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Highlights

- Co-administration of rifampicin significantly reduced the trough concentration of dolutegravir when dosed at 100 mg once-daily.
- However, dolutegravir concentrations from all the participants were above the concentration required to inhibit 90% of in vitro viral replication.
- Further clinical studies involving people living with HIV are warranted.
Pharmacokinetics of dolutegravir 100 mg once-daily with rifampicin

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Abstract

Background: Tuberculosis (TB) causes 25% of all deaths among HIV-infected individuals. Rifampicin (RIF) is a potent inducer of drug metabolising enzymes and drug transporters and co-administration with dolutegravir (DTG) reduces DTG exposure, which can be overcome by doubling the DTG dose to 50 mg twice-daily. We investigated the effect of RIF on the DTG exposure when dosed at 100 mg once-daily, which could provide an easier option than 50 mg twice-daily.

Methods: We conducted an open label, pharmacokinetic (PK) study. Healthy HIV-negative subjects received DTG 50 mg for seven days (PK1), DTG 100 mg for seven days (PK2), RIF only for 14 days, DTG 50 mg plus RIF for seven days (PK3), and DTG 100 mg plus RIF for seven days (PK4). Steady state full DTG PK profiles were evaluated.

Results: DTG geometric mean ratios (GMR) (90% confidence intervals, CI) of PK3/PK1 of 50 mg $C_{max}$, $AUC_{24h}$, and $C_{24h}$ were 0.65 (0.55-0.75), 0.44 (0.37-0.52), 0.15 (0.13-0.17). GMR (90% CI) of PK4/PK1 $C_{max}$, $AUC_{24h}$, and $C_{24h}$ were 1.09 (0.97-1.21), 0.74 (0.64-0.86), 0.24 (0.20-0.28). $C_{24h}$ median (range) of DTG 50 mg plus RIF and DTG 100 mg plus RIF were 251(129–706) ng/mL and 140 (73-426) ng/mL, respectively.

Conclusion: Although there were substantial reductions in DTG $C_{24h}$ when co-administered with RIF, concentrations of both DTG 50 mg and 100 mg once-daily with RIF were still above the protein binding-adjusted $IC_{90}$ of 64 ng/mL. Further studies in HIV-TB co-infected individuals are warranted to confirm these results.

Clinical trial registration number (NCT03199690)

Key words: HIV, dolutegravir, rifampicin, TB, drug-drug interaction
1. Introduction

Coinfection with tuberculosis (TB) and human immunodeficiency virus (HIV) places a tremendous burden on healthcare systems, especially in resource-limited countries. The World Health Organisation (WHO) estimated in 2017 that worldwide there are 10 million people infected with TB and with 9% of them are co-infected with HIV. People living with HIV (PLWH) are at 16-27 times higher risk of developing TB than those without HIV infection [1]. The two diseases potentiate one another, increasing the risk of death, treatment failure and relapse[2–4]. Antiretroviral therapy (ART) is recommended to be initiated soon after the initiation of TB treatment in co-infected individuals [5].

Dolutegravir (DTG) is an integrase strand transfer inhibitor (InSTI) approved for the treatment of HIV-infected naïve and experienced individuals [6–8]. DTG is dosed at 50 mg once-daily for ART-naïve and InSTI-naïve patients and at 50 mg twice-daily for patients who harbour InSTI-resistant viruses [9–11]. DTG is a substrate of drug efflux pumps, such as breast cancer resistance protein (BCRP) encoded by ABCG2, and P-glycoprotein (P-gp) encoded by ABCB1. Once absorbed, DTG is primarily metabolised by uridine 5’-diphospho-glucuronosyltransferase of the 1A1 family (UGT1A1), with cytochrome P450 3A4 (CYP3A4) as a minor route [9,10].

