Cytokine-Mediated Systemic Adverse Drug Reactions in a Drug-Drug Interaction Study of Dolutegravir with Once-Weekly Isoniazid and Rifapentine

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**Key Points:** Dolutegravir co-administered with once-weekly isoniazid-rifapentine resulted in marked cytokine release and serious toxicities including flu-like syndrome and elevated transaminase levels in 2 of 4 participants. The safety of this medication combination needs further evaluation in individuals with HIV and LTBI.
Abstract

**Background.** Once-weekly isoniazid and rifapentine for 3 months is a treatment option in persons with human immunodeficiency virus and latent tuberculosis infection. This study aimed to examine pharmacokinetic drug-drug interactions between this regimen and dolutegravir, a first-line antiretroviral medication.

**Methods.** This was a single-center, open-label, fixed-sequence, drug-drug interaction study in healthy volunteers. Subjects received oral dolutegravir 50 mg once-daily alone (Days 1-4) and concomitantly with once-weekly isoniazid 900 mg, rifapentine 900 mg, and pyridoxine 50 mg (Days 5-19). Dolutegravir concentrations were measured on days 4, 14, and 19, and rifapentine, 25-desacetyl-rifapentine, and isoniazid concentrations were measured on Day 19. Cytokines and anti-drug antibodies to isoniazid and rifapentine were examined at select time points during and after study drug completion.

**Results.** The study was terminated following the development of serious toxicities in two of four subjects after the third isoniazid-rifapentine dose. Flu-like syndrome and elevated transaminase levels occurred. Markedly elevated levels of interferon-γ, CXCL10, CRP and other cytokines were temporally associated with symptoms. Anti-drug antibodies were infrequently detected. Dolutegravir area under the curve (AUC) was decreased by 46% (90% CI [0.27, 1.10], p=0.13) on Day 14, ~48-72 hours following the second isoniazid-rifapentine dose. Rifapentine and 25-desacetyl rifapentine levels were comparable to reference data, whereas isoniazid AUCs were ~67-92% higher in the subjects who developed toxicities.

**Conclusion.** The combined use of dolutegravir with once-weekly isoniazid-rifapentine resulted in unexpected and serious toxicities that were mediated by endogenous cytokine release. Additional investigations are necessary to examine the safety and efficacy of co-administering these medications.

**Key Words:** dolutegravir, rifapentine, isoniazid, human immunodeficiency virus (HIV), latent tuberculosis infection (LTBI)

**Clinical Trials Registration.** NCT02771249
Background

Tuberculosis (TB) is the most common opportunistic infection in individuals with human immunodeficiency virus (HIV) worldwide [1], and treatment of latent TB infection (LTBI) is essential in preventing progression to active disease. Once-weekly isoniazid-rifapentine for three months (3HP) is an attractive LTBI treatment option for persons with HIV as it has similar efficacy to nine months of daily isoniazid, a shorter treatment duration, and higher rates of adherence and treatment completion [2-7]. Despite these benefits, 3HP is not widely used in adults with HIV receiving antiretroviral therapy due to limited data on drug-drug interactions with this regimen.

Rifamycins, including rifapentine, are potent inducers of drug-metabolizing enzymes [8], and can decrease systemic exposure to certain antiretroviral medications. Drug-drug interaction studies currently support the use of 3HP only in patients receiving efavirenz- or raltegravir-based regimens [9, 10]. The International Antiviral Society-USA guidelines [11] also support the use of twice-daily dolutegravir with 3HP based on extrapolation from a drug-drug interaction study with rifampin [12]. The use of dolutegravir with 3HP is of high interest as this agent is one of the first-line treatment options for persons with HIV [11, 13], and recently became available in generic form in several countries with a high prevalence of LTBI. However, whether once-weekly rifapentine will lead to induction of drug-metabolizing enzymes and significant decreases in dolutegravir exposure is unclear.

