mean (SD)	82.6 (11.8)	77.4 (7.6)
Range	52–97	57–86
BMI (kg/m ²) ^a		
Mean (SD)	26.7 (2.9)	24.7 (2.4)
Range	21.0–30.4	19.9–27.5
Height (cm)		
Mean (SD)	175.6 (9.2)	177.1 (6.0)
Range	154–190	169–187

^a BMI, body mass index.

FIG 1 Day 10 median plasma concentrations of lersivirine alone and coadministered with raltegravir (study 1). BID, twice daily; QD, once daily.

TABLE 3 Effect of steady-state raltegravir on the day 10 pharmacokinetics of lersivirine (study 1)

Parameter ^c	Lersivirine 1,000 mg QD + raltegravir 400 mg BID (<i>n</i> = 16) ^b		Lersivirine 1,000 mg QD (<i>n</i> = 16) ^b		Ratio of adjusted geometric means (A/B)	90% CI
	Geometric mean	Adjusted geometric mean (A)	Geometric mean	Adjusted geometric mean (B)		
AUC _{tau} (ng · h/ml)	10,410	10,317	10,573	10,520	0.98	0.91–1.05
C _{max} (ng/ml)	1,388	1,395	1,328	1,333	1.05	0.95–1.15
C ₂₄ (ng/ml)	143	138	139	136	1.02	0.87–1.19
T _{max} (h) ^a	2 (1–3)		3 (2–4)			

^a Median (range).^b Two subjects discontinued the study due to adverse events and were not included in the pharmacokinetic analyses.^c AUC_{tau}, area under the plasma concentration-time profile from time zero to the end of the dosing interval; BID, twice daily; CI, confidence interval; C_{max}, maximum plasma concentration; C₂₄, concentration observed at 24 h postdose; QD, once daily; T_{max}, time to maximum plasma concentration.

Blood samples were centrifuged at approximately $1,700 \times g$ for 10 min at 4°C, and the plasma was stored in polypropylene tubes at –20°C within 1 h of collection. In study 1, an additional sample for lersivirine analysis was taken at 24 h following the lersivirine dose on day 10. In study 2, samples were also taken on days 1 and 7 (2, 3, and 4 h postdose) during period 1 only. If a difference of $\geq 25\%$ was observed between the day 1 and day 7 maraviroc C_{av(2–4)} (geometric mean of the observed concentrations at 2, 3, and 4 h postdose; placebo adjusted) in this period, subjects in both periods would continue treatment on days 11 to 14, and the dose of maraviroc would be increased to compensate for the effect of lersivirine. If an estimated difference of $< 25\%$ was observed the study was to stop at day 10 in both periods.

Plasma was analyzed using validated liquid chromatography/mass spectrometry methodology with lower limits of quantification of 1.0 ng/ml for lersivirine and raltegravir (Covance Bioanalytical Services, LLC [Indianapolis, IN]), and 0.5 ng/ml for maraviroc (Tandem Labs [West Trenton, NJ]) (2). In study 1, the precision for the lersivirine assay was a $\leq 6.2\%$ coefficient of variance (CV) with an accuracy of a –3.7 to 2.0% relative error (RE), and the precision and accuracy for the raltegravir assay were a $\leq 4.8\%$ CV and a –0.9 to 1.0% RE, respectively. In study 2, the precision and accuracy for the maraviroc assay were a 6.0% CV and a –6.0 to 3.3% RE, respectively. Pharmacokinetic parameters for lersivirine and raltegravir (study 1) or maraviroc (study 2) were calculated for each subject, for each treatment, from plasma concentration-time profiles using standard noncompartmental methods with eNCA, a validated Pfizer-developed PK software package. Pharmacokinetic assessments included the area under the plasma concentration-time profile from time zero to the end of the dosing interval (AUC_{tau}), maximum plasma concentration (C_{max}), concentration observed at 24 h postdose (C₂₄) (for lersivirine only), concentration observed at 12 h postdose (C₁₂) (for maraviroc and raltegravir), and time to maximum plasma concentration (T_{max}).

Safety. Safety was evaluated in both studies by assessment of clinical laboratory tests and physical examinations, including vital signs and electrocardiogram, at screening and at various points during each study. Adverse events (AEs) and serious AEs (SAEs) were monitored and recorded throughout each study.

