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ARTICLE

Twice-Daily Doravirine Overcomes the Interaction Effect from Once-Weekly Rifapentine and Isoniazid in Healthy Volunteers

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Doravirine (DOR) is a non-nucleoside reverse transcriptase inhibitor indicated for the treatment of HIV-1. Its use in combination with rifapentine (RPT), an antituberculosis (TB) antibiotic, may reduce the exposure of DOR compromising viral suppression in those living with HIV-1 co-infected with TB. We conducted a prospective, phase I, open label, two-period, fixed sequence, drug interaction study to evaluate the effect of once-weekly RPT and isoniazid (INH) on the pharmacokinetics (PKs) of DOR in healthy volunteers. DOR 100 mg was administered alone twice-daily for 4 days in period 1. In period 2, once-weekly RPT + INH were co-administered with multiple doses of DOR 100 mg twice-daily for study days 7, 14, and 21. Plasma was obtained for DOR PKs when given alone and co-administered with RPT + INH. Eleven healthy volunteers enrolled and completed the study. The geometric mean ratios and 90% confidence intervals for DOR area under the concentration-time curve from zero to 12 hours (AUC_{0-12}) and C_{12} in the presence of RPT + INH compared with DOR alone were 0.71 (0.60–0.85) and 0.69 (0.54–0.89), respectively. Although exposures were moderately reduced in the presence of RPT + INH, trough DOR values were within the concentration range associated with virological suppression. These results demonstrate that a modest decrease in DOR exposure would unlikely be clinically relevant in a virally suppressed patient co-administered once-weekly RPT + INH.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Co-infection with latent tuberculosis (TB) in persons living with HIV-1 is common. Rifapentine (RPT) is an antiTB antibiotic available as once-weekly treatment for latent TB and is a potent inducer of CYP3A metabolic enzyme. There are limited studies that evaluate RPT in the presence with antiretrovirals, including doravirine (DOR), a novel non-nucleoside reverse transcriptase inhibitor metabolized by CYP3A.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This study evaluated the pharmacokinetics of twice-daily DOR when co-administered with once-weekly RPT and isoniazid (INH).

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Following RPT-mediated CYP3A induction, DOR steady-state trough concentrations declined in a time-dependent manner. Steady-state clearance of DOR increased with a > 50% reduction in plasma half-life following co-administration with RPT and INH. Despite this reduction, DOR exposure is in a range that is likely to maintain viral suppression.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ DOR 100 mg given twice-daily can mitigate the interactive effects of once-weekly RPT. Co-administration was generally well-tolerated with a modest decrease in DOR exposure unlikely to be clinically relevant. This dosing regimen may offer an alternative to virally suppressed patients on antiretroviral therapy co-infected with latent TB and considering an RPT-based regimen.

Doravirine (DOR) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used in combination with other antiretrovirals (ARVs) for the treatment of HIV-1 infection in adults. It is noninferior to current standard of care ARV regimens with fewer adverse events.[1,2] The elimination of DOR is primarily through metabolism via cytochrome P450 (CYP) 3A mediated oxidation to an M9 metabolite.[3] ***In vitro*** studies demonstrate low potential of interference from the parent or metabolite on phase I and II metabolizing enzymes and drug transporters.[3] Therefore, DOR has a lower potential for drug-drug interactions compared with other NNRTIs and does not impact the pharmacokinetics (PKs) of other drugs. Considering the predominant route of elimination is through CYP3A, co-administration with strong inhibitors and inducers may alter the PK profile of DOR.

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The Centers for Disease Control and Prevention (CDC) currently recommends several latent tuberculosis (TB) infection (LTBI) treatment options for persons with HIV and includes either once-daily isoniazid (INH) for 9 months, rifampin or rifabutin once-daily for 4 months, or once-weekly rifapentine (RPT) and INH for 3 months.[4] The rifamycin class of antiTB agents are strong inducers of CYP enzymes, including CYP3A, with rifabutin being the less potent inducer of the three. Co-administration with multiple-doses of rifampin significantly reduced DOR trough concentrations by 97% with multiple-dose rifabutin similarly reducing troughs by 68%.[5,6] With the exception of rifabutin, where twice-daily doses of DOR are predicted to overcome the interaction,[6] the use of rifampin and rifabutin together with once-daily doses of DOR is contraindicated. A 3 month RPT-based regimen has comparable efficacy and safety compared with lengthy once-daily antiTB regimens.[7] The magnitude of drug-drug interactions between DOR when co-administered with RPT and INH has not been defined.

