The Effect of Single and Multiple Dose Rifampin on the Pharmacokinetics of Doravirine

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Abstract

Background: Doravirine is a novel, potent, HIV-1 non-nucleoside reverse transcriptase inhibitor that is primarily metabolized by oxidation via CYP3A4. Based on in vitro data, doravirine is a substrate of P-gp but not of OATP1B1. This study assessed the impact of single dose (SD) and multiple dose (MD) rifampin administration on the pharmacokinetics (PK) of doravirine. After multiple dosing, rifampin is a strong inducer of CYP3A4, while SD administration of rifampin was performed to assess the effects of hepatic OATP1B1 inhibition and intestinal P-gp inhibition on the absorption and metabolism of doravirine.

Methods: This was an open-label, 2-period, fixed-sequence study in healthy adult men (n=11). In Period 1, a SD of 100 mg doravirine was administered on Day 1. In Period 2, following a 7-day washout, a SD of 600 mg rifampin and 100 mg doravirine were coadministered on Day 1. Following a 3-day washout, 600 mg rifampin was administered once daily for 15 days (Days 4-18) and 100 mg doravirine was coadministered on Day 17. Safety evaluations were performed throughout the study.

Results: There were no serious clinical or laboratory adverse experiences (AEs) and all reported AEs were judged as mild in intensity. Following coadministration of single doses of rifampin and doravirine, the geometric mean ratio (GMR) (90% confidence interval [CI]) (doravirine + SD rifampin/doravirine) for $AUC_{0-\infty}$ and C_{24} were 0.91 (0.78, 1.06) and 0.90 (0.80, 1.01), respectively, suggesting that OATP1B1 inhibition does not impact the PK of doravirine. The GMR (90% CI) for C_{max} was 1.40 (1.21, 1.63). This small increase in C_{max} is attributable to P-gp inhibition given that doravirine is a substrate and rifampin is an inhibitor for this transporter. After coadministration with multiple doses of rifampin, doravirine exposure was reduced as expected based on the role of CYP3A4 in doravirine metabolism. The GMRs (doravirine + MD rifampin/ doravirine) and 90% CIs for $AUC_{0-\infty}$, C_{24}, and C_{max} were 0.12 (0.10, 0.15), 0.03 (0.02, 0.04), and 0.43 (0.35, 0.52), respectively.

Conclusions: Doravirine was generally well tolerated when administered alone or with rifampin. Inhibition of OATP1B1 and P-gp by SD rifampin did not have a clinically meaningful effect on the PK of doravirine. Multiple dosing of rifampin reduced doravirine $AUC_{0-\infty}$, C_{max}, and C_{24}. Thus, doravirine should not be administered with strong CYP3A4 inducers.

Background

- Doravirine (MK-1439) is a novel next generation non-nucleoside reverse transcriptase inhibitor for the treatment of HIV-1 infection and is primarily metabolized by oxidation via CYP3A4.
- Based on in vitro data, doravirine is a substrate of P-gp but not of OATP1B1. However, doravirine has high permeability in vitro, suggesting that P-gp effects in the gut may be limited.
- Rifampin, when acutely dosed, has the potential to capture the effects of both hepatic OATP1B1 and OATP1B3 inhibition and intestinal P-gp inhibition on the absorption and metabolism of doravirine.
- Upon chronic dosing, rifampin is a strong inducer of drug clearance enzymes through its activation of the nuclear pregnane X receptor. Rifampin is a potent inducer of hepatic and intestinal CYP3A4 and is an inducer of P-gp following chronic dosing. Clinical data indicate that the inductive effect of rifampin on CYP3A4 is near maximal after 7 days of chronic administration.

Aims

- To evaluate the effect of coadministration of a single dose of rifampin on the plasma pharmacokinetic profile of doravirine.
- To evaluate the effect of coadministration of multiple doses of rifampin on the plasma pharmacokinetic profile of doravirine.