Sample size calculation. In study 1, for estimating the effect on pharmacokinetics of lersivirine, a sample size of 18 subjects was required to provide 90% confidence intervals (CIs) for the difference between treatments of ± 0.101 and ± 0.140 on the natural log scale for AUC_{tau} and C_{max}, respectively, with 90% coverage probability. For estimating the effect on the pharmacokinetics of raltegravir, a sample size of 18 subjects (three subjects per sequence) was required to provide 90% CIs for the difference between treatments of ± 0.189 and ± 0.270 on the natural log scale for AUC₁₂ and C_{max}, respectively, with 90% coverage probability. In study 2 (maraviroc), a sample size of 12 subjects was required to provide 90% CIs for the difference between treatments of ± 0.215 and ± 0.392 on the natural log scale for maraviroc AUC_{tau} and C_{max}, respectively, with 80% coverage probability.

Data analysis. For all studies, the natural log AUC_{tau} and C_{max} (for lersivirine, maraviroc and raltegravir), C₂₄ (for lersivirine), and C₁₂ (for maraviroc and raltegravir) values were analyzed separately for each compound in each study using a mixed-effect model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect using SAS software package 8.2 (SAS Institute Inc., Cary, NC). Estimates of the adjusted mean differences (test-reference) and corresponding 90% CIs were obtained from the model. Exponentiation was applied to the adjusted mean differences and 90% CIs for the differences to provide estimates of the ratio of adjusted geometric means (test/reference) and 90% CIs for the ratios. In study 1, for the lersivirine comparison, lersivirine plus raltegravir was the test treatment and lersivirine alone was the reference treatment. For the raltegravir comparison, raltegravir plus lersivirine was the test treatment and raltegravir alone was the reference treatment. In study 2, maraviroc plus lersivirine was the test treatment and maraviroc alone was the reference treatment.

RESULTS

Subjects. In total, 18 subjects participated in study 1 and 14 subjects participated in study 2. None of the subjects had presenting conditions or medical histories that were considered sufficient to affect the conduct of the study or to represent a potential risk to the subject during study participation. Subject demographics and baseline characteristics are shown in Table 2. Two subjects discontinued study 1 due to AEs (vomiting and dizziness) while receiving lersivirine 1,000 mg QD and raltegravir 400 mg BID during period 1 of the study.

Pharmacokinetics. (i) Study 1: lersivirine and raltegravir. When administered in the presence of raltegravir at steady state,

FIG 2 Day 10 median plasma concentrations of raltegravir alone and coadministered with lersivirine (study 1). BID, twice daily; QD, once daily.

TABLE 4 Effect of steady-state lersivirine on the day 10 pharmacokinetics of raltegravir (study 1)

Parameter ^c	Raltegravir 400 mg BID + lersivirine 1,000 mg QD (<i>n</i> = 16) ^b		Raltegravir 400 mg BID (<i>n</i> = 16) ^b		Ratio of adjusted geometric means (A/B)	90% CI
	Geometric mean	Adjusted geometric mean (A)	Geometric mean	Adjusted geometric mean (B)		
AUC _{tau} (ng · h/ml)	5,402	5,944	6,760	7,029	0.85	0.64–1.11
C _{max} (ng/ml)	1,265	1,433	1,899	2,004	0.71	0.48–1.06
C ₁₂ (ng/ml)	122	123	99	98	1.25	1.03–1.53
T _{max} (h) ^a	2 (0–6)		2 (0.5–4.0)			

^a Median (range).

^b Two subjects discontinued the study due to adverse events and were not included in the pharmacokinetic analyses.

^c AUC_{tau}, area under the plasma concentration-time profile from time zero to the end of the dosing interval; BID, twice daily; CI, confidence interval; C_{max}, maximum plasma concentration; C₁₂, concentration observed at 12 h postdose; QD, once daily; T_{max}, time to maximum plasma concentration.

FIG 3 Day 10 median plasma concentrations of maraviroc alone and coadministered with lersivirine (study 2). BID, twice daily.

the median plasma exposure of lersivirine was unchanged compared with that observed for lersivirine alone (Fig. 1). The ratios of adjusted geometric means of lersivirine were close to 1.0 for AUC_{tau}, C_{max}, and C₂₄ (Table 3), and median T_{max} was reduced in the presence of raltegravir from 3 h to 2 h.