The objective of this study was to evaluate the effects of once-weekly RPT and INH on the steady-state PKs of twice-daily DOR, and to assess the safety and tolerability of these co-administered drugs.

METHODS

This study was approved by the Thomas Jefferson University Institutional Review Board and registered on clinicaltrials.gov (NCT03886701). The study was conducted in accordance with Good Clinical Practice standards and applicable federal and/or local regulatory requirements. All participants provided written informed consent prior to beginning the study.

Study population

Healthy HIV and TB negative adult men or nonpregnant women between 18 and 60 years old with a body mass index of 19–33 kg/m^2 weighing between 45 and 120 kg at screening were enrolled in the study. Women of childbearing potential and their partners were required to use acceptable methods of contraception during the time of the study and until 4 weeks after the last dose of drug. Women who were postpartum for < 12 months were excluded. Other exclusion criteria included any clinically significant disease, current drug or alcohol abuse, known anaphylactic or systemic reactions to doravirine, RPT, or INH, and those who have received another study drug within 4 weeks or 5 half-lives (whichever occurrs first).

Study design and treatments

This was a phase I, prospective, open-label, two-period, fixed-sequence, drug-drug interaction study conducted in healthy volunteers (**Figure 1**). Subjects received DOR 100 mg twice-daily for 4 study days during the first period. In the second period, once-weekly weight-based RPT and INH and pyridoxine 50 mg was co-administered with DOR 100 mg twice-daily. The doses of RPT were weight-based and included 900 mg (≥ 50 kg) or 750 mg (32.1–49.9 kg) with a 900 mg maximum dose. Isoniazid was given as a 15 mg/kg dose and rounded up to the nearest 50 or 100 mg with a maximum dose of 900 mg. The doses and dosing schedule for RPT, INH, and pyridoxine were selected based on the CDC treatment regimens for LTBI.[4] Subjects received a light meal prior to each DOR dose for study days 1–4. For the morning of study days 7, 14, and 21, INH and pyridoxine were dosed following an overnight fast with DOR and RPT dosed after the subject received a meal. For days 8–13 and 15–20, subjects received a light meal before each dose of DOR. All subjects received 8 ounces of water with each dose.

PK sampling and bioanalysis

Plasma samples for DOR were collected at predose (0 hour), 0.5, 1, 1.5, 2, 3, 6, 12, 24, 36, 48, and 72 hours postdose on study days 4–7 (period 1) and study days 21–24 (period 2). A predose sample was taken for all subjects prior to starting period 1 and DOR dosing to ensure no previous doses of DOR were taken. A DOR trough concentration was collected on study days 15, 16, and 20 prior to the administration of the second DOR dose. Approximately 3 mL of blood was collected into K2-EDTA vials and inverted 8–10 times before being centrifuged at 3,000 rpm for 10 minutes. Plasma was aliquoted into a cryotube and was stored at –20°C before analysis. Plasma DOR concentrations were