The current study was undertaken to examine the drug-drug interaction between once-daily dolutegravir and once-weekly isoniazid-rifapentine in HIV-negative healthy volunteers. The study was terminated early due to the development of flu-like syndrome and serum transaminase elevations in two out of four participants. Here, we describe these adverse reactions and the results of cytokine, anti-drug antibody, and pharmacokinetic evaluations throughout the study and acute reaction periods.
Methods

Study Design

This was a single-center, open-label, fixed-sequence, intrasubject drug-drug interaction study conducted in healthy volunteers, with ten subjects targeted for enrollment (ClinicalTrials.gov identifier NCT02771249). This study was approved by the National Institute of Allergy and Infectious Diseases Institutional Review Board and was overseen by an independent safety monitoring committee. All participants provided written informed consent.

The study was comprised of two phases for each subject: (1) dolutegravir (Tivicay®, ViiV Healthcare) 50 mg once-daily alone (days 1-4), and (2) dolutegravir 50 mg once-daily in combination with once-weekly rifapentine (Priftin®, Sanofi-Aventis) (900 mg dose if weight ≥50 kg) and isoniazid (Teva Pharmaceuticals USA, Inc.) (15 mg/kg per dose, maximum dose of 900 mg) with pyridoxine 50 mg (days 5-19) (see Supplementary Figure S1). Serial blood sampling for pharmacokinetic analysis was performed on Days 4, 14, and 19, with a single trough collection on Day 18. Symptom and safety laboratory assessments were performed at all pharmacokinetic visits and 24 hours after each isoniazid-rifapentine dose, and were graded according to the Division of AIDS AE table (November 2014, v2.0).

Study Population

Healthy volunteers between 18 to 65 years of age, weights between 45-120 kg, and body mass index between 18-30 kg/m$^2$ were recruited for the study. Subjects were deemed to be healthy based on physical exam, current and previous medical history, and normal hematologic, renal, and liver function tests. Subjects were required to have no evidence of HIV, active or latent TB, or active hepatitis A, B, or C infection, and were instructed to abstain from alcohol consumption throughout the study period. Female subjects of childbearing potential were required to have negative serum or urine pregnancy tests at screening and throughout the study period, and be willing to use non-hormonal contraceptive methods. Key exclusion criteria included known hypersensitivity to any of the study agents or related analogues,
Cytokine and Anti-Drug Antibody Assessments

After early study termination, stored plasma samples from pharmacokinetic and safety assessments were used to examine multiple cytokines/chemokines. Samples from all subjects were examined on Day 4 (time 0, 8, and 24 hours post-dose), Day 14 (time 0), and Day 19 (time 0, 2, 4, 6, 8, 10, and 24 hours post-dose). Additional plasma samples were collected from Subject 4 during follow-up safety assessments on days 22, 26, 30, 33, and 40. Cytokines/chemokines examined included: granulocyte macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, interleukin (IL)-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-8 (HA), IL-10, IL-12/IL-23p40, IL-12p70, IL-13, IL-15, IL-16, IL-17A, C-X-C motif chemokine ligand 10 (CXCL10), chemokine (C-C motif) ligand (CCL) 2, CCL3, CCL4, CCL11, CCL13, CCL17, CCL22, CCL26, tumor necrosis factor (TNF)-α, TNF-β, and vascular endothelial growth factor (VEGF)-A (V-PLEX® Human Cytokine 30-Plex Kit, Meso Scale Discovery®, Rockville, MD), soluble cluster of differentiation 14 (sCD14) (R&D Systems, Minneapolis, MN), sCD163 (Aviscera Bioscience, Santa Clara, CA), and C-reactive protein (CRP) (Meso Scale Discovery®, Rockville, MD). For IFN-γ specifically, samples were diluted (1:10 and 1:100) to quantify IFN-γ levels above the upper assay limit of 10,000 pg/mL (V-PLEX Human IFN-γ Kit, Meso Scale Discovery®, Rockville, MD). Otherwise, assays were performed according to the manufacturer’s instructions for each kit.