First-line anti-TB regimen consists of rifampicin (RIF), isoniazid, pyrazinamide, and ethambutol. RIF activates pregnane X receptor (PXr), consequently inducing the expression of CYP3A4, UGT1A1, ABCG2 and ABCB1 [14,15]. Therefore, RIF has potential to lower the concentration of DTG. A phase I, open-label, cross-over study in healthy volunteers was conducted to evaluate doubling the dose of DTG to 50 mg twice-daily with RIF, which resulted in a modest increase in plasma DTG AUC (33%), C_{max} (18%) and C_{24h} (22%) compared with DTG 50 mg once-daily alone, suggesting that DTG 50 mg twice-daily with RIF could be used in patients who require concomitant treatment for HIV and TB [16]. Interim 24 week analysis from the phase 2 INSPIRING study showed that DTG 50 mg
administered twice-daily in combination with RIF-based anti-TB treatment was effective and well-tolerated in HIV/TB co-infected individuals [17].

However, there is no published data on the exposure of DTG 50 mg once-daily or of increased doses once-daily with RIF. It is likely that trough concentrations will be significantly lowered by RIF induction, but the inhibitory quotient may still be adequate given that the inhibitory quotient (C_{24h}/IC_{90}) of DTG 50 mg once-daily is 19 [18]. If once-daily doses of DTG achieve adequate concentrations with RIF, this could lead to better virologic outcomes than 50 mg twice-daily as it is well-established that once-daily HIV/TB treatments are beneficial as they improve adherence [19–21]. In this study, we investigated the exposure of DTG 50 mg and 100 mg once-daily with RIF versus DTG 50 mg and 100 mg alone.
2. Methods

2.1 Study population and design

This open label, sequential PK study was conducted in the St Stephen’s Centre in London, UK. Regulatory and ethical approvals (London Riverside Research Ethics Committee) were obtained before initiating the study. Written informed consent was obtained from participants prior to being enrolled in the study. Recruits were healthy HIV-negative male and non-pregnant and non-lactating female participants aged between 18 and 60 years with a BMI between 18 and 35 kg/m². Eligibility was determined by medical history, physical examination, 12-lead electrocardiogram, and clinical laboratory evaluation. We excluded subjects with any clinical significant acute or chronic medical illness including HIV, hepatitis B and C, evidence of organ dysfunction or abnormal physical examination, vital signs, ECG or clinical laboratory determinations, current or recent (within 3 months) gastrointestinal disease, clinically relevant alcohol or drug use that might adversely affect compliance with trial procedures, use of any other drugs including over-the-counter medications and herbal preparations within 2 weeks of the first dose of study drug, history with allergy to any medications used during the trials, and exposure to any investigational drug within 3 months of the first dose of the study drug.

The study duration was 43 days, excluding screening and follow-up. The participants received DTG 50 mg once-daily from day 1 to day 7, DTG 100 mg once-daily from day 8 to day 14, RIF 600 mg once-daily from day 15 to day 28, RIF 600 mg once-daily plus DTG 50 mg once-daily from day 29 to day 35, and RIF 600 mg once-daily plus DTG 100 mg once-daily from day 36 to day 42. Intensive PK visits were scheduled on days 7 (PK1), 14 (PK2), 35 (PK3) and 42 (PK4). Blood samples were collected pre-dose, and at 2, 4, 8, 12 and 24 hours post-dose. On the intensive PK days, DTG dosing was witnessed following a standard breakfast. RIF was taken on an empty stomach. When RIF and DTG were taken in combination, subjects took RIF on an empty stomach had breakfast 30 minutes later and
then took their DTG dose. These were also the instructions that subjects received when dosed at home in the morning at the same time every day.

2.2 Collection and quantification of plasma dolutegravir

At each scheduled PK blood draw, approximately 6 mL of whole blood were collected into one 6 mL spray coated EDTA tube from an indwelling venous catheter or by direct venepuncture. Plasma was obtained after blood samples being centrifuged for 10 minutes at 2000 g at 4 °C and aliquoted into two Sarstedt storage tubes. Plasma samples were stored at -80 °C until being shipped on dry ice to the Jefferiss Trust Laboratory, Imperial College London. DTG plasma concentrations were measured by a validated reverse-phase ultra-high performance liquid chromatography (UPLC) method modified from a previously published method [22]. DTG was measured at a wavelength of 258 nm and the assay was validated over a calibration range of 50 – 10,000 ng/mL. The laboratory adhered to the International Inter-laboratory Quality Control Program for Measurement of Antiretroviral Drugs in Plasma [23].

