Effect of Rifampin and Rifabutin on the Pharmacokinetics of Lersivirine and Effect of Lersivirine on the Pharmacokinetics of Rifabutin and 25-O-Desacetyl-Rifabutin in Healthy Subjects

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Lersivirine is a nonnucleoside reverse transcriptase inhibitor (NNRTI) with a unique resistance profile exhibiting potent antiviral activity against wild-type HIV and several clinically relevant NNRTI-resistant strains. Lersivirine, a weak inducer of the cytochrome P450 (CYP) enzyme CYP3A4, is metabolized by CYP3A4 and UDP glucuronosyltransferase 2B7 (UGT2B7). Two open, randomized, two-way (study 1; study A5271008) or three-way (study 2; study A5271043) crossover phase I studies were carried out under steady-state conditions in healthy subjects. Study 1 ($n = 17$) investigated the effect of oral rifampin on the pharmacokinetics (PKs) of lersivirine. Study 2 ($n = 18$) investigated the effect of oral rifabutin on the PKs of lersivirine and the effect of lersivirine on the PKs of rifabutin and its active metabolite, 25-O-desacetyl-rifabutin. Coadministration with rifampin decreased the profile of the lersivirine area under the plasma concentration-time curve from time zero to 24 h postdose (AUC_{24}), maximum plasma concentration (C_{max}), and plasma concentration observed at 24 h postdose (C_{24}) by 85% (90% confidence interval [CI], 83, 87), 83% (90% CI, 79, 85), and 92% (90% CI, 89, 94), respectively, versus the values for lersivirine alone. Coadministration with rifabutin decreased the lersivirine AUC_{24}, C_{max}, and C_{24} by 34% (90% CI, 29, 39), 25% (90% CI, 16, 33), and 58% (90% CI, 52, 64), respectively, compared with the values for lersivirine alone. Neither the rifabutin concentration profile nor overall exposure was affected following coadministration with lersivirine. Lersivirine and rifabutin reduced the 25-O-desacetyl-rifabutin AUC_{24} by 27% (90% CI, 21, 32) and C_{max} by 27% (90% CI, 19, 34). Lersivirine should not be coadministered with rifampin, which is a potent inducer of CYP3A4, UGT2B7, and P-glycoprotein activity and thus substantially lowers lersivirine exposure. No dose adjustment of rifabutin is necessary in the presence of lersivirine; an upward dose adjustment of lersivirine may be warranted when it is coadministered with rifabutin.

L ersivirine is a nonnucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1) that displays potent antiviral activity against wild-type virus and also against certain clinically relevant NNRTI-resistant viruses (23).

X-ray crystallography has demonstrated that lersivirine binds to the reverse transcriptase in a novel way, which is thought to contribute to antiviral activity against key class resistant mutants, such as those with the K103N, Y181C, and G190A mutations (5, 28). However, the mechanism of lersivirine resilience against several drug-resistant virus strains is not yet fully understood. The antiviral activity and the safety and tolerability of lersivirine have been explored in a phase IIa study in treatment-naïve patients (12).

Lersivirine is metabolized by the cytochrome P450 (CYP) enzyme CYP3A4 and UDP glucuronosyltransferase 2B7 (UGT2B7); it is also a weak inhibitor of glucuronidation (10, 35). Lersivirine has been shown to be a weak inducer of CYP3A4 activity at clinical doses (9) and, on the basis of *in vitro* data, is an inhibitor and substrate for P-glycoprotein (P-gp) (Pfizer Inc., data on file). However, experiments in human hepatocytes have shown a concentration-dependent increase in induction with lersivirine. In general, lersivirine is considered unlikely to inhibit metabolism of other substances cleared by CYP enzymes at clinical doses.

Rifampin is a bacterial RNA polymerase inhibitor that is used to treat tuberculosis and nontuberculosis mycobacterial infections and is a potent CYP and P-glycoprotein inducer (17, 31). Rifampin is metabolized by B-esterases to 25-desacetyl-rifampin

(16) and is an autoinducer of metabolism. The terminal half-life of rifampin is estimated to be approximately 3 h (range, 2 to 5 h) (1).

Rifabutin and its active metabolite, 25-O-desacetyl-rifabutin, have demonstrated *in vitro* activity against the *Mycobacterium avium* complex organism isolated from HIV-positive and -negative individuals. Rifabutin has also demonstrated *in vitro* activity and clinical efficacy against *Mycobacterium tuberculosis* (27).

Rifabutin is metabolized and eliminated mainly by the CYP3A pathway and is a moderate inducer of CYP3A4 activity (3, 18). Rifabutin has an apparent terminal half-life of 45 h (range, 16 to 69 h) (32). Due to the potent CYP induction liability of rifampin, rifabutin is used as an alternative to rifampin in individuals infected with HIV who are coinfected with *Mycobacterium tuberculosis* (3).

