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

Edwin Lam  
*Thomas Jefferson University*

Joseph Schaefer  
*Thomas Jefferson University*

Richard Zheng  
*Thomas Jefferson University*

Tingting Zhan  
*Thomas Jefferson University*

Follow this and additional works at: [https://jdc.jefferson.edu/petfp](https://jdc.jefferson.edu/petfp)

**Recommended Citation**

Lam, Edwin; Schaefer, Joseph; Zheng, Richard; Zhan, Tingting; and Kraft, Walter K., "Twice-Daily Doravirine Overcomes the Interaction Effect from Once-Weekly Rifapentine and Isoniazid in Healthy Volunteers." (2020). *Department of Pharmacology and Experimental Therapeutics Faculty Papers*. Paper 120.

https://jdc.jefferson.edu/petfp/120
Title: Twice-Daily Doravirine Overcomes the Interaction Effect from Once-Weekly Rifapentine and Isoniazid in Healthy Volunteers

Authors: Edwin Lam¹, Joseph Schaefer², Richard Zheng¹, Tingting Zhan¹, & Walter K. Kraft¹

Affiliations: Department of Pharmacology & Experimental Therapeutics¹ and Sidney Kimmel Medical College², Thomas Jefferson University, Philadelphia, PA, USA

Corresponding Author:
Edwin Lam, PharmD
Department of Pharmacology & Experimental Therapeutics
Thomas Jefferson University
132 South 10th Street, 1170 Main Building
Tel: 215-955-9076
Email: Edwin.lam@jefferson.edu

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

Funding: This work was supported by an Investigator Studies Program grant provided by Merck & Co, Inc. [MISP58495]. Edwin Lam is supported by the National Institutes of Health institutional training grant [T32GM008562].

Keywords: Human immunodeficiency virus; tuberculosis, non-nucleoside reverse transcriptase inhibitor; rifamycin; drug interaction; doravirine
Abstract:

Doravirine (DOR) is a non-nucleoside reverse transcriptase inhibitor indicated for the treatment of human immunodeficiency virus-1 (HIV-1). Its use in combination with rifapentine (RPT), an anti-tuberculosis antibiotic, may reduce the exposure of DOR compromising viral suppression in those living with HIV-1 co-infected with tuberculosis. 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 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 was co-administered with multiple doses of DOR 100 mg twice-daily for study days 7, 14, and 21. Plasma was obtained for DOR pharmacokinetics 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 AUC$_{0-12}$ and C$_{12}$ in the presence of RPT+INH compared to 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 doravirine exposure would unlikely be clinically relevant in a virally suppressed patient co-administered once-weekly RPT+INH.
Doravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used in combination with other antiretrovirals (ARV) for the treatment of HIV-1 infection in adults. It is non-inferior to current standard of care ARV regimens with fewer adverse events.\(^1\,^2\) The elimination of doravirine 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, doravirine has a lower potential for drug-drug interactions compared to other NNRTIs and does not impact the pharmacokinetics of other drugs. Considering the predominant route of elimination is through CYP3A, co-administration with strong inhibitors and inducers may alter the pharmacokinetic profile of doravirine.

The Centers for Disease Control and Prevention (CDC) currently recommends several latent tuberculosis infection (LTBI) treatment options for persons with HIV and includes either once-daily isoniazid for nine months, rifampin or rifabutin once-daily for four months, or once-weekly rifapentine and isoniazid for three months.\(^4\) The rifamycin class of anti-tuberculosis 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 doravirine 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 doravirine are predicted to overcome the interaction\(^6\), the use of rifampin and rifabutin together with once-daily doses of doravirine is contraindicated. A three month rifapentine based regimen has comparable efficacy and safety compared to lengthy once-daily anti-tuberculosis regimens.\(^7\) The magnitude of drug-drug interaction between doravirine when co-administered with rifapentine and isoniazid has not been defined.
The objective of this study was to evaluate the effects of once-weekly rifapentine and isoniazid on the steady-state pharmacokinetics of twice-daily doravirine, and to assess the safety and tolerability of these co-administered drugs.