2.3 Pharmacokinetic and statistical analysis

Given the experience from similar studies conducted previously with DTG [16], a within-subject variability (expressed as a coefficient of variation, CV) of 33% and an expected withdrawal rate of 30%, a sample size of 12 subjects completing the study was considered sufficient to allow relevant conclusions to be drawn. Up to 16 subjects were therefore enrolled in the trial, 14 completed the study. All PK parameters were calculated using noncompartmental modelling techniques (WinNonlin Phoenix, version 7.0; Pharsight, Mountain View, CA, USA) based on plasma DTG concentration-time data, including C24h, Cmax and the AUC24h. Descriptive statistics, including geometric mean (GM) and 95% confidence intervals (CI), were calculated for all parameters. Within-subject changes of drug concentrations (PK2 vs PK1, PK4 vs PK3, PK3 vs PK1, PK4 vs PK2, PK3 vs PK1) were evaluated by calculating GM ratios (GMR) and 90% CI. Individual inter-variability in DTG PK
parameters was expressed as a percentage CV \([\text{standard deviation/mean}} \times 100]\). Bioavailability (F) was calculated as \((\text{AUC of dose 1/AUC of dose 2}) \times (\text{dose 2/dose 1})\).
3. Results

3.1 Study populations

A total of 16 subjects were screened and enrolled in the study, 14 completed all PK sampling days. One withdrew consent for personal reasons and one stopped the study at day 22 while taking RIF alone due to the development of an allergic reaction. The median (range) age was 32 (22-55) years and BMI 27 (18-32) kg/m². Nine (64%) were male, 11 (79%) were of white ethnicity, two black Caribbean and one subject was of ethnic Asian origin.

3.2 Dolutegravir pharmacokinetics

The GM (95% CI) plasma concentration-time profiles of DTG alone (50 mg or 100 mg) and with RIF 600 mg are shown in Fig. 1. Steady state DTG PK parameters are summarised in Table 1 and GMRs are summarised in Table 2.

The changes in PK parameters when DTG was administered at the doubled dose of 100 mg once-daily compared to the standard dose of 50 mg (PK2/PK1) were assessed. We found that DTG $C_{\text{max}}$, $\text{AUC}_{24\text{h}}$ and $C_{24\text{h}}$ were increased by 70%, 77% and 90% respectively. We subsequently assessed the relative bioavailability of DTG 100 mg compared to DTG 50 mg when administered without RIF (PK2/PK1), and observed that $\text{AUC}_{0-24}$ was 89% and $C_{\text{max}}$ 85%, confirming a less than dose proportional increase in DTG exposure.

3.3 Effect of rifampicin on dolutegravir pharmacokinetics

We investigated the effect on RIF on DTG, when DTG dose was doubled from 50 mg to 100 mg (PK4/PK3) and we observed that $C_{\text{max}}$, $\text{AUC}_{24\text{h}}$ and $C_{24\text{h}}$ increased by 68%, 70% and 60%, respectively. Following RIF addition, the relative bioavailability of DTG 100 mg compared to DTG 50 mg did not change compared to the aforementioned values observed in absence of RIF, been the calculated $\text{AUC}_{0-24}$ 85% and $C_{\text{max}}$ 84%.
As expected, DTG concentrations were reduced when co-administrated with RIF (PK3/PK1; PK4/PK2). DTG median (range) of $C_{24h}$ concentrations with RIF for 50 mg and 100 mg daily doses were 140 (73-426) ng/mL and 277 (129-706) ng/mL, which were all above the protein binding-adjusted IC$_{90}$ of 64 ng/mL. RIF induced similar reductions in DTG PK parameters regardless of the dose of DTG. GMRs of PK3/PK1 and PK4/PK2 are similar for $C_{\text{max}}$, $\text{AUC}_{24h}$ and $C_{24h}$. When comparing PK parameters of the proposed double dose of DTG 100 mg in co-administration with RIF to the standard DTG 50 mg dose administered alone (PK4/PK1), GMR (90%CI) $C_{\text{max}}$, $\text{AUC}_{24h}$, and $C_{24h}$ were 1.09 (0.97-1.21), 0.74 (0.64-0.86), and 0.24 (0.20-0.28) respectively.