Select time points prior to and after initiating once-weekly isoniazid-rifapentine were also examined for antibodies to rifapentine, 25-desacetyl-rifapentine, and isoniazid by Colorado State University using indirect and competitive enzyme-linked immunosorbent assays (see Supplementary Methods). All plasma samples for each subject were tested in the same plate. Baseline samples were used to calculate 95% and 99% CI for Optical Density (OD) and Delta OD (average OD of sample incubated without drug – average OD of sample incubated with excess free drug). Delta ODs of samples
after isoniazid-rifapentine was initiated were individually compared to their respective baselines. Any values above the 95% CI were considered positive. Results were analyzed in GraphPad Prism 7.

Pharmacokinetic Analyses

Blood pharmacokinetic samples were drawn at time 0 (pre-dose), 2, 3, 4, 5, 6, 8, 10, and 24 hours post-dose on days 4 (dolutegravir alone), 14 (48 hours after the 2nd isoniazid-rifapentine dose), and 19 (simultaneously with the 3rd dose of isoniazid-rifapentine). A single pharmacokinetic sample was also collected on Day 18 before the morning dose of dolutegravir. Blood samples were centrifuged at 3200 rpm for 10 minutes at 4°C, and plasma was then separated and stored at -80°C until further analysis. Subjects were also genotyped for N-acetyltransferase 2 (NAT2) polymorphisms, one of the primary enzymes involved in metabolizing isoniazid (Affymetrix® DMET™ Plus Array, Affymetrix, Inc., Santa Clara, CA).

Dolutegravir plasma concentrations were determined using an ultra-high performance liquid chromatography method with fluorescence detection (see Supplementary Methods). Rifapentine, 25-desacetyl-rifapentine, and isoniazid plasma concentrations were measured only on Day 19, and were analyzed by the Infectious Disease Pharmacokinetics Laboratory, University of Florida, using methods as previously described [14]. Pharmacokinetic parameters were calculated using noncompartmental methods (Phoenix WinNonlin, v7.0) (see Supplementary Methods). Rifapentine, 25-desacetyl-rifapentine, and isoniazid pharmacokinetic results were compared to published data [15-17].

Statistical Analyses

Dolutegravir pharmacokinetic parameters were log-transformed and compared between Study Days 4 and 14, and 4 and 19 to generate geometric mean ratios with 90% confidence intervals (CI). P-values for were calculated using two-tailed paired t-tests with no adjustments for multiples comparisons (GraphPad Prism, v7.03). All results were back-transformed to the original scale.
Results

Study Population

Between June 2016 and December 2016, four subjects (3 males; 3 white, 1 black) between the ages of 21 to 44 years were enrolled prior to study termination (Table 1). Subject 3 voluntarily withdrew prior to drug administration on Day 19 due to time constraints; the other three subjects completed the study. The study was terminated following the development of flu-like syndrome and elevated serum transaminases in Subjects 1 and 4.

Safety Results

Flu-like syndrome developed in Subjects 1 and 4 approximately 8-10 hours after the last doses of dolutegravir, rifapentine, and isoniazid on Day 19. Symptoms in subjects 1 and 4 included nausea (Grade 2 and 1, respectively), vomiting (Grade 1), and fever (Tmax of 38.7°C [Grade 2] and 39.5°C [Grade 3], respectively), which all resolved within 48 hours. Both subjects also experienced headache (Grade 1), tachycardia (Grade 1), and dizziness (Grades 1 and 2, respectively). Subject 4 required a 24-hour hospitalization at the study site following symptom onset for management of orthostatic hypotension requiring intravenous fluids (Grade 3), and also developed a mild rash.