In contrast, coadministration with lersivirine reduced the median plasma exposure of raltegravir, compared with that observed for raltegravir alone (Fig. 2). The ratios of adjusted geometric means for AUC_{tau} and C_{max} suggested reductions of 15% and 29%, respectively; however, C₁₂ was increased by 25% (Table 4). There was no change in median T_{max} between the treatment groups.

(ii) Study 2: maraviroc and lersivirine. In period 1, the maraviroc C_{av(2–4)}, day 7/day 1 ratio was estimated to be 98% (90% CI, 59%, 165%), indicating that no dose adjustment was required for days 11 to 14. Therefore, the last dose in both periods was administered on day 10. Coadministration of maraviroc and lersivirine resulted in a small increase in the median maraviroc exposure compared with maraviroc and placebo (Fig. 3). The ratios of adjusted geometric means of maraviroc for AUC_{tau}, C_{max}, and C₁₂ showed increases of approximately 6.2%, 3.4%, and 8.6%, respectively, for the combination of maraviroc and lersivirine compared to maraviroc and placebo (Table 5). Coadministration had no effect on median T_{max}, 3 h.

Safety. Coadministration of lersivirine with raltegravir or maraviroc was generally well tolerated in these small cohorts of healthy subjects. AEs in the two studies were predominantly gastrointestinal related (Table 6) and were mostly either mild (75/95 [79%] for study 1 and 38/40 [95%] for study 2) or moderate (19/95 [20%] for study 1 and 2/40 [5%] for study 2) in severity. One severe AE was reported in study 1: dizziness in the lersivirine-plus-raltegravir treatment group. In study 1, the incidence of reported AEs was similar between lersivirine and raltegravir administered alone, although the frequency of some AEs such as gastrointestinal disorders appeared to be higher when lersivirine and raltegravir were coadministered. In study 1, there were two discontinuations due to AEs during lersivirine (1,000 mg QD) and raltegravir (400 mg BID) administration during period 1 of the study: one subject experienced moderate vomiting on day 1 and moderate dizziness on day 3, both of which resolved by day 3; a second subject experienced severe dizziness on day 2 which resolved by day 4. There were no withdrawals or discontinuations in study 2. In study 2, there were more treatment-related AEs re-

TABLE 5 Effect of steady-state lersivirine on the day 10 pharmacokinetics of maraviroc (study 2)

Parameter ^c	Maraviroc 300 mg BID + lersivirine 500 mg BID (<i>n</i> = 14) (A)	Maraviroc 300 mg BID + placebo (<i>n</i> = 14) (B)	Ratio of adjusted geometric means (A/B)	90% CI
AUC _{tau} (ng · h/ml) ^a	2,481	2,335	1.06	0.96–1.18
C _{max} (ng/ml) ^a	588	569	1.03	0.83–1.29
C ₁₂ (ng/ml) ^a	52	48	1.09	0.99–1.19
T _{max} (h) ^b	3 (0.5–4.0)	3 (0.5–4.0)		

^a Adjusted geometric mean (geometric mean and adjusted geometric mean were the same).^b Median (range).^c AUC_{tau}, area under the plasma concentration-time profile from time zero to the end of the dosing interval; BID, twice daily; CI, confidence interval; C_{max}, maximum plasma concentration; C₁₂, concentration observed at time 12 h postdose; T_{max}, time to maximum plasma concentration.

ported among subjects receiving maraviroc plus lersivirine treatment than those receiving maraviroc plus placebo (Table 6). There were no SAEs in either study.

DISCUSSION

The risk of undesirable pharmacokinetic interactions between antiretroviral drugs that could potentially be used together in cART regimens requires that new agents be thoroughly investigated for such drug-drug interactions. The results from these two studies, conducted in small cohorts of healthy male subjects, demonstrate that coadministration of lersivirine with either raltegravir or maraviroc appears to be generally well tolerated.

