Pharmacokinetic Effects of Co-Administration of Lersivirine with Raltegravir or Maraviroc in Healthy Subjects

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Target journal: Antimicrobial Agents and Chemotherapy

Running title (limit 54 characters including spaces): Lersivirine co-administered with raltegravir/maraviroc

Key words: Lersivirine, UK-453,061, pharmacokinetics, maraviroc, raltegravir, drug interaction
Abstract (242/250 words)

Lersivirine (UK-453,061) is a next-generation non-nucleoside 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, co-administered 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 or maraviroc when co-administered with lersivirine and the pharmacokinetics of lersivirine when co-administered with raltegravir. Minor, clinically non-significant effects were observed on the pharmacokinetics of raltegravir when co-administered with lersivirine at steady-state, with estimated mean changes of -15%, -29%, and +25% in raltegravir area under the concentration-time profile from time zero to the end of the dosing interval (AUC\textsubscript{tau}), maximum plasma concentration (C\textsubscript{max}), and concentration observed 12 hours postdose (C\textsubscript{12}) respectively. There were no clinically relevant effects of steady-state raltegravir on lersivirine AUC\textsubscript{tau}, C\textsubscript{max}, or concentration observed 24 hours postdose (C\textsubscript{24}) (estimated mean changes of -2 to +5%). Co-administration of lersivirine at steady-state with maraviroc resulted in no clinically relevant effects on maraviroc AUC\textsubscript{tau}, C\textsubscript{max}, or C\textsubscript{12} (estimated mean changes of +3.4 to +8.6%). Lersivirine appeared to be generally well tolerated in these studies and appears suitable for co-administration with raltegravir or maraviroc without the need for dose modification.
INTRODUCTION

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), non-nucleoside 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 a next-generation 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 receiving 500 and 750 mg once daily (QD), respectively, and $1.6 \log_{10}$ copies/mL after receiving 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.
Lersivirine has been assessed at doses up to 1800 mg QD and is currently undergoing Phase IIb studies in combination with tenofovir/emtricitabine in treatment-naive patients with HIV (lersivirine doses 500 mg BID and 750 mg QD) and in combination with darunavir/ritonavir plus an optimized NRTI in treatment-experienced patients with HIV (lersivirine doses 750 mg QD and 1000 mg QD; higher dose in the experienced patient study was to compensate for a reduced lersivirine exposure due to co-administration with boosted PI).

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 µL/pmol CYP/min (17). The only other enzyme shown to metabolize lersivirine based upon a substrate depletion approach was CYP3A5, with a greater than 10-fold lower rate of metabolism (<0.08 µL/pmol CYP/min) compared with 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 activity of important drug-metabolizing enzymes and transporters, such as CYP3A4 and P-gp (3). As patients are likely to receive treatment for life and due to 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 co-administered with lersivirine and the pharmacokinetics of lersivirine when co-administered with raltegravir. Raltegravir is a 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 co-administration 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, Connecticut, USA 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 Harmonization Good Clinical Practice guidelines. All subjects provided written informed consent.