As an estimated one-third of individuals living with HIV infec-

TABLE 1 Design for study 1[a]

Randomized sequence group	Period 1			Period 2		
	Days 1–10	Days 11–13	Day 14	Days 1–10	Days 11–13	Day 14
Sequence 1	Treatment A	Treatment C	Treatment E	Treatment B	Treatment D	Treatment F
Sequence 2	Treatment B	Treatment D	Treatment F	Treatment A	Treatment C	Treatment E
Day(s) of PK data collection	1, 9, 10	11, 13	14	1, 9, 10	11, 13	14

[a] A ≥14-day washout was used between periods 1 and 2. Treatment A, lersivirine at 1,000 mg q.d. plus rifampin at 600 mg q.d.; treatment B, lersivirine at 1,000 mg q.d. plus placebo; treatment C, lersivirine at 1,000 mg BID plus rifampin at 600 mg q.d.; treatment D, lersivirine at 1,000 mg BID plus placebo; treatment E, lersivirine at 1,000 mg plus rifampin at 600 mg q.d.; treatment F, lersivirine at 1,000 mg plus placebo.

tion are coinfected with *M. tuberculosis* (37), it is important that treatments in development be compatible for coadministration (11). This report describes the findings from two pharmacokinetic (PK) studies, of similar design, of the antituberculosis agents rifampin and rifabutin when each is coadministered with lersivirine.

The objective of study 1 (study A5271008) was to investigate the effects of rifampin on the steady-state PKs of lersivirine administered at 1,000 mg once daily (q.d.). The objective of study 2 (study A5271043) was to investigate the effects of lersivirine and rifabutin on each other's PKs and also the effect that lersivirine has on the PKs of the active metabolite of rifabutin (25-*O*-desacetyl-rifabutin). Both studies also investigated the safety and tolerability of lersivirine when it was coadministered with rifabutin or rifampin.

MATERIALS AND METHODS

Subjects. Eligible subjects were healthy males aged 21 to 55 years (study 1) or healthy male or female subjects aged 18 to 55 years (study 2), who had a body mass index (BMI) of 18 to 30 kg/m^2 (study 1) or 17.5 to 30.5 kg/m^2 (study 2) and a total body weight of >45 kg (study 1) or >50 kg (study 2). Subjects with a history of significant disease, HIV infection, or hepatitis B or C were excluded. Prescription and nonprescription drugs, vitamins, and dietary supplement medications were not permitted during the study and had to be discontinued within 7 days or 5 half-lives (whichever was longer) prior to the first dose of study medication.

Study designs. These were phase I, open, randomized, two-way crossover (study 1; study A5271008) or three-way crossover (study 2; study A5271043) studies conducted at the Pfizer Singapore Clinical Research Unit to investigate the effect of oral doses of rifampin (study 1) and rifabutin (study 2) on the steady-state PKs of lersivirine and the effect of lersivirine on the PKs of rifabutin and 25-*O*-desacetyl-rifabutin (the active metabolite of rifabutin) (study 2). The studies consisted of a screening visit up to 28 days before the start of dosing, two 14-day treatment periods (study 1; Table 1), or three 10-day treatment periods (study 2; Table 2) with a minimum washout period of 14 days between each.

In study 1, subjects received lersivirine at 1,000 mg q.d. on days 1 to 10

TABLE 2 Design for study 2[a]

Randomized sequence group	Period 1	Period 2	Period 3
Sequence 1	Treatment A	Treatment B	Treatment C
Sequence 2	Treatment B	Treatment C	Treatment A
Sequence 3	Treatment C	Treatment A	Treatment B
Sequence 4	Treatment B	Treatment A	Treatment C
Sequence 5	Treatment A	Treatment C	Treatment B
Sequence 6	Treatment C	Treatment B	Treatment A

[a] A ≥14-day washout was used between periods 1 and 2 and periods 2 and 3, and PK data were collected on day 10. All treatments are from days 1 to 10. Treatment A, lersivirine at 1,000 mg q.d.; treatment B, rifabutin at 300 mg q.d.; treatment C, lersivirine at 1,000 mg q.d. plus rifabutin at 300 mg q.d.

and 1,000 mg twice a day (BID) on days 11 to 13, with a single dose given on the morning of day 14 during both treatment periods in the fasted state. On days 1 to 14, subjects received rifampin at 600 mg q.d. in one period and placebo q.d. in the other period, according to randomization, with the morning dose of lersivirine. Only the PK and adverse event (AE) data relating to lersivirine administered q.d. are presented in this report. In study 2, subjects were randomized to receive lersivirine at 1,000 mg q.d. alone, rifabutin at 300 mg q.d. alone, and lersivirine at 1,000 mg q.d. and rifabutin 300 mg q.d. combined, in a random order across the three treatment periods. In study 2, lersivirine and rifabutin were administered with a meal, as it has been shown that food may help increase rifabutin tolerability. Administration with food does not significantly affect the exposures of lersivirine or rifabutin (8, 24).