Multiple laboratory abnormalities were seen in both subjects. A slight increase in neutrophils with concomitant lymphopenia (Grade 4) occurred acutely (Figure 1A and 1B). Transient increases in direct bilirubin occurred after each dose of isoniazid-rifapentine, with the largest increases (Grade 3) following the third once-weekly dose (Figure 1C and 1D). Transaminase elevations (Grades 2-4) developed ~24-72 hours after the last doses of study medications (Figure 1E and 1F), and gradually resolved after ~2-3 weeks. All symptoms and lab abnormalities resolved without sequelae in both subjects.

Subject 2 did not report any AEs during the study, and Subject 3 reported headache following the first and second doses of isoniazid-rifapentine (Grade 2 and 1, respectively). Laboratory abnormalities included a single asymptomatic lipase elevation in subject 2 (Grade 2), and transient increases in direct
and total bilirubin following each isoniazid-rifapentine dose in both subjects. A summary of all reported AEs is provided in Supplementary Table S1.

**Cytokine and Anti-drug Antibody Results**

Multiple mediators increased during the flu-like syndrome events in subjects 1 and 4 on Day 19, most notably IFN-γ and CXCL10, the former of which peaked ~24 hours after the final doses of study drugs at ~2,500 and 14,800 pg/mL in subjects 1 and 4, respectively (Figure 2). Consistent with this, plasma levels of both chains of interleukin (IL)-12 (p40 and p70), an important mediator of IFN-γ production, were also increased. Elevations in CRP, TNF-α, IL-2, IL-5, IL-6, IL-8, IL-10, IL-15, IL-17, CCL2, CCL4, and CCL17 were also seen (Figure 2 and Supplementary Figure S3). IFN-γ and CRP levels were slightly increased in these subjects ~48 hours after the second isoniazid-rifapentine dose. No other cytokines/chemokines were elevated in these subjects. Subject 2, who reported no symptoms, had elevated CRP and IL-6 at all time-points tested on Day 19, and a small increase in IFN-γ and IL-12p70 ~8-10 hours after dosing (see Supplementary Figure S2). Plots of all remaining cytokines can be viewed in Supplementary Figure S3. Isolated samples were positive for antibodies to rifapentine (Subject 1: IgM at Day 246 (borderline); Subject 4: IgG at Day 20), 25-desacetyl rifapentine (Subject 3: IgM at Day 14 and IgG at Day 95), and isoniazid (Subject 2: IgG at Day 99) (see Supplementary Figure S4).

**Pharmacokinetic Results**

Dolutegravir area under the concentration-time curve (AUC) decreased following the initiation of once-weekly isoniazid-rifapentine (Figure 3A), by 46% (90% CI [0.27, 1.10]) on Day 14 and 14% (90% CI [0.55, 1.29]) on Day 19, in comparison to dolutegravir alone (Table 2). These decreases were not statistically significant, possibly due to the small number of subjects. Trough concentrations prior to morning doses were maximally decreased by 74% (90% CI [0.07, 0.99]) on Day 15 (Supplementary Figure S5). Individual pharmacokinetic profiles are presented in Supplementary Figure S5.
Isoniazid AUCs in subjects 1 and 4 were ~67 and 92% higher, respectively, than published reference data (Figure 3B and Supplementary Table S2) [17]. NAT2 genotyping revealed that subjects 1 and 4 were slow acetylators, and subject 2 was an intermediate acetylator (Table 1). Exposure to rifapentine and its active metabolite were similar to reference PK data across all subjects on Day 19 (Figures 3C, 3D and Supplementary Table S2).
Discussion

Our study found a higher than expected frequency of flu-like symptoms in healthy volunteers after receiving three once-weekly doses of isoniazid-rifapentine concomitantly with once-daily dolutegravir, and demonstrated a temporal relationship between symptoms and plasma levels of cytokines, most prominently IFN-γ. While the number of participants studied is small, these preliminary findings suggest co-administration of dolutegravir and 3HP should be done cautiously, ideally in a clinical research setting, to further evaluate this combination.