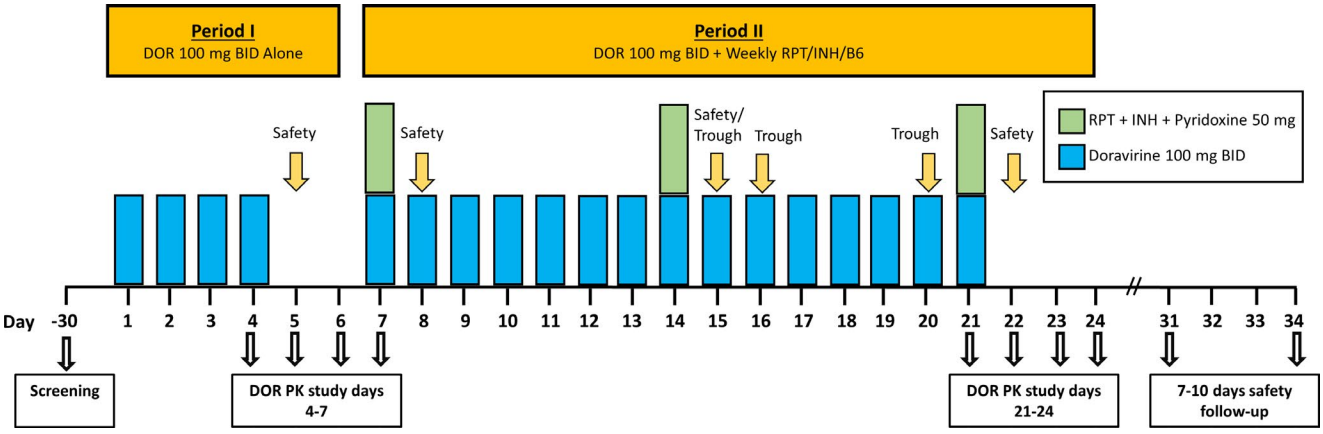

Figure 1 Study schematic. Arrows indicate blood for PK or safety laboratory. B_6 = vitamin B_6 (pyridoxine); DOR = doravirine; INH = isoniazid; PK = pharmacokinetics; RPT = rifapentine.

determined using a validated ultra-performance liquid chromatography tandem mass spectrometry with a lower limit of quantification of 1 ng/mL over a calibration range of 1–1,000 ng/mL (developed and validated by Syneos Health Clinique, Quebec, Canada).

Safety and tolerability

Safety and tolerability were assessed throughout the study and included monitoring for adverse events, physical examinations, vital signs, electrocardiograms, and laboratory safety tests (blood chemistry, hematology, and urinalysis). Laboratory safety assessments were conducted in period 1 (study day 5) and period 2 (study days 8, 15, and 22).

PK and statistical analysis

Plasma DOR PK parameters were estimated using a noncompartmental analysis and performed on R version 3.6.1 with the PKNCA and ncappc packages. DOR PK parameters included the area under the concentration-time curve during the dosing interval from zero to 12 hours ($AUC_{0–12}$), steady-state trough plasma concentration at the end of the dosing interval (C_{12}), average steady-state plasma drug concentration during multiple dose administration (C_{avg}), peak plasma concentration at steady-state (C_{max}), terminal elimination half-life, apparent clearance at steady-state, and the accumulation ratio for both periods.

The parameters $AUC_{0–12}$, C_{12}, C_{avg}, and C_{max} were separately evaluated using a generalized estimating equation model with log-link with the primary predictor of period. Geometric means and corresponding 95% confidence intervals (CIs) were calculated for each treatment group. The 90% CIs were estimated from the generalized estimating equation model for the geometric mean ratios for (DOR + RPT + INH/DOR) alone. The statistical analysis was performed on R version 3.6.1 with the geepack package.[8] Sample size was calculated from the reported variability in DOR trough concentration in HIV-infected men (1,540 nmol/L and 95% CI 1,110–2,140 nmol/L).[9] Using a significance level of 5% with a two-sided paired *t*-test, a sample size of 11 provided > 80% power to detect a change of 50% in DOR trough concentrations. The magnitude of change was selected on the assumption that a 50% change in trough concentrations would be clinically significant.

RESULTS

Subject demographics

Eleven subjects (10 men and 1 woman) were enrolled and completed the study with a mean (±SD) age of 46.4 (±9.9) years old. Subjects were Black or African American (73%) or white (27%). Mean body weights were 92.9 kg (range 75.5–109.4 kg), which allowed the maximum doses of RPT and INH (900 mg) for all subjects during the study. The mean (±SD) body mass index was 31.2 (±2.6) kg/m^2. All subjects were included in the PK and safety analysis.