Investigator site personnel administered the study treatment during each period with water at ambient temperature to a total volume of 240 ml. Subjects were asked to swallow the whole tablet or capsule and not chew it prior to swallowing. In order to standardize the conditions on PK sampling days, all subjects were required to refrain from lying down (except when required for blood pressure, pulse rate, and electrocardiographic measurements), eating, and drinking beverages other than water during the first 4 h after dosing. The mouth of each subject was examined following dosing to ensure that the study medication was taken.

Sampling and analytical methods. In study 1, blood samples were collected on days 1, 9, 11, and 13 at 0 h (predose), on day 10 at 0 h (predose) and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, and 24 h postdose, and on day 14 at 0 h (predose) and at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 h postdose. In study 2, blood samples were collected on day 10 at 0 h (postdose) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 h postdose.

In studies 1 and 2, blood samples of 5 ml and 4 ml, respectively, were taken to provide a minimum of 2 ml plasma for lersivirine PK analysis and transferred into appropriately labeled tubes containing lithium heparin. In addition, for study 2, blood samples of 6 ml were taken to provide a minimum of 2.5 ml plasma for rifabutin and 25-*O*-desacetyl-rifabutin PK analysis and were transferred into appropriately labeled tubes containing sodium heparin. All samples were centrifuged at approximately 1,700 × *g* for 10 min at 4°C. Plasma was stored in appropriately labeled screw-cap polypropylene tubes at approximately −20°C within 1 h of collection. Samples were analyzed using solid-phase extraction and a validated high-performance liquid chromatography/dual mass spectrometry (HPLC/MS/MS) assay.

The assay precision was 5.5% (coefficient of variance [CV]; study 1) and ≤8.5% (study 2) for lersivirine, ±69.9% (±10.3% without one potential outlier) for rifabutin (study 2), and ±9.3% for 25-*O*-desacetyl-

TABLE 3 Demographic characteristics (studies 1 and 2)[a]

Characteristic	Study 1 (*n* = 17)	Study 2 (*n* = 18)
Age (yr)	30.8 (5.7)	32.0 (5.9)
Wt (kg)	68.1 (10.7)	67.0 (9.7)
BMI (kg/m^2)	23.0 (2.9)	22.8 (2.2)
Ht (cm)	171.9 (6.9)	171.5 (9.0)

[a] Data represent means (standard deviations).

TABLE 4 Lersivirine pharmacokinetics when coadministered with rifampin (study 1) or rifabutin (study 2)

| Parameter (units) | Study 1 (effect of rifampin on PKs of lersivirine) | | | | | | Study 2 (effect of rifabutin on PKs of lersivirine) | | | | | |
| | Treatment 1 ($n = 13$)[a] | | Treatment 2 ($n = 14$)[b] | | | | Treatment 1 ($n = 17$)[c] | | Treatment 2 ($n = 17$)[d] | | | |
	Geometric mean (% CV)	Adjusted geometric mean (A)[e]	Geometric mean (% CV)	Adjusted geometric mean (B)	Ratio of adjusted geometric means (A/B)	90% CI	Geometric mean (% CV)	Adjusted geometric mean (A)	Geometric mean (% CV)	Adjusted geometric mean (B)	Ratio of adjusted geometric means (A/B)	90% CI
AUC_{24} (ng · h/ml)	2,023 (24)	2,016	13,868 (22)	13,691	0.15	0.13, 0.17	11,670 (18)	11,700	17,870 (21)	17,760	0.66	0.61, 0.71
C_{max} (ng/ml)	375 (34)	373	2,185 (25)	2,145	0.17	0.15, 0.21	2,139 (24)	2,127	2,880 (31)	2,837	0.75	0.67, 0.84
C_{24} (ng/ml)	6 (65)	6.2	78 (49)	78.1	0.08	0.06, 0.11	48.5 (34)	49	117.3 (42)	117.6	0.42	0.36, 0.48
$t_{1/2}$ (h)	4.7 (35)		5.8 (23)				4.9 (16)		6.1 (30)			
T_{max} (h)[f]	2 (1–3)		2.5 (0.5–4.0)				3 (1–6)		3 (1–6)			

[a] Treatment was with lersivirine at 1,000 mg q.d. plus rifampin at 600 mg q.d. Four subjects did not have samples for PK analysis collected due to discontinuations.