Subjects and Methods

- **Study Design:** Open-label, 2-period, fixed-sequence study, to assess the effects of coadministration of single and multiple doses of rifampin on the single-dose pharmacokinetics of doravirine.
- **Subjects:** A total of 11 non-tobacco-using male adult subjects between the ages of 19 and 55 years (inclusive), with a body mass index (BMI) ≥18.5 to ≤32.0 kg/m^2 (inclusive) were enrolled.
- **Treatments**
  - Treatment A (Period 1): a single oral dose of 100 mg doravirine administered on Day 1.
  - Washout Period: 7 days.
  - Treatment B (Period 2): a single oral dose of 600 mg rifampin coadministered with a single oral dose of 100 mg doravirine on Day 1.
  - Treatment C (Period 2): oral doses of 600 mg rifampin QD for 15 days (Days 4 to 18), with a single oral dose of 100 mg doravirine coadministered on Day 17.
- **Assessments**
  - **Doravirine PK:** Plasma samples for determination of doravirine concentrations were collected from each subject at predose and at specified time points over 72 hours following the administration of doravirine alone on Day 1 of Period 1 and following the coadministration of a SD of 600 mg rifampin and 100 mg doravirine on Day 1 of Period 2. Plasma samples were collected from each subject at predose and at specified time points over 48 hours on Day 17 of Period 2, following the once daily administration of rifampin for 15 days with the coadministration of 100 mg doravirine on Day 17.
  - **Safety:** Safety was monitored throughout the study via adverse experiences (AEs), physical examination, vital signs, electrocardiograms (ECGs), and laboratory safety tests.
  - **Statistical Analyses:** Exposure parameters were natural-log transformed and analyzed with a linear mixed-effects model, with a fixed-effect term for treatment (doravirine alone, doravirine + SD rifampin, and doravirine + MD rifampin). An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the treatment measurements within the same subject. The least-squares means (LSMs) and corresponding 95% confidence intervals (CIs) were calculated by treatment and the differences in treatment LSMs and corresponding 90% CIs were estimated for each parameter. The back-transformed summary results were reported for each exposure parameter as the geometric means (GMs) and corresponding 95% CIs as well as the geometric mean ratios (GMRs) for each comparison and corresponding 90% CIs.

Results and Discussion

Subject Demographics

- Subject characteristics can be found in **Table 1.**

Table 1. Subject Characteristics

	Demographics
Entered	11
Completed	10
Male N (age range, years)	11 (22-52)
Female N (age range, years)	0
Height (mean and range, cm)	177.0 (168.0-188.0)
Weight (mean and range, kg)	82.7 (60.5-93.9)
BMI (mean and range, kg/m^2)	26.40 (20.71-31.86)
Race	
White	9
Black or African American	2

Safety and Tolerability

- Doravirine was generally well tolerated when administered alone or coadministered with single or multiple oral doses of rifampin in healthy adult male subjects.
- No deaths, serious adverse experiences, or laboratory adverse experiences were reported and no subject discontinued because of an adverse experience.
- Six (6) subjects reported a total of 19 clinical adverse experiences. The most common adverse experience was oropharyngeal pain reported by 2 (18.2%) subjects. Only 1 adverse experience was considered by the Investigator to be drug related (increased appetite considered related to rifampin only). All adverse experiences were of mild intensity and resolved by the end of the study.

Pharmacokinetics of Doravirine

- Overall, a single-dose administration of rifampin coadministered with a single oral dose of doravirine does not affect the $AUC_{0-\infty}$ and C_{24} of doravirine compared to a single oral dose of doravirine alone. A modest increase in C_{max} was observed following the coadministration of a single dose of rifampin with a single oral dose of doravirine compared to a single oral dose of doravirine alone (**Figure 1, Table 2**).
  - GMRs (90% CIs) for the doravirine $AUC_{0-\infty}$ and C_{24} were 0.91 (0.78, 1.06), and 0.90 (0.80, 1.01), respectively. The GMR (doravirine + SD rifampin/doravirine alone) and 90% CIs for C_{max} were 1.40 (1.21, 1.63).
  - The GM CL/F of doravirine was 7.09 L/hr when doravirine was coadministered with a single oral dose of rifampin compared to 6.44 L/hr when doravirine was administered alone.
  - The GM apparent terminal $t_{½}$ was 5.50 hours when doravirine was coadministered with a single oral dose of rifampin compared to 18.60 hours when doravirine was administered alone.
- Doravirine $AUC_{0-\infty}$, C_{max}, and C_{24} were reduced following a single oral dose of doravirine coadministered with multiple oral doses of rifampin (**Figure 2, Table 3**).
  - The GMRs and 90% CIs for doravirine $AUC_{0-\infty}$, C_{24}, and C_{max} for the comparison of a single oral dose of 100 mg doravirine coadministered with multiple oral doses of 600 mg rifampin versus a single oral dose of 100 mg doravirine alone were 0.12 (0.10, 0.15), 0.03 (0.02, 0.04), and 0.43 (0.35, 0.52), respectively.
  - The GM CL/F of doravirine was 51.6 L/hr following the coadministration of multiple oral doses of rifampin with a single oral dose of doravirine compared to 6.44 L/hr following the administration of doravirine alone.
  - The GM apparent terminal $t_{½}$ was 6.30 hours when doravirine was coadministered with multiple oral doses of rifampin compared to 18.60 hours when doravirine was administered alone.