3.4 Safety and tolerability

Overall DTG with RIF was well tolerated with no grade 3 or grade 4 or serious adverse events reported. One subject discontinued due to a Grade 2 urticarial rash, characteristic for allergic reaction probably related to RIF and another withdrew the consent due to personal reasons.
4. Discussion

RIF, together with isoniazid, is the core of the anti-TB first line regimen. However, RIF is a potent inducer of metabolising enzymes and transporters, causing complex PK interactions with co-administered drugs including antiretrovirals, which in turn might undermine drug efficacy and increase risk of virological failure and drug resistance. In this study, we investigated the PK of DTG 50 mg or 100 mg once-daily in the presence or absence of RIF 600 mg in HIV-negative healthy volunteers. The key objective of this phase I study was to compare the PK of DTG given at 100 mg once-daily in presence of RIF to the standard dose of DTG given at 50 mg once-daily alone, as 100 mg DTG once-daily with RIF to treat HIV patients co-infected with TB is more desirable than 50 mg DTG twice-daily with RIF in resource limited settings.

Three PK parameters (C$_{\text{max}}$, AUC$_{24\text{h}}$ and C$_{24\text{h}}$) were used to evaluate the effect of RIF on DTG at steady-state. Dose-proportional increases in plasma exposure (AUC$_{24\text{h}}$) were linear when increased from 25 mg DTG to 50 mg DTG in a previous trial [24]. However, in our study DTG AUC$_{24\text{h}}$ was increased in a less than dose proportional manner (by 77%) when we doubled the dose of DTG (without RIF co-administration) from 50 mg to 100 mg, which indicates drug absorption reached saturation limit in the range of 50 – 100 mg DTG. DTG AUC$_{24\text{h}}$ was increased to a similar extent (70%) when doubled the dosage of DTG in presence of RIF, which suggests RIF has no additional effect on the saturation limit of DTG absorption.

An E$_{\text{max}}$ model developed in a phase 2 DTG monotherapy study demonstrated DTG efficacy was optimal when C$_{24\text{h}}$ is above 300 ng/mL [25]. In our study, RIF significantly reduced DTG 100 mg once-daily C$_{24\text{h}}$ by 76% and 50 mg once-daily by 85% when compared with 50 mg DTG once-daily alone. This reduction of C$_{24\text{h}}$ suggests RIF has a great influence on hepatic clearance of DTG, likely by inducing the activity of UGT1A1 and CYP3A4. In particular, out of 14 subjects who are given 100 mg DTG with RIF, only five subjects achieved C$_{24\text{h}}$ above
300 ng/mL. It is however crucial to highlight that DTG $C_{24h}$ measured in all study subjects during RIF intake remained 2-14 fold above the in vitro, protein-adjusted IC_{90} of 64 ng/mL, which is the drug concentration required to inhibit 90% of in vitro viral replication [25]. The in-vivo-generated effective concentrations might be more relevant to clinical practice than in-vitro IC concentrations. However, it should be noted that the effective concentrations are derived from monotherapy studies, and no exposure-response relationship was shown in the subsequent phase 2 study when DTG was combined with dual nucleoside reverse transcriptase inhibitors [18]. Therefore the effective concentrations may differ with a combination therapy [26].