Flu-like syndrome has typically been associated with the intermittent use of rifampin [18], although case reports also describe its occurrence with isoniazid [19, 20]. Flu-like syndrome and hepatotoxicity were previously reported in 3.8% and 0.4%, respectively, of nearly 4,000 subjects in large-scale efficacy studies of 3HP, and severe AEs were reported in 0.3% of subjects [21]. The infrequent occurrence of these AEs in large-scale clinical trials raises a concern that dolutegravir is contributing to these toxicities in some unknown manner. With 3HP alone, flu-like syndrome developed after a median of three doses, with symptom onset around four hours post-dose and resolution ~24 hours later [21], similar to what was observed in our subjects. Demographic risk factors for developing flu-like syndrome included white/non-Hispanic race/ethnicity, female sex, age over 35 years, and low BMI [21]. Re-challenge with either or both agents in these subjects found that rifapentine was better tolerated than isoniazid [21].

The cytokine data from our participants strongly support a role for acute release of endogenous IFN-γ alone or in combination with other cytokines in the development of these AEs. Increases in IFN-γ were detected after the second isoniazid-rifapentine dose, with marked elevations on Day 19 beginning ~4-6 hours post-dose, and peak levels ~24 hours after the third isoniazid-rifapentine dose. The timing of these elevations aligned with clinical symptoms as well as the neutrophilia and lymphocytopenia during the acute reaction period, and preceded the transaminase elevations. Flu-like symptoms are nearly universally seen in patients treated with IFN-γ, and transaminase elevations are also common [22]. Elevations in IFN-γ (and CXCL10) have been reported with a number of conditions, including idiosyncratic drug-induced liver injury (DILI) [23], bacterial sepsis [24], and cytokine storm/response syndrome to immunotherapy [25], with IFN-γ levels up to 5000 pg/mL measured in the latter two conditions, though lower than what was measured in this study. The extremely high IFN-γ and CXCL10 levels observed in
this study suggest a primary role for T cells, especially CD4+ helper (T\(_h\),1) and CD8+ cytotoxic or natural killer cells, in mediating these AEs. IFN-γ is predominantly secreted by these cells, and CXCL10 is secreted by a variety of cells in response to IFN-γ. Rifampin- and isoniazid-specific T-cells have previously been identified in patients whom developed drug reactions with eosinophilia and systemic symptoms syndrome [26]. Another recent study demonstrated isoniazid-specific cytokine release of IFN-γ, IL-10, IL-12, and IL-17A following isoniazid incubation with primary hepatocytes and dendritic cells [27]. Further investigations are needed to identify specific cell types and drugs involved with eliciting these immune responses.

Idiosyncratic drug reactions have previously been reported with rifamycins and isoniazid. Several theories regarding the mechanisms of these reactions exist, including hapten formation with the parent drug or reactive metabolites, anti-drug antibody development [18, 28], inhibition of bile salt excretion [29], and other patient-specific factors. One or more of these mechanisms may have factored into the toxicities observed in this study. Hypersensitivity reactions to dolutegravir alone have also been reported in <1% of patients [30]. Anti-rifapentine antibodies were detected in subjects 1 and 4 on single occasions, but are unlikely causative given the inconsistent pattern in antibody development. Furthermore, antibodies to isoniazid and 25-desacetyl rifapentine were detected in subjects 2 and 3, respectively, who did not develop reactions. However, sensitivity and selectivity issues in the current experimental assay may not have detected antibodies at other time points.