Figure 1. Arithmetic Mean (± SD) Plasma Concentration-Time Profiles of Doravirine Following the Administration of a Single Dose of Doravirine With or Without the Coadministration of a Single Dose of Rifampin in Healthy Adult Subjects (N=11 for Period 1 and N=11 for Period 2)

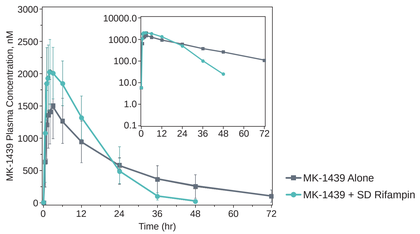


Table 2. Statistical Comparisons of Plasma Pharmacokinetics of Doravirine Following the Administration of a Single Oral Dose of 100 mg Doravirine With or Without the Coadministration of a Single Oral Dose of 600 mg Rifampin in Healthy Adult Subjects

	Doravirine Alone			Doravirine + SD Rifampin			Doravirine + SD Rifampin/ Doravirine Alone		Pseudo Within-Subject % CV[‖]
Pharmacokinetic Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0-\infty}$[†] (µM•hr)	11	36.5	(26.7, 49.8)	11	33.1	(28.2, 38.9)	0.91	(0.78, 1.06)	19.441
C_{max}[†] (nM)	11	1540	(1230, 1920)	11	2160	(1890, 2470)	1.40	(1.21, 1.63)	19.164
C_{24}[†] (nM)	11	511	(360, 725)	11	459	(347, 608)	0.90	(0.80, 1.01)	15.131
CL/F[§] (L/hr)	11	6.44	48.9	11	7.09	24.2			
T_{max}[‡] (hr)	11	3.00	(1.00, 6.00)	11	2.00	(1.00, 6.00)			
Apparent terminal $t_{½}$[§] (hr)	11	18.60	44.52	11	5.50	18.93			

Doravirine Alone: Single oral dose of 100 mg doravirine (1 x 100 mg tablet) on Day 1 of Period 1.
Doravirine + SD rifampin: Single oral dose of 100 mg doravirine (1 x 100 mg tablet) coadministered with a single oral dose of 600 mg rifampin (2 x 300 mg capsules) on Day 1 of Period 2.
[†]Back-transformed least squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[‡]Median (Minimum, Maximum) reported for T_{max}.
[§]Geometric mean and geometric coefficient of variation reported for CL/F and apparent terminal $t_{½}$.
[‖]Pseudo Within-Subject %CV=100*sqrt (σ_A2 + σ_B2 – 2*σ_{AB})/2), where σ_A2 and σ_B2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
GM=Geometric least-squares mean; GMR=Geometric least-squares mean ratio; CI=Confidence interval.