Doravirine plasma concentration time profile

All PK data were included in the analysis and figures. All subjects had undetectable DOR concentrations in plasma at predose prior to beginning study day 1. Two subjects had undetectable DOR concentrations in plasma at the 72-hour time point in the second period (study day 24). Mean DOR plasma concentration profiles alone and in combination with RPT and INH for all sampled points was plotted against time (**Figure 2).** The mean DOR plasma concentration during the dosing interval for DOR alone or in combination with RPT and INH is shown in **Figure 3**. Co-administration with once-weekly RPT and INH modestly reduced the steady-state $AUC_{0–12,}$ C_{12}, C_{avg}, and C_{max} by 29%, 31%, 29%, and 25%, respectively. **Figure 4** displays the individual and geometric mean ratios for RPT + INH + DOR/DOR alone $AUC_{0–12,}$ C_{12}, C_{avg}, and C_{max}. RPT co-administration reduced DOR half-life

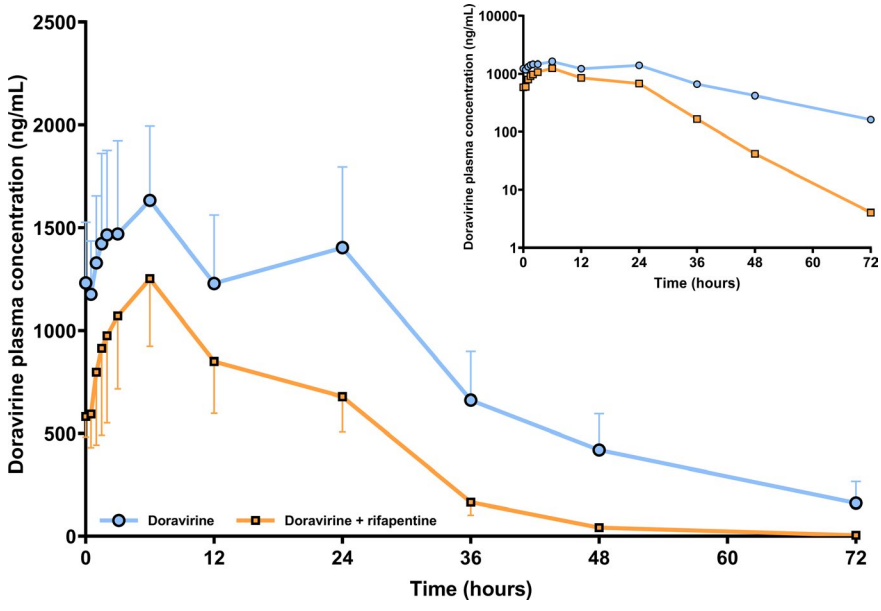

Figure 2 Mean (±SD) doravirine plasma concentration-time profiles following twice-daily doses of doravirine 100 mg alone or together with once-weekly rifapentine and isoniazid. The inset represents the concentration-time profile plotted on a log-linear scale.