Previous drug-drug interaction studies between rifamycins and antiretroviral agents, particularly ritonavir-boosted protease inhibitors, have been associated with unexpected, high-grade toxicities including elevated transaminases and hypersensitivity reactions [31-33]. These were partially attributed to either the use of higher than FDA-approved doses of the antiretroviral agents [33], or increased levels of rifamycins and their metabolites [31, 32] due to cytochrome P450 3A4 (CYP3A4) inhibition by ritonavir. These studies were also conducted in healthy volunteers, and when the same combinations were studied in HIV/TB-coinfected patients, the safety findings were not replicated [34, 35]. Thus, unidentified mechanisms for differences in immune response or tolerability of these agents may also exist between these populations. Our study was performed in healthy volunteers, but exposure to rifapentine and its
active metabolite were within previously reported ranges, and FDA-approved doses of all study medications were given. However, isoniazid AUCs were markedly higher in subjects 1 and 4, the mechanism behind which is unclear. Rifapentine does not alter the pharmacokinetics of isoniazid [17]. Subjects 1 and 4 were both slow acetylators, which may partially explain the higher isoniazid AUCs. However, 20-80% of the population share this phenotype depending on their ethnicity, and flu-like syndrome reactions are infrequently reported. Isoniazid is metabolized into several reactive metabolites that are capable of forming protein adducts with hepatocytes and activating macrophages [36]. The contribution of isoniazid metabolites to the AEs in this study is unclear as their levels were not examined.

The limited PK data obtained from this study suggests that induction of UDP glucuronosyltransferase family 1 member A1 and CYP3A4, the enzymes involved in dolutegravir metabolism, will occur with once-weekly administration of rifapentine, resulting in decreased dolutegravir exposure. The extent of induction appears time-dependent, with maximal induction ~48-72 hours after rifapentine administration as evidenced by a 46% decrease in dolutegravir AUC, and 74% decrease in trough concentrations at this time point. Despite the decreased AUC that was observed, the geometric mean trough concentration for dolutegravir at this time point was still 5.3x the protein-adjusted *in vitro* concentration for 90% inhibition of 0.064 μg/mL reported for dolutegravir. However, one subject did have multiple trough concentrations below 0.3 ug/mL, a threshold below which higher rates of treatment failure with dolutegravir are observed [37]. Whether transient decreases in exposure may compromise the virologic efficacy of dolutegravir is unknown. Dolutegravir AUC on Day 19 was nearly restored to levels when administered alone, which may be due the waning of enzymatic induction, and mixed enzyme inhibition by rifapentine and isoniazid with simultaneous coadministration [38].

Though not the original intent, this study provides important insights into potential mechanisms resulting in the AEs seen in subjects receiving once-weekly isoniazid-rifapentine with dolutegravir. Further studies are needed to carefully evaluate the safety and efficacy of dolutegravir-based regimens when co-administered with isoniazid-rifapentine, especially given the recent availability of generic dolutegravir in countries with high TB burden, and the desire to use this once-weekly regimen in patients living with HIV.
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Disclaimer

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Conflicts of Interest

The authors have no other relevant conflicts of interest or financial support to disclose.
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Table 1. Demographic Information and NAT2 Status of Enrolled Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>BMI (kg/m²)</th>
<th>Race/Ethnicity</th>
<th>NAT2 Genotype</th>
<th>Predicted NAT2 Phenotype</th>
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<td>Male</td>
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<td>80.1</td>
<td>28.2</td>
<td>White/Hispanic</td>
<td>*6A/*6A</td>
<td>Slow</td>
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* Subject 3 withdrew prior to Day 19 drug administration and assessment
Table 2. Individual and Summary Dolutegravir PK Parameters with GMR Comparisons