Methods

The study was approved by the Thomas Jefferson University Institutional Review Board and registered on clinicaltrials.gov (NCT03886701). The study was conducted in accordance to 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 non-pregnant women between 18-60 years old with a body mass index of 19-33 kg/m² weighing between 45-120 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 four weeks after the last dose of drug. Women who were postpartum for less than 12 months were excluded. Other exclusion criteria included any clinically significant disease, current drug or alcohol abuse, known anaphylactic or systemic reactions to doravirine, rifapentine, or isoniazid, and those who have received another study drug within four weeks or five half-lives (whichever occurring 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 doravirine 100 mg twice-daily for four study days during the first period. In the second period, once-weekly weight based rifapentine and isoniazid and pyridoxine 50 mg was co-administered with doravirine 100 mg twice-daily. The doses of rifapentine 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 rifapentine, isoniazid, and pyridoxine were selected based on the Centers for Disease Control and Prevention treatment regimens for LTBI. Subjects received a light meal prior to each doravirine dose for study days 1-4. For the morning of study days 7, 14, and 21, isoniazid and pyridoxine was dosed following an overnight fast with doravirine and rifapentine dosed after the subject received a meal. For days 8-13 and 15-20, subjects received a light meal before each dose of doravirine. All subjects received 8 ounces of water with each dose.

**Pharmacokinetic sampling and bioanalysis**

Plasma samples for doravirine were collected at pre-dose (0 hour), 0.5, 1, 1.5, 2, 3, 6, 12, 24, 36, 48 and 72 hours post dose on study days 4-7 (period one) and study days 21-24 (period two). A pre-dose sample was taken for all subjects prior to starting period 1 and doravirine dosing to ensure no previous doses of doravirine were taken. A doravirine trough concentration was collected on study days 15, 16, and 20 prior to the administration of the second doravirine dose. Approximately 3 mL of blood was collected into K2-EDTA vials and inverted 8-10 times before being centrifuged at 3000 rpm for 10 minutes. Plasma was aliquoted into a cryotube and was stored at -20°C before analysis. Plasma doravirine concentrations were 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 1-1000 ng/mL (developed and validated by Syneos Health Clinique, Quebec, QC, Canada).

**Safety and tolerability**

Safety and tolerability were assessed throughout the study and included monitoring for adverse events, physical exams, 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).

**Pharmacokinetic and statistical analysis**
Plasma doravirine pharmacokinetic parameters were estimated using a non-compartmental analysis and performed on R version 3.6.1 with the PKNCA and ncappc packages. Doravirine pharmacokinetic parameters included the area under the concentration-time curve during the dosing interval (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 (t_{1/2}), apparent clearance at steady-state (CL_{ss}/F), 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 equations (GEE) model with log-link with the primary predictor of period. Geometric means and corresponding 95% confidence intervals were calculated for each treatment group. The 90% confidence intervals were estimated from the GEE model for the geometric mean ratios for (doravirine + rifapentine + isoniazid)/doravirine alone. The statistical analysis was performed on R version 3.6.1 with the geepack package. Sample size was calculated from the reported variability in doravirine trough concentration in HIV-infected men (1540 nmol/L and 95% CI: 1110-2140 nmol/L). Using a significance level of 5% with a two-sided paired t-test, a sample size of 11 provided greater than 80% power to detect a change of 50% in doravirine 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 male and 1 female) 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 rifapentine and
isoniazid (900 mg) for all subjects during the study. The mean (±SD) body mass index was 31.2 (±2.6) kg/m². All subjects were included in the PK and safety analysis.

**Doravirine plasma concentration time profile**

All pharmacokinetic data were included in the analysis and figures. All subjects had undetectable doravirine concentrations in plasma at pre-dose prior to beginning study day 1. Two subjects had undetectable doravirine concentrations in plasma at the 72-hour time point in the second period (study day 24). Mean doravirine plasma concentration profiles alone and in combination with rifapentine and isoniazid for all sampled points was plotted against time (figure 2). The mean doravirine plasma concentration during the dosing interval for doravirine alone or in combination with rifapentine and isoniazid is shown in figure 3. Co-administration with once-weekly rifapentine and isoniazid modestly reduced the steady-state AUC₀-₁₂, C₁₂, Cavg, and Cmax by 29%, 31%, 29%, and 25%, respectively. Figure 4 displays the individual and geometric mean ratios for rifapentine + isoniazid + doravirine/doravirine alone AUC₀-₁₂, C₁₂, Cavg, and Cmax. Rifapentine co-administration reduced doravirine half-life by 58% while increasing the steady-state total plasma clearance by 41% (table 1).