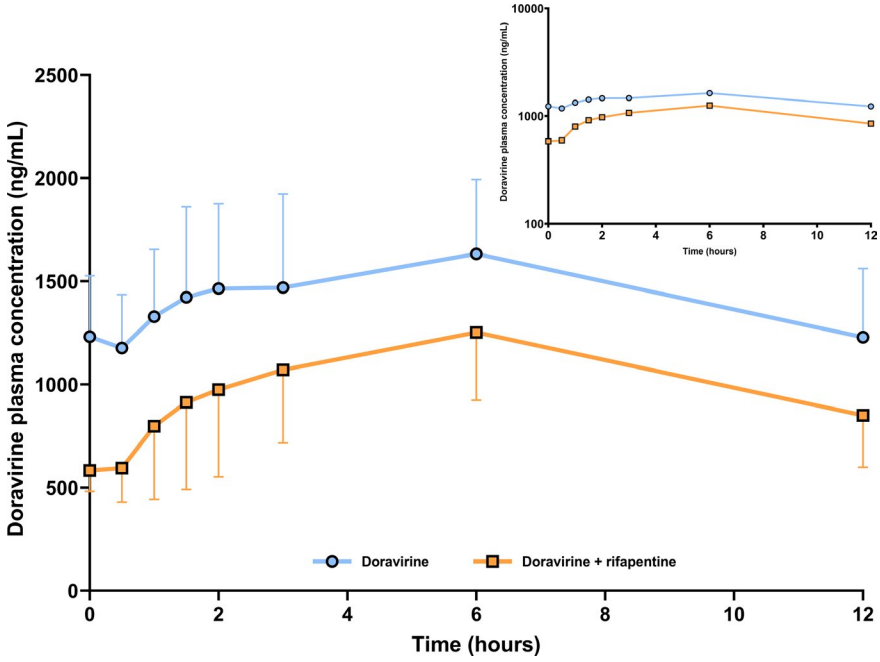

Figure 3 Mean (±SD) doravirine (DOR) plasma concentration-time profiles during the 12-hour dosing interval following twice-daily doses of DOR 100 mg alone or together with once-weekly rifapentine and isoniazid. Sampling at time 0 and 12 hours were taken prior to the second dose of DOR. The inset represents the concentration-time profile plotted on a log-linear scale.

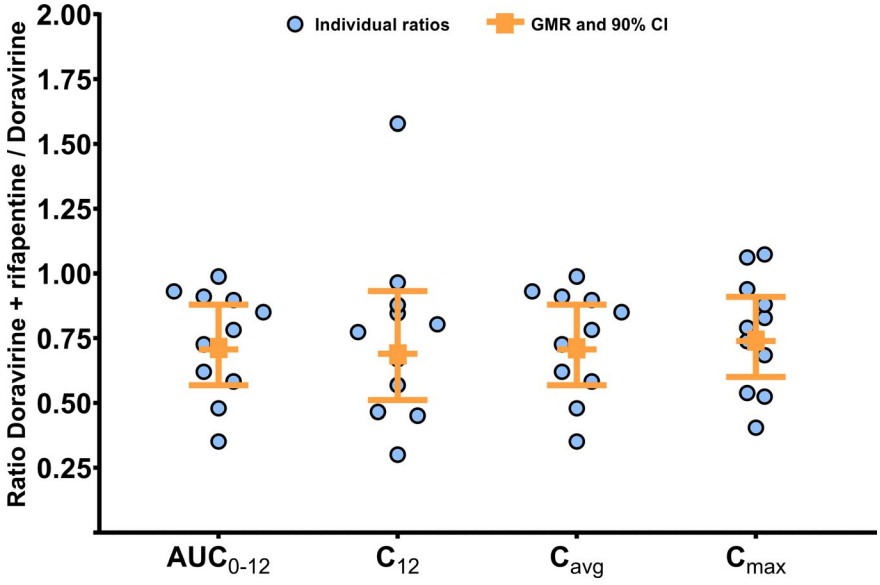

Figure 4 Individual ratios (doravirine (DOR)/DOR + rifapentine), geometric mean ratios (GMRs), and corresponding 90% confidence intervals (CIs) for doravirine exposure parameters. AUC_{0-12} = area under the concentration time curve during the 12-hour dosing interval, C_{12} = plasma concentration at the end of the dosing interval prior to the second dose, C_{avg} = average steady-state plasma concentration during the dosing interval, C_{max} = maximum steady-state concentration.

by 58% while increasing the steady-state total plasma clearance by 41% (**Table 1**).

Safety and tolerability

DOR in combination with RPT and INH was generally well-tolerated with no serious adverse events. Adverse events were mild in intensity with 9 of 11 subjects (82%) reporting at least one adverse event. The most common adverse event throughout the study was intravenous catheter site pain and redness (45.5%) where blood sampling occurred. Nausea and vomiting were the most common reported adverse event (9%) during period 1 where DOR was dosed alone. During the second period where DOR was co-administered with weekly RPT and INH, one subject

(9%) reported dysuria following the second week of RPT and INH dosing. The same subject reported chills, headache, and a fever following the third week of dosing RPT and INH. These symptoms subsided and were resolved 2 days after the reported adverse event. All laboratory parameters were within normal limits during the course of the study.