**Subjects.**

Both studies were conducted in healthy adult subjects (HIV-negative) aged 18–55 years inclusive. All subjects were required to be healthy and have a body mass index of 18–30 kg/m² and a total body weight >50 kg. Healthy was defined as the absence of clinically relevant abnormalities, identified by a detailed medical history, 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/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 co-administered drug, the number of subjects, study design, length of treatment, and washout periods, is shown in Table 1. In both studies, on the PK sampling day (final day of treatment) subjects were dosed in a fasted state (Study 1, morning dose only). Food was allowed from 4 hours postdose and water was allowed starting from 1 hour 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 hours (pre-dose) and 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dose. Lersivirine and maraviroc PK samples were collected into lithium heparin and raltegravir PK samples into Di-potassium EDTA. Blood samples were centrifuged at approximately 1700 x g for 10 minutes at 4° C and the plasma stored in
polypropylene tubes at -20°C within 1 hour of collection. In Study 1, an additional sample for lersivirine analysis was taken at 24 hours following the lersivirine dose on Day 10. In Study 2, samples were also taken on Days 1 and 7 (2, 3, and 4 hours post-dose) during Period 1 only. If a difference of ≥25% was observed between the Day 1 and Day 7 maraviroc C_{av(2-4)} (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, USA]), and 0.5 ng/mL for maraviroc (Tandem Labs [West Trenton, NJ, USA]) (2). In Study 1 the precision for the lersivirine assay was ≤6.2% coefficient of variance (%CV) with an accuracy of -3.7-2.0% relative error (%RE), and the precision and accuracy for the raltegravir assay were ≤4.8 %CV and -0.9-1.0 %RE, respectively. In Study 2 the precision and accuracy for the maraviroc assay were 6.0 %CV and -6.0-3.3 %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 non-compartmental 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 hours postdose ($C_{24}$) (for lersivirine only), concentration observed at 12 hours postdose ($C_{12}$) (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 ECG, 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 $\text{AUC}_{\text{tau}}$ and $C_{\text{max}}$, 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 $\text{AUC}_{12}$ and $C_{\text{max}}$, 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 $\text{AUC}_{\text{tau}}$ and $C_{\text{max}}$, respectively with 80% coverage probability.
Data analysis

For all studies, the natural log $AUC_{\text{tau}}$ and $C_{\text{max}}$ (for lersivirine, maraviroc and raltegravir), $C_{24}$ (for lersivirine), and $C_{12}$ (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, USA). Estimates of the adjusted mean differences (test-reference) and corresponding 90% CIs were obtained from the model. The adjusted mean differences and 90% CIs for the differences were exponentiated 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 from Study 1 due to AEs (vomiting and dizziness)
Pharmacokinetics.

Study 1: lersivirine and raltegravir.

When administered in the presence of raltegravir at steady state, 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 $\text{AUC}_{\text{tau}}$, $C_{\text{max}}$, and $C_{24}$ (Table 3) and median $T_{\text{max}}$ was reduced in the presence of raltegravir from 3 hours to 2 hours.

In contrast, co-administration 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 $\text{AUC}_{\text{tau}}$ and $C_{\text{max}}$ suggested reductions of 15% and 29%, respectively; however, $C_{12}$ was increased by 25% (Table 4). There was no change in median $T_{\text{max}}$ between the treatment groups.

Study 2: maraviroc and lersivirine.

In Period 1 the maraviroc $C_{\text{av}(2-4)}$, Day7/Day1 ratio was estimated to be 98% (90% CI: 59%, 165%), indicating that no dose adjustment was required for Days 11–14. Therefore the last dose in both periods was administered on Day 10. Co-administration of maraviroc and lersivirine resulted in a small increase in the median maraviroc exposure when compared with maraviroc and placebo (Fig. 3). The ratios of adjusted geometric
means of maraviroc for AUC$_{\text{tau}}$, C$_{\text{max}}$, and C$_{12}$ showed increases of approximately 6.2%, 3.4%, and 8.6%, respectively, while receiving maraviroc and lersivirine when compared to maraviroc and placebo (Table 5). Co-administration had no effect on median T$_{\text{max}}$, 3 hours.

Safety.

Co-administration 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 when administered alone, although the frequency of some AEs such as gastrointestinal disorders appeared to be higher when lersivirine and raltegravir were co-administered. In Study 1 there were two discontinuations due to AEs while receiving lersivirine 1,000 mg QD and raltegravir 400 mg BID 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 reported while receiving maraviroc plus lersivirine treatment than while receiving maraviroc plus placebo (Table 6). There were no SAEs in either study.
237 DISCUSSION

238 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, have demonstrated that co-
administration of lersivirine with either raltegravir or maraviroc appears to be generally
well tolerated.

240 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
(0.80-1.25). In contrast, raltegravir exposures were not contained within the no effect
limits when it was co-administered with lersivirine. It is interesting that while raltegravir
AUC$_{\text{tau}}$ and C$_{\text{max}}$ decreased in the presence of lersivirine, raltegravir C$_{12}$ increased.