[b] Treatment was with lersivirine at 1,000 mg q.d. plus placebo q.d. Three subjects did not have PK samples collected due to discontinuations. $n = 13$ for adjusted geometric means.

[c] Treatment was with lersivirine at 1,000 mg q.d. plus rifabutin at 300 mg q.d. One subject discontinued due to an AE of pyrexia.

[d] Treatment was with lersivirine at 1,000 mg q.d. One subject discontinued due to an AE of pyrexia.

[e] The adjusted geometric mean was obtained by exponentiation of the mean estimate from the statistical analysis. Natural log-transformed data were analyzed using a mixed-effect model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect.

[f] Data represent median (range).

rifabutin (study 2). The between-day assay accuracy (percent relative error [RE]) of the estimated quality control samples ranged from −5.6% to 2.4% (study 1) and −3.3% to 6.3% (study 2) for lersivirine, −6.5% to 21.7% (1.1% without one potential outlier) for rifabutin (study 2), and −4.8% to 5.7% for 25-O-desacetyl-rifabutin (study 2). Calibration ranges were 1.0 to 2,000 ng/ml for lersivirine (studies 1 and 2), 2.5 to 1,000 ng/ml for rifabutin (study 2), and 1.0 to 1,000 ng/ml for 25-O-desacetyl-rifabutin (study 2).
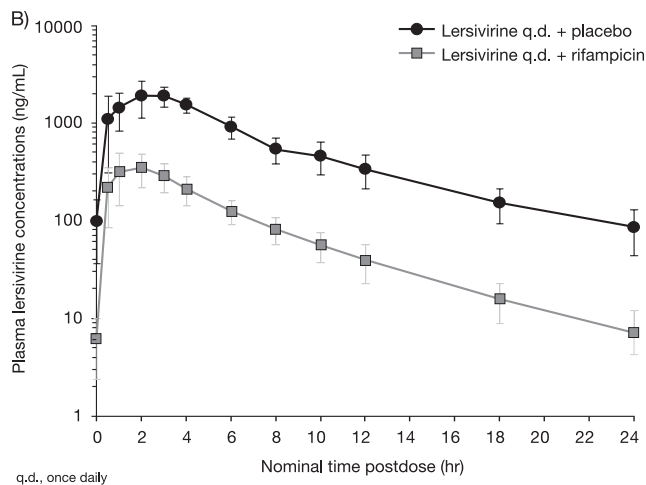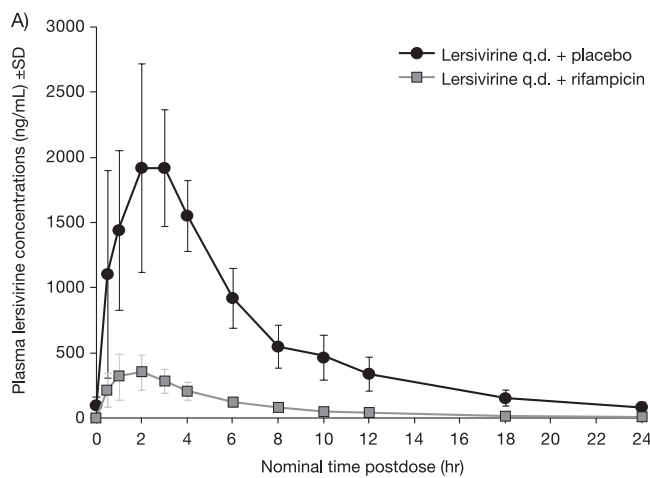

FIG 1 Mean plasma lersivirine concentration following lersivirine or rifampin and lersivirine administration on linear (A) and semilog (B) scales (study 1).
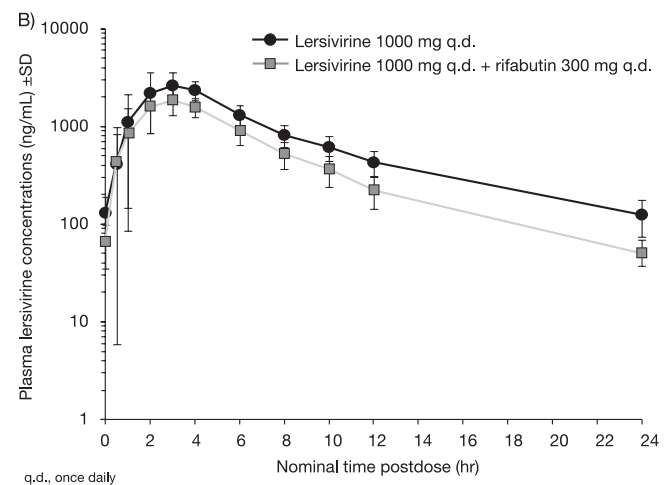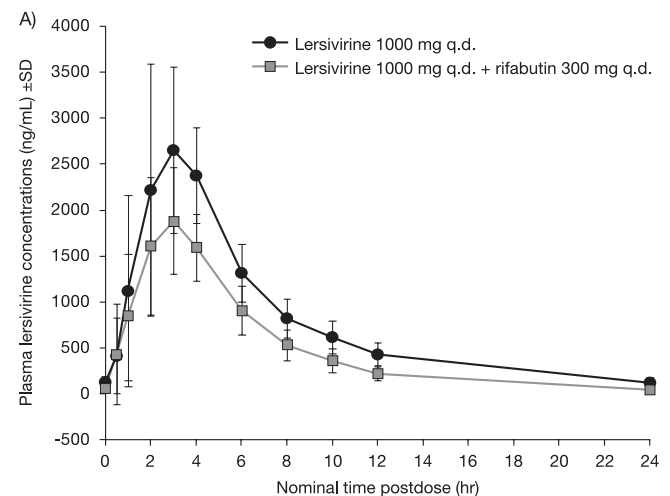