Table 1 Steady-state DOR pharmacokinetic parameters[a] and summary statistics following twice-daily doses of DOR 100 mg alone or twice-daily DOR 100 mg co-administered with once-weekly RPT and INH

Parameter	DOR + RPT	DOR	DOR + RPT/DOR
	GMR (95% CI)		GMR (90% CI)
AUC_{0-12}, hour × µg/mL	12.3 (10.4–14.3)	17.3 (14.9–20.0)	0.71 (0.60–0.85)
C_{12}, µg/mL	0.9 (0.7–1.0)	1.2 (1.0–1.4)	0.69 (0.54–0.89)
C_{avg}, µg/mL[b]	1.0 (0.8–1.2)	1.4 (1.2–1.7)	0.71 (0.60–0.85)
C_{max}, µg/mL	1.3 (1.1–1.5)	1.7 (1.5–2.0)	0.75 (0.63–0.88)
$t_{1/2}$, hour[c]	6.4 (17.0)	15.2 (19.4)	
CL/F, L/hour[c]	8.4 (26.1)	5.9 (24.0)	
Accumulation ratio	1.2–1.6	1.8–3.2	

AUC_{0-12}, area under the concentration-time curve from zero to 12 hours; C_{12}, observed trough concentration prior to the second dose for a twice-daily regimen; C_{avg}, average steady-state plasma drug concentration during multiple dose administration; CI, confidence interval; CL/F, total apparent clearance; C_{max}, peak plasma concentration at steady-state; DOR, doravirine; GMR, geometric mean ratio; INH, isoniazid; RPT, rifapentine; $t_{1/2}$, terminal half-life.
[a]Parameters with exposures are expressed as µg/mL.
[b]The average steady-state plasma concentration during multiple-dose administration was computed as AUC_{0-12}/dosing interval.
[c]Values for $t_{1/2}$ and CL/F are expressed as the geometric mean (percentage of coefficient of variation).

DISCUSSION

In patients infected with HIV and LTBI, the current therapeutic options include daily rifampin or rifabutin for 4 months or INH daily for 9 months. Although both INH and rifamycin-based regimens are similarly effective in the treatment of LTBI in patients with HIV, patients are more likely to complete shorter and convenient regimens. Although RPT and INH affords a shorter duration and dosing frequency for treatment than INH monotherapy, drug interaction studies are infrequent to evaluate this regimen co-administered with HIV ARV therapies.

In this study, twice-daily doses of DOR 100 mg dosed to steady-state was selected based on nonparametric superposition predictions from a single dose drug interaction study with rifabutin.[6] Furthermore, DOR was generally well-tolerated across multiple doses of up to 750 mg with robust antiviral activity at 200 mg once-daily in patients with HIV-1 with a terminal elimination half-life of ~ 15 hours.[9,10] Therefore, a twice-daily dosing regimen for 4 days was selected in the first period for several reasons: (a) given the safety profile of DOR reported previously, a 100 mg twice-daily dose of DOR is expected to not be a safety concern, (b) it is expected that the 100 mg twice-daily doses of DOR should obtain the same level of virological efficacy as seen