250 Raltegravir has been shown to have an inter-patient and intra-patient variability 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 bound of the 90%
CI for the raltegravir geometric mean ratio (with or without lersivirine) is above 0.4. The
lower bound of 0.4 is derived from comparing the mean C$_{12}$ for the approved 400 mg BID
dose with the mean C$_{12}$ for the lowest doses studied in Phase IIb, which were equally
efficacious compared with 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 co-administered with lersivirine. The 90% CI for maraviroc pharmacokinetic ratios (with or without lersivirine) were contained within no effect limits with the exception of maraviroc $C_{\text{max}}$ (90% CI: 0.83, 1.29), which fell just outside although not considered clinically relevant. Co-administration of midazolam, like maraviroc a substrate for CYP3A4, with lersivirine at clinically relevant doses (total daily doses of 500–1,000 mg) led to a 20–36% 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. Co-administration of maraviroc with the NNRTIs, efavirenz or etravirine, caused a substantial reduction (~50%) in maraviroc plasma exposure, resulting in the need for an upwards 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 suggests 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 between the two studies, it is considered that clinically relevant pharmacokinetic interactions between lersivirine and raltegravir or lersivirine and maraviroc are unlikely.
ACKNOWLEDGMENTS

All studies were sponsored by Pfizer Inc. Editorial support was provided by Bethan Hahn at Complete Medical Communications and was funded by Pfizer Inc and ViiV Healthcare.

CONFLICT OF INTEREST

Manoli Vourvahis, Robert R. LaBadie, Gary Layton and Marie-Noella Ndongo are all employees of Pfizer Inc. Subhashis Banerjee, Grant Langdon and John Davis were employees of Pfizer Inc. at the time these studies were conducted.

REFERENCES


transcriptase inhibitor, during 7-day monotherapy in HIV-1 infected patients. AIDS 23:2115–2122.


human immunodeficiency virus 1 integrase enzyme. Drug Metab. Dispos. 35:1657–
1663.

http://www.isentress.com/raltegravir/isentress/consumer/prescribing_information/in
dex.jsp.

15. **Mori, J., R. Corbau, D. Lewis, S. Ellery, H. Mayer, M. Perros, and M. Westby**.
2008. *In vitro* characterization of UK-453,061, a non-nucleoside reverse
transcriptase inhibitor. Abstr. 15th Conference on Retroviruses and Opportunistic
Infections, Boston, MA, 3-6 February.

A63:s18.

Howard, S. Kempshall, C. Collins, and R. Labadie**. 2010. Excretion and
metabolism of lersivirine (5-[(3,5-diethyl-1-(2-hydroxyethyl)(3,5-^{14}C_2)-1H-pyrazol-
4-yl]oxy)benzene-1,3-dicarbonitrile), a next-generation non-nucleoside reverse
transcriptase inhibitor, after administration of [{^{14}C}]Lersivirine to healthy volunteers.
Drug Metab. Dispos. 38:789–800.

Declaration of Helsinki: ethical principles for medical research involving human
Figure legends

FIG. 1. Day 10 median plasma concentrations of lersivirine when co-administered with or without raltegravir (Study 1).

BID, twice daily; QD, once daily.

FIG. 2. Day 10 median plasma concentrations of raltegravir when co-administered with or without lersivirine (Study 1).

BID, twice daily; QD, once daily.

FIG. 3. Day 10 median plasma concentrations of maraviroc when co-administered with or without lersivirine (Study 2).

BID, twice daily.
<table>
<thead>
<tr>
<th>Study</th>
<th>Co-administered drug</th>
<th>Number of individuals</th>
<th>Study design</th>
<th>Treatments</th>
<th>Length of treatment periods</th>
<th>Washout period (minimum)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Raltegravir</td>
<td>18</td>
<td>3-way crossover</td>
<td>Lersivirine 1000 mg QD</td>
<td>10 days</td>
<td>3 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Raltegravir 400 mg BID</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lersivirine 1000 mg QD +</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>raltegravir 400 mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Maraviroc</td>
<td>14</td>
<td>2-way crossover</td>
<td>Maraviroc 300 mg BID + lersivirine 500 mg BID</td>
<td>14 days</td>
<td>14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Maraviroc 300 mg BID + placebo BID</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Dose to be increased on Days 11–14 if ≥25% difference observed between placebo-adjusted comparison of Day 1 and Day 7.