FIG 2 Mean plasma lersivirine concentration following lersivirine or rifabutin and lersivirine administration on linear (A) and semilog (B) scales (study 2).

TABLE 5 Rifabutin and 25-O-desacetyl-rifabutin pharmacokinetics when coadministered with lersivirine (study 2)

Effect studied and parameter (units)	Treatment 1 ($n = 17$)[a]		Treatment 2 ($n = 17$)[b]		Ratio of adjusted geometric means (A/B)	90% CI
	Geometric mean (% CV)	Adjusted geometric mean (A)[c]	Geometric mean (% CV)	Adjusted geometric mean (B)		
Effect of lersivirine on PKs of rifabutin						
AUC_{24} (ng · h/ml)	5,146 (19)	5,103	5,030 (18)	5,010	1.02	0.96, 1.08
C_{max} (ng/ml)	578 (33)	572	522 (31)	519	1.10	0.98, 1.24
C_{24} (ng/ml)	78.7 (26)	78.0	78.9 (28)	78.3	1.00	0.94, 1.06
T_{max} (h)[d]	4 (1–8)		4 (2–6)			
Effect of lersivirine on PKs of 25-O-desacetyl-rifabutin						
AUC_{24} (ng · h/ml)	203 (39)	202	275 (40)	275	0.73	0.68, 0.79
C_{max} (ng/ml)	21.3 (41)	21.0	28.9 (43)	28.7	0.73	0.66, 0.81
C_{24} (ng/ml)	3.04 (37)	3.04	3.60 (46)	3.59	0.85	0.73, 0.98
T_{max} (h)[d]	4 (1–8)		4 (2–6)			

[a] Treatment was with lersivirine at 1,000 mg q.d. plus rifabutin at 300 mg q.d. One subject discontinued.
[b] Treatment was with rifabutin at 300 mg q.d. One subject discontinued.
[c] The adjusted geometric mean was obtained by exponentiation of the mean estimate from the statistical analysis. Natural log-transformed data were analyzed using a mixed-effect model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect.
[d] Data represent median (range).

Safety. Safety evaluations included AE monitoring, laboratory safety tests, liver function tests (study 1), and single 12-lead electrocardiogram, supine blood pressure, and pulse rate recording.

Sample size. In study 1, a minimum sample size of 12 was required to provide 90% confidence intervals (CIs) for the difference between treatments of ±0.0539 and ±0.1525 on the natural log scale for area under the plasma concentration-time profile from time zero to infinity postdose (AUC_τ) and maximum plasma concentration (C_{max}), respectively, with 80% coverage probability. The above-described calculations assumed the estimated intrasubject standard deviations of the natural log of the area under the plasma concentration-time profile from time zero to 24 h postdose (AUC_{24}) and C_{max} to be 0.089 and 0.252, respectively, for lersivirine.

To estimate the effect of rifabutin on the PKs of lersivirine (study 2), the effect of lersivirine on the PKs of rifabutin, and the effect of lersivirine on the PKs of 25-O-desacetyl-rifabutin in study 2, 18 subjects were required to provide 90% CIs for the difference between treatments of ±0.101 and ±0.140, ±0.098 and ±0.159, and ±0.105 and ±0.152, respectively, on the natural log scale for AUC_{24} and C_{max}, respectively, with 90% coverage probability. The calculations described above assumed the estimated intrasubject standard deviations of natural log AUC_{24} and C_{max} to be 0.155 and 0.215, respectively, for lersivirine, 0.150 and 0.244, respectively, for rifabutin, and 0.161 and 0.234, respectively, for 25-O-desacetyl-rifabutin.