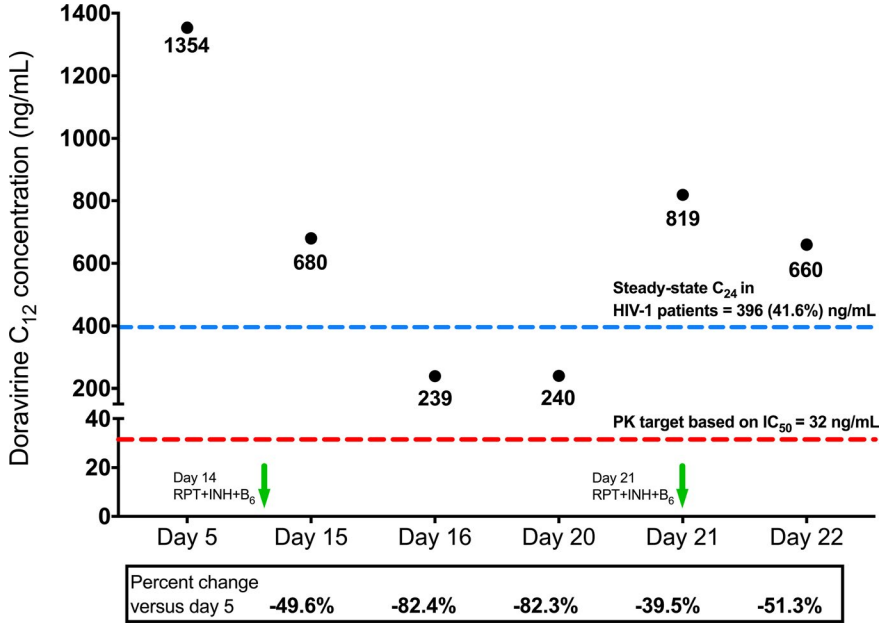

Figure 5 Trend of doravirine (DOR) C_{12} concentrations throughout the study days across the two study periods. The values represent the geometric mean C_{12} concentration reported for that study day. Day 5 was used as a reference to calculate the percent change in C_{12} concentrations for subsequent days. The green down arrows indicate rifapentine, isoniazid, and pyridoxine co-administered with the morning dose of DOR 100 mg. The horizontal red line indicates the steady-state pharmacokinetic target 6-fold above the 50% inhibitory concentration (IC_{50}) associated with 99% viral reduction. The horizontal blue line represents the steady-state C_{24} (% coefficient of variance) values observed in pivotal studies following once-daily doses of DOR 100 mg. B_6 = pyridoxine; C_{12} = observed trough concentration prior to the second dose for a twice-daily regimen; C_{24} = observed trough concentration prior to the second dose for a once-daily regimen; INH = isoniazid; PK = pharmacokinetic; RPT = rifapentine.

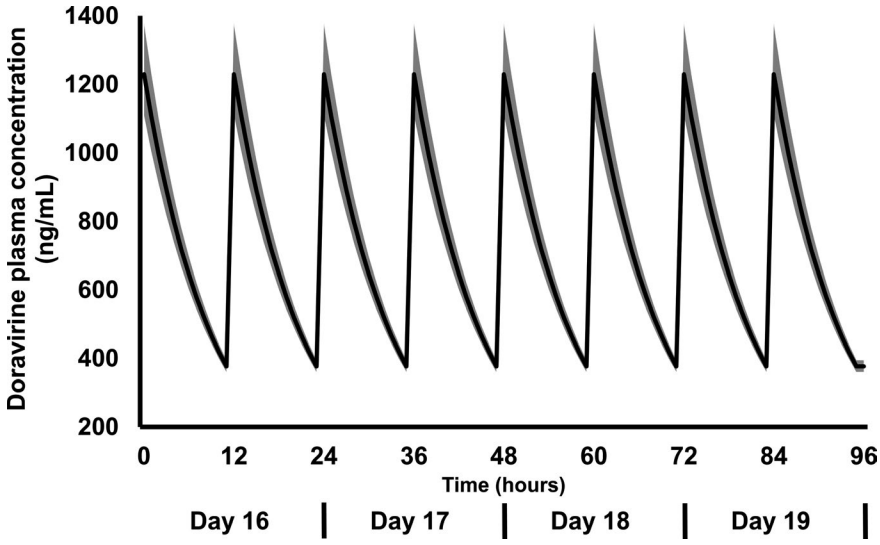

Figure 6 Predicted mean doravirine plasma concentrations at study days 16–19. The gray shaded regions represent the standard error of the mean. Predictions were based on doravirine pharmacokinetic parameters estimated following co-administration of rifapentine on day 21.

with patients dosed 200 mg once-daily, and (c) steady-state exposure is expected within 3 days of dosing allowing steady-state DOR concentrations to be sampled by the fourth study day in the first period.

DOR is contraindicated when co-administered with drugs that are strong CYP3A inducers. The current study evaluated the PKs of steady-state DOR in the presence of RPT and INH. Once-weekly doses of RPT and INH moderately reduced DOR steady-state AUC_{0-12} and C_{12} following twice-daily doses of 100 mg DOR in healthy volunteers. This reduction in exposure is reflected by the increase in DOR steady-state clearance (8.4 L/hour vs. 5.9 L/hour) and a shortened half-life (15.2 hours vs. 6.4 hours) in the presence of RPT and INH. RPT is a potent inducer of CYP450 metabolizing enzyme specifically impacting CYP3A4, CYP2C8, and CYP2C9 isoenzymes.[11] The potency of induction is 45% greater than rifabutin, with rifampin being the most potent of the anti-TB rifamycins.[12] Therefore, this reduction in exposure with subsequent increase in DOR clearance was expected as seen in previous drug interaction studies, where rifampin and rifabutin co-administration significantly reduced DOR trough values following once-daily dosing.[5,6] This study reinforces the time-dependent change in the metabolic induction capacity of once-weekly RPT. As seen in **Figure 5**, mean DOR C_{12} concentrations reached a nadir ~ 2 days following RPT dosing (study day 14).