**Safety and Tolerability**

Doravirine in combination with rifapentine and isoniazid was generally well tolerated with no serious adverse events. Adverse events were mild in intensity with 9 out 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 was the most common reported adverse event (9%) during period 1 where doravirine was dosed alone. During the second period where doravirine was co-administered with weekly rifapentine and isoniazid, one subject (9%) reported dysuria following the second week of rifapentine and isoniazid dosing. The same subject reported chills, headache, and a fever following the third week of dosing rifapentine and
isoniazid. These symptoms subsided and were resolved two days after the report adverse event. All laboratory parameters were within normal limits during the course of the study.

Discussion

In patients infected with HIV and LTBI, the current therapeutic options include daily rifampin or rifabutin for 4 months or isoniazid 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. While rifapentine and isoniazid 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 antiretroviral therapies.

In this study, twice-daily doses of doravirine 100 mg dosed to steady-state was selected based on nonparametric superposition predictions from a single dose drug interaction study with rifabutin. Furthermore, doravirine 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 half-life of approximately 15 hours. Therefore, a twice-daily dosing regimen for 4 days was selected in the first period for several reasons: 1) given the safety profile of doravirine reported previously, a 100 mg twice-daily dose of doravirine is expected to not be a safety concern, 2) it is expected that the 100 mg twice-daily doses of doravirine should obtain the same level of virological efficacy as seen with patients dosed 200 mg once-daily, and 3) steady-state exposure is expected within 3 days of dosing allowing steady-state doravirine concentrations to be sampled by the fourth study day in the first period.

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

In phase II studies doravirine 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). While 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 approximately 99% maximal viral reduction. In the case of doravirine, the in vitro $IC_{50}$ is 5.1 ng/mL which results in a pharmacokinetic target of 31.5 ng/mL. Although doravirine mean steady-state trough values at the second week of rifapentine 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 rifapentine and isoniazid 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 doravirine 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.
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 doravirine in the presence of rifapentine 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 doravirine can be sustained above the IC$_{50}$ during a once weekly course of rifapentine. Although we observed a persistent reduction of up to 82% in doravirine C$_{12}$ six days following the last dose of rifapentine, the time-dependent metabolic induction is nonetheless similar to reports in literature which observed up to 2-4 days of maximal induction following rifapentine administration.$^{13, 14}$

There were minimal adverse events observed in this study. Compared to previous reports using this regimen in drug interaction studies with other HIV-1 antiretrovirals,$^{14}$ co-administration of doravirine with once-weekly rifapentine and isoniazid 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 rifapentine, isoniazid, and doravirine. This was anticipated, as a high incidence of flu-like symptoms have been reported following high dose rifapentine and isoniazid, particularly in older aged white women.$^{18}$ Furthermore, safety lab 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 rifapentine and twice-daily dosing of doravirine, 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.$^{19}$ The study also enrolled mostly male participants (10 male vs. 1 female). Although there was a gender imbalance in this study,
gender does not impact the pharmacokinetics of doravirine. Lastly, doravirine trough concentrations were not collected for study days 17-19 during period two of the study. As such a true nadir cannot be confirmed with certainty during that period where doravirine was co-administered with rifapentine and isoniazid.

In summary, once-weekly oral rifapentine and isoniazid moderately reduced the $AUC_{0-12}$ and $C_{12}$ of twice-daily 100 mg doravirine 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, doravirine 100 mg administered twice-daily may be considered to mitigate the drug interaction effect of rifapentine where the modest reduction in doravirine exposure is unlikely to be clinically relevant in a virally suppressed patient.

**Study Highlights**

**What is the current knowledge of the topic?**

Co-infection with latent tuberculosis in persons living with Human Immunodeficiency Virus-1 (HIV-1) is common. Rifapentine is an anti-tuberculosis antibiotic available as once-weekly treatment for latent tuberculosis and is a potent inducer of cytochrome (CYP) 3A metabolic enzyme. There are limited studies that evaluate rifapentine in the presence with antiretrovirals, including doravirine, a novel non-nucleoside reverse transcriptase inhibitor metabolized by CYP3A.

**What question did this study address?**

This study evaluated the pharmacokinetics of twice-daily doravirine when co-administered with once-weekly rifapentine and isoniazid.