Interestingly, DTG $C_{\text{max}}$ GMR of PK3/PK1 and PK4/PK2 was decreased by only 35% and 36%, respectively, a lower reduction compared to $AUC_{0-24}$ and $C_{24h}$, suggesting that RIF has a limited role in reducing DTG absorption by induction of P-gp and BCRP, and it is mainly involved in the induction of DTG clearance. The effect of RIF on DTG PK parameters was compared with another phase 1 study by Dooley et al looking at 50 mg DTG twice-daily in presence and absence of RIF [16]. There was a smaller decrease in $C_{\text{max}}$ and $AUC_{24h}$ in presence of RIF in our study. The discrepancies may originate from whether DTG was administered in the fasted state or with meal. Food has been shown to increase DTG plasma exposure and reduce the rate of absorption as food contributes to the solubilisation of DTG. When administered with low-, moderate, or high-fat meals, compared with fasting, the AUC from 0 h to infinity ($AUC_{0-\infty}$) increased by 33%, 41% and 66% respectively, and $C_{\text{max}}$ increased by 46%, 53% and 67% respectively. Moreover, DTG is rapidly absorbed, with an observed $T_{\text{max}}$ of two hours in the fasted state, prolonged to three, four and five hours with low-, moderate- and high-fat meals respectively [27]. In our study, patients were instructed to dose DTG after a standardised meal in order to maximise DTG exposure with 20 gram of fat content. However, DTG GM $C_{24h}$ when DTG was administered 50 mg BD with RIF was 670 ng/mL (CV 55%) [16], which is remarkably higher than $C_{24h}$ of 156 ng/mL (CV 60%) and 251 ng/mL (CV 56%), when dosed OD at 50 mg and 100 mg with RIF, respectively. Importantly,
our study was conducted in healthy volunteers who received witnessed dose of DTG with food. In real world settings where drugs may be taken on a fasted state and not always at the same time, inter-individual variability may be wider with a higher number of subjects showing concentrations lower than in vivo established cut-off.

Ideally drug-drug interactions with RIF should be done at maximum induction. Maximum induction of CYP3A4 occurs at about two weeks [28], and RIF auto-induction is 90% maximal at two weeks [29]. In our study, therefore subjects were exposed to two weeks of RIF alone before starting the co-administration of DTG and were subsequently assessed for DTG PK parameters after three (PK3) and four (PK4) weeks of RIF intake. GMRs of PK3/PK1 and PK4/PK2 were similar for $C_{\text{max}}$, $\text{AUC}_{24\text{h}}$ and $C_{24\text{h}}$ (0.65 versus 0.64, 0.15 versus 0.12, 0.44 versus 0.42, respectively), suggesting RIF induction had already reached steady state (i.e. maximum) at three weeks.

5. Conclusion

- DTG $C_{24\text{h}}$ was reduced by 76% when dosed at 100 mg with RIF when compared with 50 mg DTG once-daily alone. ‘DTG $C_{24\text{h}}$ was reduced by 76% when dosed at 100 mg with RIF when compared with 50 mg DTG once-daily alone. This study enrolled a relatively small sample of healthy volunteers in a highly-monitored environment. In real-world settings, it is not always possible to guarantee patients’ optimal adherence to medications and their intake with food, with possible consequent reduction in DTG exposure. Nonetheless, considering that concentrations of DTG 100 mg once-daily with RIF were all above the protein binding-adjusted $IC_{90}$ of 64 ng/mL, the results of this study open to the possibility of testing this regimen in further trials enrolling in PLWH undergoing RIF-containing TB treatment. However, in presence of subjects displaying integrase resistances, doses of DTG 100mg administered once daily may results in insufficient DTG exposure. In conclusion, given the potential benefits of improved adherence to once-daily drug combinations, DTG 100 mg once-daily with RIF may present an option for patients who require co-management of HIV
and TB. Further studies in PLWH with TB are warranted before introducing this strategy into clinical practice.
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Author contribution

MB was awarded the grant. MC, FF and NC recruited and looked after study subjects. MB and GM designed the study. XW and MC analysed the data and wrote the manuscript. XW and MM carried out all the analysis and provided analytical tools. All authors have approved the final article.

Declarations

Funding: The study is made possible thanks to the funding and support from Unitaid. Unitaid accelerates access to innovation so that critical health products can reach the people who most need them.

Competing Interests: Marta Boffito has received travel and research grants from and has been advisor for Janssen, Roche, ViiV, Bristol-Myers Squibb, Merck Sharp & Dohme, Gilead, Mylan, Cipla, Teva. Maddalena Gervone has received travel grant from Gilead. Xinzhu Wang, Nadia Castrillo, Francesca Ferretti, Gary Maartens and Myra McClure report no conflicts of interest.