Figure 2. Arithmetic Mean (± SD) Plasma Concentration-Time Profiles of Doravirine Following the Administration of a Single Dose of Doravirine With or Without the Coadministration of Multiple Doses of Rifampin in Healthy Adult Subjects (N=11 for Period 1 and N=10 for Period 2)

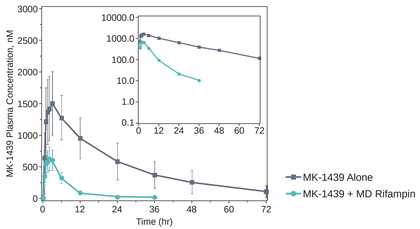


Table 3. Statistical Comparisons of Plasma Pharmacokinetics of Doravirine Following the Administration of a Single Oral Dose of 100 mg Doravirine With or Without the Coadministration of Multiple Oral Doses of 600 mg Rifampin in Healthy Adult Subjects

	Doravirine Alone			Doravirine + MD Rifampin				Doravirine + MD Rifampin/ Doravirine Alone		Pseudo Within-Subject % CV[‖]
Pharmacokinetic Parameter	N	GM	95% CI	N	GM	95% CI	90% CI	GMR	90% CI	
$AUC_{0-\infty}$[†] (µM•hr)	11	36.5	(26.7, 49.8)	10	4.47	(3.87, 5.15)	(3.98, 5.01)	0.12	(0.10, 0.15)	28.078
C_{max}[†] (nM)	11	1540	(1230, 1920)	10	661	(562, 778)	(579, 755)	0.43	(0.35, 0.52)	24.702
C_{24}[†] (nM)	11	511	(360, 725)	10	16.4	(11.6, 23.2)	(12.4, 21.7)	0.03	(0.02, 0.04)	39.388
CL/F[§] (L/hr)	11	6.44	48.9	10	51.6	19.6				
T_{max}[‡] (hr)	11	3.00	(1.00, 6.00)	10	2.00	(0.50, 3.04)				
Apparent terminal $t_{½}$[§] (hr)	11	18.60	44.52	10	6.30	40.12				

Doravirine Alone: Single oral dose of 100 mg doravirine (1 x 100 mg tablet) on Day 1 of Period 1.
Doravirine + MD rifampin: Multiple oral doses of 600 mg rifampin QD on Day 4 to 18 of Period 2, with a single oral dose of 100 mg doravirine (1 x 100 mg tablet) coadministered on Day 17 of Period 2.
[†]Back-transformed least squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[‡]Median (Minimum, Maximum) reported for T_{max}.
[§]Geometric mean and geometric coefficient of variation reported for CL/F and apparent terminal $t_{½}$.
[‖]Pseudo Within-Subject %CV=100*sqrt (σ_A2 + σ_B2 – 2*σ_{AB})/2), where σ_A2 and σ_B2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
GM=Geometric least squares mean; GMR=Geometric least-squares mean ratio; CI=Confidence interval.
One subject was dropped on Day 17 of Period 2 due to failed Period 2 Day 16 check-in drug screen.

Conclusions/Discussion

- Coadministration of single-dose rifampin with a single oral dose of doravirine results in a ~40% increase in C_{max} that is not clinically meaningful and no effect on the $AUC_{0-\infty}$ and C_{24} of doravirine. The small increase in C_{max} with no change in exposure suggests that doravirine is, at best, a weak substrate for OATP1B1 and OATP1B3 uptake transporters, and the impact of P-gp inhibition at the gut wall is mild. As a result, modulation of OATP1B1 and OATP1B3 is not likely to have clinically meaningful effects on the pharmacokinetics of doravirine. Furthermore, while P-gp inhibition at the gut wall may increase doravirine C_{max}, the impact is limited by the high permeability of doravirine.
- Multiple-dose coadministration of rifampin with a single oral dose of doravirine results in a reduction in doravirine exposure, C_{max}, and C_{24}, which is consistent with the role of CYP3A4 as the predominant enzyme involved in the metabolism of doravirine and the induction of CYP3A4 by rifampin. When doravirine is coadministered with multiple oral doses of rifampin, doravirine $AUC_{0-\infty}$ and C_{24} are decreased 88% and 97%, respectively.
- When a single oral dose of 100 mg doravirine is coadministered with multiple oral doses of rifampin, the resulting doravirine C_{24} and projected steady-state C_{24} is below the 78 nM C_{24} target for efficacy against wild-type HIV based on in vitro studies, suggesting that the clinical efficacy of doravirine is likely reduced when coadministered with chronic rifampin therapy or other strong CYP3A4 inducers.

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