**What does this study add to our knowledge?**

Following rifapentine-mediated CYP3A induction, doravirine steady-state trough concentrations declined in a time-dependent manner. Steady-state clearance of doravirine increased with a $>50\%$
reduction in plasma half-life following co-administration with rifapentine and isoniazid. Despite this reduction, doravirine exposure is in a range that is likely to maintain viral suppression.

**How might this change clinical pharmacology or translational science?**

Doravirine 100 mg given twice-daily can mitigate the interactive effects of once-weekly rifapentine. Co-administration was generally well tolerated with a modest decrease in doravirine exposure unlikely to be clinically relevant. This dosing regimen may offer an alternative to virally suppressed patients on antiretroviral therapy co-infected with latent tuberculosis and considering a rifapentine based regimen.

**Acknowledgements**

We thank the volunteers, nurses, and staff of the Clinical Research Unit at Thomas Jefferson University for their contributions to this research.

**Author Contributions**

E.L. designed the wrote the manuscript, research, and analyzed the data; J.S. and T.Z. contributed to analytical tools and analyzed the data; R.Z. and W.K.K. performed the research.
References


Table 1. Steady-state doravirine pharmacokinetic parameters and summary statistics following twice-daily doses of doravirine 100 mg alone or twice-daily doravirine 100 mg co-administered with once-weekly rifapentine and isoniazid.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Doravirine + rifapentine</th>
<th>Doravirine</th>
<th>Doravirine + rifapentine / Doravirine</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-12&lt;/sub&gt; (hr x ug/mL)</td>
<td>12.3 (10.4-14.3)</td>
<td>17.3 (14.9-20.0)</td>
<td>0.71 (0.60-0.85)</td>
</tr>
<tr>
<td>C&lt;sub&gt;12&lt;/sub&gt; (ug/mL)</td>
<td>0.9 (0.7-1.0)</td>
<td>1.2 (1.0-1.4)</td>
<td>0.69 (0.54-0.89)</td>
</tr>
<tr>
<td>C&lt;sub&gt;avg&lt;/sub&gt; (ug/mL)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.0 (0.8-1.2)</td>
<td>1.4 (1.2-1.7)</td>
<td>0.71 (0.60-0.85)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ug/mL)</td>
<td>1.3 (1.1-1.5)</td>
<td>1.7 (1.5-2.0)</td>
<td>0.75 (0.63-0.88)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (hr)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6.4 (17.0)</td>
<td>15.2 (19.4)</td>
<td></td>
</tr>
<tr>
<td>CL/F (L/hr)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.4 (26.1)</td>
<td>5.9 (24.0)</td>
<td></td>
</tr>
<tr>
<td>Accumulation ratio</td>
<td>1.2-1.6</td>
<td>1.8-3.2</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Parameters with exposures are expressed as ug/mL.

<sup>b</sup> The average steady-state plasma concentration during multiple-dose administration was computed as AUC<sub>0-12</sub>/dosing interval.

<sup>c</sup> Values for t<sub>1/2</sub> and CL/F are expressed as the geometric mean (%CV).

Figure 1. Study schematic. B<sub>6</sub> = vitamin B<sub>6</sub> (pyridoxine), BID = Twice-daily, DOR = doravirine, INH = isoniazid, PK = pharmacokinetics, RPT = rifapentine. Arrows indicate blood for PK or safety laboratory.
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 plasma concentration-time profiles during the 12 hour dosing interval following twice-daily doses of doravirine 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 doravirine. The inset represents the concentration-time profile plotted on a log-linear scale.
Figure 4. Individual ratios (Doravirine/doravirine + rifapentine), geometric mean ratios, and corresponding 90% confidence intervals for doravirine exposure parameters. AUC$_{0-12}$ = Area under the concentration time 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.
Figure 5. Trend of doravirine 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 doravirine 100 mg. The horizontal red line indicates the steady-state pharmacokinetic target 6-fold above the 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 doravirine 100 mg. B6 = 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.

<table>
<thead>
<tr>
<th>Day 5</th>
<th>Day 14</th>
<th>Day 15</th>
<th>Day 16</th>
<th>Day 20</th>
<th>Day 21</th>
<th>Day 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>1354</td>
<td>660</td>
<td>819</td>
<td>240</td>
<td>680</td>
<td>239</td>
<td>1354</td>
</tr>
</tbody>
</table>

**Percent change versus day 5**

-49.6%  -82.4%  -82.3%  -39.5%  -51.3%
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.