Statistical analyses. The PK parameters AUC_{24}, plasma concentration observed at 24 h postdose (C_{24}), C_{max}, and time to C_{max} (T_{max}) were summarized by treatment. An *ad hoc* analysis was performed to assess the elimination half-life ($t_{1/2}$) for lersivirine in the presence of rifampin and rifabutin. AUC parameters were determined using the linear/log trapezoidal method, and C_{max}, C_{24}, and T_{max} were determined by observation. Natural log-transformed data were analyzed using a mixed-effect model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect. The adjusted geometric mean for each treatment was obtained by exponentiation of the mean estimate on the natural log scale obtained from the model. Estimates of the adjusted mean differences (test/reference) and the 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), where the test was lersivirine plus rifampin (study 1) or lersivirine plus rifabutin (study 2) and the reference was lersivirine plus placebo (study 1), lersivirine alone (study 2), or rifabutin alone (study 2).

RESULTS

Subjects. All the 17 subjects in study 1 were Asian males. The majority of subjects in study 2 were Asian (17/18) and male (16/18). The baseline demographic characteristics are shown in Table 3. In study 1, 13 out of the 17 randomized subjects completed the study. Four subjects discontinued as they were unwilling to participate further in the study. The subjects discontinued on days 1 (lersivirine plus placebo), 6 (lersivirine plus placebo), and 7 (lersivirine plus rifampin) of period 1 and day 3 (lersivirine plus rifampin) of period 2. Out of the 18 subjects randomized in study 2, 17 subjects completed the study; 1 subject permanently discontinued on day 6 of period 1 due to a treatment-related AE of moderate pyrexia, an adverse event historically associated with rifabutin (26), while receiving lersivirine coadministered with rifabutin.

Pharmacokinetics. (i) Study 1. Mean lersivirine AUC_{24}, C_{max}, and C_{24} were substantially lower in the presence of rifampin with lersivirine (Table 4; Fig. 1). The mean $t_{1/2}$ and median T_{max} at day 10 were decreased for lersivirine plus rifampin compared with those for lersivirine plus placebo.

(ii) Study 2. Coadministration with rifabutin lowered the steady-state plasma concentrations of lersivirine as well as the lersivirine $t_{1/2}$ (Table 4; Fig. 2). No difference in lersivirine median T_{max} was observed between when lersivirine was administered alone and when lersivirine was coadministered with rifabutin (Table 4).

The rifabutin concentration profile or overall exposure did not change following coadministration with lersivirine (Table 5; Fig. 3). Following coadministration of lersivirine and rifabutin, lower exposure of the active rifabutin metabolite, 25-O-desacetyl-rifabutin, was observed (Table 5; Fig. 3).