Data from study 1 demonstrate that raltegravir does not alter the pharmacokinetics of lersivirine, as the 90% CI for the ratios of all lersivirine pharmacokinetic parameters, when administered with or without raltegravir, were contained within the no-effect limits (0.80 to 1.25). In contrast, values for raltegravir were not contained within the no-effect limits when it was coadministered with lersivirine. It is interesting that while raltegravir AUC_{tau} and C_{max} decreased in the presence of lersivirine, raltegravir C₁₂ increased. Raltegravir has been shown to have interpatient and inpatient variabilities of 212% and 122%, respectively (14). Although the mechanism for this interaction is unclear, the observed interaction is not considered clinically significant, as the lower

boundary of the 90% CI for the raltegravir geometric mean ratio (with or without lersivirine) is above 0.4. The lower boundary of 0.4 is derived from comparing the mean C₁₂ for the approved 400-mg BID dose with the mean C₁₂ for the lowest doses studied in phase IIb, both of which were as efficacious as the 400-mg BID dose (9, 10). Alternatively, the observed difference could be due to the small number of subjects and large raltegravir PK variability. The data suggest that raltegravir can be administered with lersivirine without alteration to the dose of either drug.

Similarly, data from study 2 suggest that no dose adjustment of maraviroc is required when it is coadministered with lersivirine. The 90% CI for maraviroc pharmacokinetic ratios (with or without lersivirine) were contained within no-effect limits with the exception of maraviroc C_{max} (90% CI, 0.83 to 1.29), which fell just outside, although the result was not considered clinically relevant. Coadministration of midazolam, like maraviroc a substrate for CYP3A4, with lersivirine at clinically relevant doses (total daily doses of 500 to 1,000 mg) led to a 20 to 36% reduction in midazolam plasma exposure in a dose-dependent manner (7). This likely represents a worst-case scenario, given that midazolam is a sensitive CYP3A4 substrate, as it is almost completely metabolized by CYP3A4. Coadministration of maraviroc with the NNRTI efavirenz or etravirine caused a substantial reduction (~50%) in

TABLE 6 Treatment-emergent adverse events (all causality) occurring in two or more subjects in any one study or treatment group

MedDRA ^b preferred term	No. (%) with AE in:				
	Study 1			Study 2	
	Lersivirine 1,000 mg QD (<i>n</i> = 16) ^a	Raltegravir 400 mg BID (<i>n</i> = 16) ^a	Lersivirine 1,000 mg QD + raltegravir 400 mg BID (<i>n</i> = 18)	Maraviroc 300 mg BID + lersivirine 500 mg BID (<i>n</i> = 14)	Maraviroc 300 mg BID + placebo (<i>n</i> = 14)
Nausea	2 (12.5)	0	9 (50.0)	5 (35.7)	0
Vomiting	2 (12.5)	0	3 (16.7)	0	0
Abdominal discomfort	1 (6.3)	2 (12.5)	1 (5.6)	2 (14.3)	0
Abdominal pain upper	0	0	2 (11.1)	2 (14.3)	0
Diarrhea	2 (12.5)	2 (12.5)	4 (22.2)	4 (28.6)	0
Dizziness	1 (6.3)	0	6 (33.3)	2 (14.3)	0
Dyspepsia/epigastric discomfort	1 (6.3)	0	2 (11.1)	2 (14.3)	1 (7.2)
Fatigue	0	1	0	5 (35.7)	3 (21.4)
Feeling abnormal	2 (12.5)	0	0	0	0
Headache	2 (12.5)	3 (18.8)	8 (44.4)	4 (28.6)	1 (7.2)
Musculoskeletal chest pain	0	0	2 (11.1)	0	0
Nasopharyngitis	0	0	0	4 (28.6)	0

^a Two subjects had discontinued the study earlier due to adverse events after receiving lersivirine with raltegravir.^b Medical Dictionary for Regulatory Activities (www.meddrasmo.com).

maraviroc plasma exposure, resulting in the need for an upward dose adjustment of maraviroc. A decrease in maraviroc PK was expected; however, the induction by lersivirine of the CYP3A4 pathway may have been counterbalanced by P-glycoprotein (P-gp) inhibition. *In vitro* data suggest that lersivirine is a P-gp inhibitor; therefore, lersivirine inhibiting P-gp may potentially mask an effect on CYP3A4 induction.

A limitation of these studies is the male bias in the study populations. However, based on the results observed in the two studies, clinically relevant pharmacokinetic interactions between lersivirine and raltegravir and between lersivirine and maraviroc are considered unlikely.

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