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<tr>
<th>Subject</th>
<th>AUC_{24,SS} (μg*h/mL)</th>
<th>C_{0hr} (μg/mL)</th>
<th>C_{max} (μg/mL)</th>
<th>CL_{SS}/F (L/h)</th>
<th>V_{ss}/F (L)</th>
<th>t_{1/2} (h)</th>
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<td>0.91</td>
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<td>1.69</td>
<td>17.5</td>
<td>7.3</td>
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<td>3.9</td>
<td>1.08</td>
<td>16.3</td>
<td>10.4</td>
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<tr>
<td>Day 14 vs. 4</td>
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<tr>
<td>GMR [90% CI]</td>
<td>0.54</td>
<td>0.57</td>
<td>0.66</td>
<td>1.85</td>
<td>1.06</td>
<td>0.58*</td>
</tr>
<tr>
<td>[0.27, 1.10]</td>
<td>[0.15, 2.22]</td>
<td>[0.31, 1.43]</td>
<td>[0.91, 3.77]</td>
<td>[0.49, 2.31]</td>
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<td>Day 19 vs. 4</td>
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<tr>
<td>GMR [90% CI]</td>
<td>0.85</td>
<td>0.48</td>
<td>0.88</td>
<td>1.18</td>
<td>0.97</td>
<td>0.82</td>
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<tr>
<td>[0.62, 1.52]</td>
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<tr>
<td>0.55, 1.29</td>
<td>0.09, 1.73</td>
<td>0.65, 1.20</td>
<td>0.77, 1.80</td>
<td>0.65, 1.03</td>
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</table>

Key: \( \text{AUC}_{24,SS} \) = area under the plasma concentration-time curve at steady-state from time 0–24 hours; \( C_{0hr} \) = concentration at time 0; CI = confidence interval; CL\( \text{ss/F} \) = apparent oral clearance at steady state; \( C_{\text{max}} \) = maximum (peak) concentration; GMR = geometric mean ratio; \( t_{1/2} \) = elimination half-life; V\( \text{ss/F} \) = apparent volume of distribution at steady-state.

*p<0.05
Figure Legends

Figure 1. Trends in Select Safety Laboratory Parameters in Subjects 1 and 4 during the Study Period. Arrows along the x-axis indicate when isoniazid-rifapentine was administered. Dashed lines indicate the reference range for each laboratory parameter. Transient increases in neutrophils (A) and lymphopenia (B) were observed in both subjects following the development of flu-like syndrome, reaching peak and nadir levels, respectively, ~24 hours post-dose. Transient increases in direct (C) and total (D) bilirubin were observed after the 1st and 2nd doses of isoniazid-rifapentine. Transaminase (ALT, AST) elevations occurred ~72 hours and 24 hours after the final doses of dolutegravir, rifapentine, and isoniazid were administered in subjects 1 and 4, respectively, and resolved after 2-3 weeks (E and F).

Figure 2. Trends in Select Cytokines and Chemokines in Subjects 1 and 4. Arrows indicate when isoniazid-rifapentine was administered. Reference (dashed) lines for each cytokine/chemokine reflect the upper range of values reported in healthy controls per the assay manufacturer’s product information. Values below the lower limit of detection in each subject were graphed as half the lower limit, and values above the upper range of each cytokine/chemokine were graphed as the maximum assay cut-off. Evaluations of inflammatory markers demonstrated significant increases in all markers displayed during the flu-like syndrome events after the 3rd weekly dose of rifapentine and isoniazid. Transient increases in IFN-Υ and CRP were also after the 2nd doses of rifapentine and isoniazid. For IFN-Υ and CXCL10, the Y-axis is displayed on a log10 scale to facilitate visualization. Stored samples were only available through 24 hours after the third dose of isoniazid-rifapentine in Subject 1.

Figure 3. Plasma concentration-versus-time profiles for (A) dolutegravir, (B) isoniazid, (C) rifapentine, and (D) 25-desacetyl-rifapentine. Profiles for dolutegravir reflect mean (standard deviation) values measured in all subjects at each time point for dolutegravir alone (Day 4), dolutegravir two days after the second dose of isoniazid-rifapentine (Day 14), and dolutegravir simultaneously with the third
dose of isoniazid-rifapentine (Day 19). Plots for isoniazid, rifapentine, and 25-desacetyl-rifapentine reflect measurements from subjects 1, 2, and 4, with a reference line obtained from published pharmacokinetic data utilizing the same doses administered in this study.