**C**_{av(2–4)}.

BID, twice daily; **C**_{av(2–4)}, geometric mean of the observed concentrations at 2, 3, and 4 hours postdose; QD, once daily.
TABLE 2. Demographics and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
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<tbody>
<tr>
<td></td>
<td>Lersivirine and raltegravir</td>
<td>Lersivirine and maraviroc</td>
</tr>
<tr>
<td></td>
<td>(n=18)</td>
<td>(n=14)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
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<tr>
<td>Mean (SD)</td>
<td>40.6 (8.8)</td>
<td>37.5 (9.8)</td>
</tr>
<tr>
<td>Range</td>
<td>24–53</td>
<td>24–53</td>
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<tr>
<td><strong>Gender (n, %)</strong></td>
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</tr>
<tr>
<td>Male</td>
<td>17 (94.4)</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Female</td>
<td>1 (5.6)</td>
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<td><strong>Weight (kg)</strong></td>
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<tr>
<td>Mean (SD)</td>
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<td>77.4 (7.6)</td>
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<td>Range</td>
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<td>57–86</td>
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<tr>
<td>Mean (SD)</td>
<td>26.7 (2.9)</td>
<td>24.7 (2.4)</td>
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<tr>
<td>Range</td>
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<td><strong>Height (cm)</strong></td>
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<tr>
<td>Mean (SD)</td>
<td>175.6 (9.2)</td>
<td>177.1 (6.0)</td>
</tr>
<tr>
<td>Range</td>
<td>154–190</td>
<td>169–187</td>
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</table>
376 BMI, body mass index.

377
TABLE 3. Effect of steady-state raltegravir on the Day 10 pharmacokinetics of lersivirine (Study 1)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lersivirine 1000 mg QD + raltegravir 400 mg BID (n=16)</th>
<th>Lersivirine 1000 mg QD (n=16)</th>
<th>Ratio of adjusted geometric means (A/B)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;tau&lt;/sub&gt; (ng·hr/mL)</td>
<td>10410</td>
<td>10317</td>
<td>10573</td>
<td>10520</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>1388</td>
<td>1395</td>
<td>1328</td>
<td>1333</td>
</tr>
<tr>
<td>C&lt;sub&gt;24&lt;/sub&gt; (ng/mL)</td>
<td>143</td>
<td>138</td>
<td>139</td>
<td>136</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (hr)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 (1–3)</td>
<td>–</td>
<td>3 (2–4)</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup> Estimated from the log-linear model.
 Median (range).

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

AUC<sub>tau</sub>, area under the plasma concentration-time profile from time zero to the end of the dosing interval; BID, twice daily;

CI, confidence interval; C<sub>max</sub>, maximum plasma concentration; C<sub>24</sub>, concentration observed at time 24 hours postdose; QD, once daily;

T<sub>max</sub>, time to maximum plasma concentration.
TABLE 4. Effect of steady-state lersivirine on the Day 10 pharmacokinetics of raltegravir (Study 1)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Raltegravir 400 mg BID</th>
<th>Raltegravir 400 mg BID + lersivirine 1000 mg QD (n=16)</th>
<th>Ratio of adjusted geometric means (A/B)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCτ (ng.hr/mL)</td>
<td>5402</td>
<td>5944</td>
<td>6760</td>
<td>7029</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>1265</td>
<td>1433</td>
<td>1899</td>
<td>2004</td>
</tr>
<tr>
<td>C12 (ng/mL)</td>
<td>122</td>
<td>123</td>
<td>99</td>
<td>98</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>2 (0–6)</td>
<td>–</td>
<td>2 (0.5–4.0)</td>
<td>–</td>
</tr>
</tbody>
</table>
Median (range).