Safety. There were no deaths, serious AEs, severe AEs, dose reductions, or temporary discontinuations due to AEs in either study. AEs that occurred in more than two subjects are summarized by study and treatment group in Tables 6 and 7. One subject in study 2 discontinued due to an AE of pyrexia (day 6) and also presented with nausea (day 11), chills (day 6), decreased appetite (day 6), headache (day 6), and chromaturia (day 1), as well as labo-
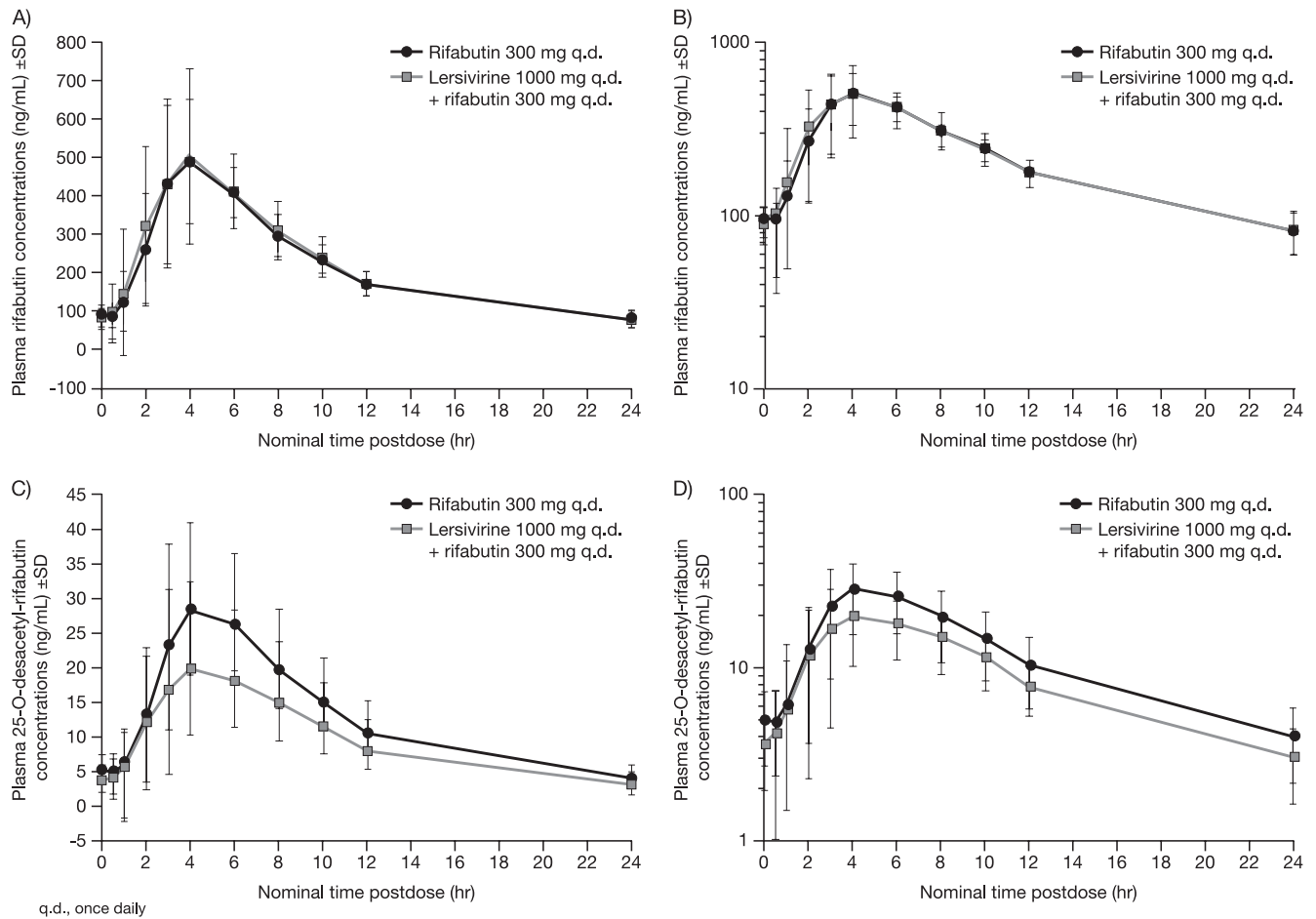
FIG 3 Mean plasma rifabutin (A and B) and 25-*O*-desacetyl-rifabutin (C and D) concentrations following rifabutin or lersivirine and rifabutin administration on linear (A and C) and semilog (B and D) scales (study 2).

ratory abnormalities (reduced lymphocytes [absolute; day 10], increased lymphocytes [percent; day 12], and reduced total neutrophils [absolute; day 12]). No unexpected clinically significant AEs or laboratory abnormalities were observed in either study.

TABLE 6 Incidence of all causality treatment-emergent adverse events that occurred in ≥2 subjects in any one treatment arm in study 1[a]

	No. (%) of subjects			
	Lersivirine at 1,000 mg q.d. + rifampin at 600 mg q.d. (n = 15)		Lersivirine at 1,000 mg q.d. + placebo q.d. (n = 16)	
Adverse event	Mild	Moderate	Mild	Moderate
Chromaturia	15 (100)	0	0	0
Dizziness	8 (53)	0	7 (44)	1 (6)
Nausea	2 (13)	1 (7)	7 (44)	0
Somnolence	1 (7)	0	2 (13)	0
Insomnia	2 (13)	0	1 (6)	0
Flatulence	0	0	3 (19)	0
Headache	1 (8)	0	1 (6)	1 (6)
Abdominal distension	0	0	2 (13)	0
Diarrhea	2 (13)	0	1 (6)	0
Lip dry	0	0	2 (12)	0

[a] No cases of severe treatment-emergent adverse events were recorded.

DISCUSSION

Coadministration of lersivirine with either rifampin or rifabutin decreased lersivirine exposure by 85% and 34% (as measured by AUC_{24}), respectively, and decreased $t_{1/2}$, which is representative of an increase in lersivirine clearance. The substantial decrease in exposure of lersivirine in the presence of rifampin is indicative of induction of both glucuronidation and CYP-mediated lersivirine clearance pathways. Lersivirine is a substrate for CYP3A4, as has been shown with recombinant CYP3A4, where the intrinsic clearance rate of lersivirine was 0.9 μl/pmol CYP/min, and to a far lesser extent with CYP3A5 (<0.08 μl/pmol CYP/min) (35). On the basis of *in vitro* data, lersivirine is also an inhibitor and substrate for P-gp (Pfizer Inc., data on file). UGT2B7 is also involved in the metabolism of lersivirine, such that with recombinant UGT2B7, glucuronide formation was linear with time up to 60 min and glucuronide at up to 1 mg/ml (35). The lersivirine plasma concentration was lowered to a greater extent with rifampin, a more potent inducer, than rifabutin.