In phase II studies, DOR doses of 25 mg and 200 mg have comparable virological efficacy in patients with HIV-1 with geometric mean C_{24} values at 107 ng/mL (77–149 ng/mL).[9] Although there is no established therapeutic range that correlates with clinically sustained virological suppression and efficacy, an NNRTI class-specific steady-state concentration 6-fold above the *in vitro* 50% inhibitory concentration (IC_{50}) for wild-type HIV would result in ~ 99% maximal viral reduction.[13] In the case of DOR, the *in vitro* IC_{50} is 5.1 ng/mL, which results in a PK target of 31.5 ng/mL.[14] Although DOR mean steady-state trough values at the second week of RPT dosing were below the observed C_{24} in pivotal trials **(Figure 5)**, concentrations still remained 7.6-fold above the values associated with maximal viral load reduction. Moreover, the nadir trough values seen at the second week of RPT and INH dosing were > 50% of the values following a 25 mg dose in the patient population where the antiviral activity was comparable to the higher dose levels. Based on the strong correlation of DOR trough values in the exposure-response relationship, trough concentrations seen in this study are within the ranges associated with a ≥ 80% proportion of individuals achieving HIV-1 RNA copies of < 50 copies/mL.[15]

It should be noted that a true nadir cannot be defined given the absence of trough collections on study days 17–19. Using the elimination rate and distribution volume of DOR in the presence of RPT observed in this study, trough values were predicted for study days 16–19 (**Figure 6)**. The mean plasma trough concentrations at 12 and 24 hours was predicted to be 376.4 ng/mL suggesting that concentrations of DOR can be sustained above the IC_{50} during a once weekly course of RPT. Although we observed a persistent reduction of up to 82% in DOR C_{12} 6 days following the last dose of RPT, the time-dependent metabolic induction is nonetheless similar to reports in literature that observed up to 2–4 days of maximal induction following RPT administration.[16,17]

There were minimal adverse events observed in this study. Compared with previous reports using this regimen in drug interaction studies with other HIV-1 ARVs,[17] co-administration of DOR with once-weekly RPT and INH at maximum doses was well-tolerated. The most common adverse event reported by 45.5% of subjects was intravenous catheter site pain and redness, which was unrelated to the study drugs. Only one female subject reported flu-like symptoms, which included fever, chills, and headache after the second dose of RPT, INH, and DOR. This was anticipated, as a high incidence of flu-like symptoms have been reported following high dose RPT and INH, particularly in older aged white

women.[18] Furthermore, safety laboratory value trends were within the normal ranges throughout the entirety of the study.

Several limitations should be noted. The study did not analyze the primary metabolite, M9, which is a direct result of CYP-mediated oxidation. In the presence of an inducer, such as RPT and twice-daily dosing of DOR, the exposure of M9 is expected to increase. The impact of the M9 metabolite on safety is unclear, as M9 is present as only 13% of parent dose, does not accumulate with repeated dosing, and does not have activity against HIV reverse transcriptase.[3] The study also enrolled mostly male participants (10 men vs. 1 woman). Although there was a sex imbalance in this study, sex does not impact the PKs of DOR.[15] Last, DOR trough concentrations were not collected for study days 17–19 during period 2 of the study. As such, a true nadir cannot be confirmed with certainty during that period where DOR was co-administered with RPT and INH.

In summary, once-weekly oral RPT and INH moderately reduced the $AUC_{0–12}$ and C_{12} of twice-daily 100 mg DOR by 29% and 31%, respectively. This reduction, however, was within the trough values associated with virological efficacy seen in pivotal clinical studies. As a result, DOR 100 mg administered twice-daily may be considered to mitigate the drug interaction effect of RPT where the modest reduction in DOR exposure is unlikely to be clinically relevant in a virally suppressed patient.

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Conflicts of Interest. All authors declared no competing interests for this work.

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