Ethical Approval: All procedure performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.
References


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Fig. 1 Geometric mean (95% confident intervals) plasma dolutegravir (DTG) concentration-time curves

DTG 50 mg once-daily (PK1, black solid line), DTG 100 mg once-daily (PK2, grey solid line), DTG 50 mg once-daily plus RIF (PK3, black hollow line), DTG 100 mg once-daily plus RIF (PK4, grey hollow line). Short-dashed lines represent 95% confident intervals. The black dotted line represents an *in vitro* protein-adjusted IC$_{90}$ of 64 ng/mL. The black solid line represents optimal C$_{24h}$ concentration derived from an E$_{max}$ model in a phase 2 DTG monotherapy study [23].
**Table 1** Summary of steady-state plasma dolutegravir (DTG) pharmacokinetic (PK) parameters following seven days of administration of DTG 50 mg (PK1), seven days of administration of DTG 100 mg (PK2), seven days of co-administration of DTG 50 mg with RIF 600 mg (PK3), and seven days of co-administration of DTG 100 mg with RIF 600 mg (PK4).

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>50 mg DTG (PK1)</th>
<th>100 mg DTG (PK2)</th>
<th>50 mg DTG with RIF (PK3)</th>
<th>100 mg DTG with RIF (PK4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</strong></td>
<td>4903 (3213-6746 (5571)</td>
<td>8169) (5571-8169)</td>
<td>2569 (2184-3023)</td>
<td>4312 (3546-5245)</td>
</tr>
<tr>
<td>CV%</td>
<td>34</td>
<td>31</td>
<td>28</td>
<td>38</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;24h&lt;/sub&gt; (ng/mL)</strong></td>
<td>1509) (745-2017 (1401-2017)</td>
<td>2904) (1401-2017)</td>
<td>156 (115 - 214)</td>
<td>251 (187 - 337)</td>
</tr>
<tr>
<td>CV%</td>
<td>59</td>
<td>53</td>
<td>60</td>
<td>56</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;24h&lt;/sub&gt; (hr*ng/mL)</strong></td>
<td>52101 (40195-92806 (72227)</td>
<td>92806) (72227-92806)</td>
<td>22750 (19012-38731 (31867-38731)</td>
<td>37222 (31867-47073)</td>
</tr>
<tr>
<td>CV%</td>
<td>42</td>
<td>39</td>
<td>32</td>
<td>38</td>
</tr>
</tbody>
</table>

PK values are provided as geometric mean with 95% confidence interval (CI) and coefficient of variation (CV). C<sub>max</sub> = maximum concentration, AUC<sub>24h</sub>=area under the curve, C<sub>24h</sub>=24 hour post-dose concentration.
Table 2: The geometric mean ratios (GMR) with 90% confident intervals (CI) of plasma dolutegravir (DTG) pharmacokinetic (PK) parameters following 7 days of administration of DTG 50 mg (PK1), 7 days of administration of DTG 100 mg (PK2), 7 days of co-administration of DTG 50 mg with RIF 600 mg (PK3), and 7 days of co-administration of DTG 100 mg with RIF 600 mg (PK4).

<table>
<thead>
<tr>
<th>GMR (90% CI)</th>
<th>100 mg DTG</th>
<th></th>
<th>50 mg DTG + RIF vs 50 mg DTG</th>
<th>100 mg DTG + RIF vs 50 mg DTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK parameter</td>
<td></td>
<td>100 mg DTG</td>
<td>50 mg DTG</td>
<td>PK2/PK1</td>
</tr>
<tr>
<td>Cmax</td>
<td>1.70 (1.56-1.85)</td>
<td>1.68 (1.43-1.97)</td>
<td>0.65 (0.55-0.75)</td>
<td>0.64 (0.55-0.74)</td>
</tr>
<tr>
<td>C24h</td>
<td>1.90 (1.74-2.08)</td>
<td>1.60 (1.40-1.84)</td>
<td>0.15 (0.13-0.17)</td>
<td>0.12 (0.10-0.15)</td>
</tr>
<tr>
<td>AUC24h</td>
<td>1.77 (1.61-1.94)</td>
<td>1.70 (1.49-1.95)</td>
<td>0.44 (0.37-0.52)</td>
<td>0.42 (0.35-0.50)</td>
</tr>
</tbody>
</table>

Values are provided as geometric mean ratio with 90% confidence interval. $C_{\text{max}}$ = maximum concentration, $AUC_{24h}$=area under the curve, $C_{24h}$=24 hour post-dose concentration.