Lersivirine did not affect the exposure of rifabutin but did reduce the exposure of 25-*O*-desacetyl-rifabutin. The decrease in exposure of the active metabolite of rifabutin may indicate that there is induction of the CYP3A4 pathway by lersivirine and/or autoinduction by rifabutin when rifabutin and lersivirine are co-

TABLE 7 Incidence of all causality treatment-emergent adverse events that occurred in ≥2 subjects in any one treatment arm in study 2[a]

| | No. (%) of subjects | | | | | |
| | Lersivirine at 1,000 mg q.d. (n = 17) | | Rifabutin at 300 mg q.d. (n = 17) | | Lersivirine at 1,000 mg q.d. + rifabutin at 300 mg q.d. (n = 18) | |
Adverse event	Mild	Moderate	Mild	Moderate	Mild	Moderate
Chromaturia	0	0	14 (82)	1 (6)	18 (100)	0
Abdominal distension	1 (6)	0	0	0	2 (11)	0
Diarrhea	2 (12)	0	1 (6)	0	1 (6)	0
Nausea	6 (35)	2 (12)	0	0	5 (28)	1 (6)
Vomiting	1 (6)	0	0	0	3 (17)	0
Chills	0	0	1 (6)	0	3 (17)	0
Pyrexia	1 (6)	0	4 (24)	0	1 (6)	1 (6)
Dizziness	6 (35)	0	0	0	3 (17)	1 (6)
Head discomfort	1 (6)	0	0	0	2 (11)	0
Headache	4 (24)	1 (6)	3 (18)	1 (6)	6 (33)	1 (6)
Oropharyngeal pain	0	0	2 (12)	0	1 (6)	0

[a] No cases of severe treatment-emergent adverse events were recorded.

administered. However, given that 25-O-desacetyl-rifabutin contributes up to 10% of the total antimicrobial activity (26) with rifabutin treatment, the decrease in metabolite exposure is not thought to be clinically relevant.

A limitation of the study was that all participants were Asian males. However, race has been shown to have only a marginal effect on lersivirine PKs, with Asian subjects having slightly lower lersivirine apparent oral clearance (CL/F), after adjusting for weight (36). A formal analysis comparing lersivirine PKs between men and women has not been conducted; however, preliminary data suggest that the difference between gender and age is not significant, after adjusting for weight and race. These data and the fact that genetic variants of both CYP3A and UGT2B7, enzymes predominantly responsible for lersivirine metabolism, have been shown not to be of clinical relevance (6, 13, 14, 25) suggest that the results of this study are generalizable to other populations.

Exposures of other NNRTIs, such as efavirenz, nevirapine, and rilpivirine, have been shown to change in the presence of rifampin and rifabutin (7, 15, 17, 19, 34). In one study, the change in efavirenz exposure following coadministration with rifampin ranged from a decrease of 65% to an increase of 37% (21), which suggests interindividual differences in enzyme activity. Furthermore, studies have shown that individuals with CYP2B6 516 TT genotypes are at risk of high efavirenz plasma exposures even in the presence of rifampin (20, 29). However, efavirenz trough concentrations, the best predictor of virological activity, have been shown to remain above the concentration necessary to suppress HIV in vitro in patients on concomitant rifampin (22). In contrast, efavirenz exposure is not significantly affected by rifabutin (2). A marked decrease (10 to 68%) in nevirapine concentrations is consistently observed in most PK studies in the presence of rifampin (33), and studies carried out in Indian (30) and African (4) patients coinfected with HIV and M. tuberculosis reported a significant proportion with subtherapeutic plasma nevirapine concentrations. Rifabutin has also been shown to induce a small decrease in the nevirapine exposure; however, the clinical significance is unclear. Two PK studies have investigated the effect of rifampin and rifabutin on rilpivirine exposure. When combined with rifampin, the rilpivirine AUC_{24} decreased by 80% and the C_{max} and the minimum concentration in plasma (C_{min}) decreased by 69% and

89%, respectively (34). When combined with rifabutin, the rilpivirine AUC_{24} decreased by 46% and the C_{max} and C_{min} decreased by 35% and 49%, respectively (7).

In conclusion, rifampin was shown to be a more potent inducer of lersivirine metabolism than rifabutin; therefore, lersivirine should not be coadministered with rifampin. No dose adjustment is necessary for rifabutin in the presence of lersivirine; however, an upward daily dose adjustment of lersivirine may be warranted when it is coadministered with rifabutin.

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