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

AUC<sub>τ</sub>, area under the plasma concentration-time profile from time zero to the end of the dosing interval; BID, twice daily;

CI, confidence interval; C<sub>max</sub>, maximum plasma concentration; C<sub>12</sub>, concentration observed at time 12 hours postdose; QD, once daily;

T<sub>max</sub>, time to maximum plasma concentration.
TABLE 5. Effect of steady-state lersivirine on the Day 10 pharmacokinetics of maraviroc (Study 2)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Maraviroc 300 mg BID + lersivirine 500 mg BID (n=14) (A)</th>
<th>Maraviroc 300 mg BID + placebo (n=14) (B)</th>
<th>Ratio of adjusted geometric means (A/B)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AU*C&lt;sub&gt;τ&lt;/sub&gt; (ng.hr/mL)&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td>2481</td>
<td>2335</td>
<td>1.06</td>
<td>0.96, 1.18</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td>588</td>
<td>569</td>
<td>1.03</td>
<td>0.83, 1.29</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;12&lt;/sub&gt; (ng/mL)&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td>52</td>
<td>48</td>
<td>1.09</td>
<td>0.99, 1.19</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;max&lt;/sub&gt; (hr)&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>3 (0.5–4.0)</td>
<td>3 (0.5–4.0)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup> AUC<sub>τ</sub> and C<sub>max</sub> are presented as geometric means, and C<sub>12</sub> is presented as geometric mean. The 90% CI for C<sub>12</sub> is presented as geometric mean with 90% CI.
Adjusted geometric mean (geometric mean and adjusted geometric mean were the same).

Median (range).

AUC, area under the plasma concentration-time profile from time zero to the end of the dosing interval; BID, twice daily;

CI, confidence interval; C\text{max}, maximum plasma concentration; C\text{12}, concentration observed at time 12 hours postdose; T\text{max}, time to maximum plasma concentration.
TABLE 6. Treatment-emergent adverse events (all causality) occurring in ≥2 subjects in any one study/treatment group

<table>
<thead>
<tr>
<th>Study 1 treatment group</th>
<th>Study 2 treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lersivirine 1000 mg QD</td>
<td>Maraviroc 300 mg BID +</td>
</tr>
<tr>
<td>Raltegravir 400 mg BID</td>
<td>lersivirine 500 mg BID</td>
</tr>
<tr>
<td>+ raltegravir 400 mg BID</td>
<td>BID + placebo</td>
</tr>
<tr>
<td>(n=16)(^a)</td>
<td>(n=14)</td>
</tr>
<tr>
<td>(n=16)</td>
<td>(n=14)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MedDRA preferred term, n (%)</th>
<th>Study 1 treatment group</th>
<th>Study 2 treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>2 (12.5)</td>
<td>5 (35.7)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (12.5)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>1 (6.3)</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td></td>
<td>2 (12.5)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1 (5.6)</td>
<td>0</td>
</tr>
<tr>
<td>Symptom</td>
<td>Primary</td>
<td>Secondary</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (12.5)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (6.3)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia/epigastric discomfort</td>
<td>1 (6.3)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Feeling abnormal</td>
<td>2 (12.5)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (12.5)</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Two subjects had discontinued the study earlier due to adverse events after receiving lersivirine with raltegravir.

BID, twice daily; MedDRA, Medical Dictionary for Regulatory Activities; QD, once daily.
Lersivirine 1000 mg QD + raltegravir 400 mg BID
Lersivirine 1000 mg QD

Plasma lersivirine concentration (ng/ml)

Time post dose (hours)

2000
1600
1200
800
400
0

0 2 4 6 8 10 12 14 16 18 20 22 24
Lersivirine 1000 mg QD + raltegravir 400 mg BID

Raltegravir 400 mg BID

Plasma raltegravir concentration (ng/ml)

Time post dose (hours)

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