Pharmacokinetic interaction between TMC114/r and omeprazole or ranitidine in HIV-negative healthy volunteers

Running title: PK of TMC114/r with omeprazole or ranitidine

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TMC114 (PREZISTA™), also known as darunavir, is a human immunodeficiency virus (HIV) protease inhibitor, used in combination with low-dose ritonavir (RTV; TMC114/r) as a pharmacokinetic enhancer. Protease inhibitor absorption may be decreased during co-administration of drugs that limit stomach acid secretion and increase gastric pH. This study was conducted to investigate the effect of ranitidine and omeprazole on the plasma pharmacokinetics of TMC114 and RTV in HIV-negative healthy volunteers. Sixteen volunteers completed the study and received TMC114/r, TMC114/r plus ranitidine and TMC114/r plus omeprazole, in three separate sessions. Treatment was given for 4 days with an additional morning dose on Day 5, and regimens were separated by a washout period of 7 days. Samples were taken over a 12-h period on Day 5 for the assessment of TMC114 and RTV plasma concentrations. Pharmacokinetic parameters assessed included TMC114 area under the curve, maximum plasma concentration and trough plasma concentration. The least squares mean ratio and 90% confidence intervals are reported with treatment of TMC114/r alone as reference. Compared with TMC114/r alone, no significant changes in TMC114 pharmacokinetic parameters were observed during co-administration of TMC114/r and either ranitidine or omeprazole. Treatment regimens were generally well tolerated and no serious adverse events were reported. In conclusion, co-administration of TMC114/r and ranitidine or omeprazole was well tolerated by the volunteers. Ranitidine and omeprazole did not have a significant influence on TMC114 pharmacokinetics. No dose adjustments are required when TMC114/r is co-administered with omeprazole or ranitidine.

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INTRODUCTION

TMC114 (PREZISTA™), also known as darunavir, is a new protease inhibitor (PI), administered in combination with low-dose ritonavir (RTV; TMC114/r). TMC114 has received its first regulatory approvals for the treatment of human immunodeficiency virus (HIV) infection in treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one PI (15). TMC114 binds to the HIV protease and is highly active against both wild-type and resistant strains of the virus (5). The development of new agents to combat HIV infection is imperative, since treatment options for patients with multi-drug resistant HIV strains are currently limited (17).

Clinically relevant interactions may occur between different antiretrovirals and between antiretrovirals and other drug types given for the treatment of co-existing medical conditions (13). Therefore, the potential interactions between any antiretroviral agent and other medications commonly used in HIV therapy should be routinely investigated during drug development.

Since the absorption of some PIs is dependent on an acidic gastric pH (10), the use of anti-acidic drugs may inhibit PI uptake. Gastrointestinal (GI) symptoms are common in HIV disease (11,12), and are frequently treated with anti-acidic drugs, such as H2-receptor antagonists and proton pump inhibitors (PPIs). It is therefore important that potential interactions between PIs and H2-receptor antagonists and/or PPIs are investigated.

This multiple-dose pharmacokinetic study was designed to assess the effect of the H2-receptor antagonist ranitidine and the PPI omeprazole on the plasma pharmacokinetics of TMC114 and RTV in HIV-negative healthy volunteers.
METHODS

Study design. The present trial was a phase I, open-label, randomized, three-way crossover pharmacokinetic interaction study (TMC114-C122). Healthy men and women between 18 and 55 years were eligible for enrollment. HIV-infected individuals, those suffering from a clinically significant medical condition and those with a known history of alcohol and/or drug abuse were excluded from the study. Concomitant therapy was not permitted with the exception of acetaminophen (paracetamol). The study protocol was reviewed and approved by the appropriate institutional ethics committee and health authorities, and was conducted in accordance with the Declaration of Helsinki. All volunteers gave written informed consent prior to study commencement.

In three separate sessions volunteers received TMC114/r, TMC114/r plus ranitidine and TMC114/r plus omeprazole, each for a period of 4 days plus a single dose on the morning of Day 5. Volunteers were consecutively assigned to a randomization group on enrollment; each of six randomization groups received the three treatments in a different sequence. The following dose and frequency of each drug was used: 400 mg TMC114 bid; 100 mg RTV bid; 150 mg ranitidine bid; 20 mg omeprazole qd. Pharmacokinetic sampling was performed on the morning of Day 5 and regimens were separated by a 7-day washout period. Individuals remained at the trial facility for the duration of treatment (Day -1 to Day 5) and drug intake was directly observed and timed. Ranitidine and omeprazole were administered within 15 min before food and TMC114/r within 15 min after food. Blood samples were taken pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9 and 12 h post-dose on Day 5 for all three regimens.

Bioanalysis. TMC114 and RTV plasma concentrations were determined using a validated liquid chromatography mass spectrometry/mass spectrometry (LC-MS/MS) method. The
internal standards were deuterated (d6)-ritonavir and (d4)-darunavir for RTV and TMC114, respectively. The mass transition was from 721.3 to 296.0 for RTV and from 548.2 to 392.0 for TMC114, respectively. The precision and accuracy for the TMC114 and RTV quality control (QC) samples in plasma were less than 12%, and met the predefined criteria of less than 20% for the low QC and 15% for the medium and high QC samples. The lower limit of quantification was 10.0 and 5.0 ng/mL for TMC114 and RTV, respectively (3). Omeprazole and ranitidine do not interfere with the quantification of TMC114 or RTV.

**Safety evaluations.** Laboratory safety tests were performed at screening, on Day 1, Day 5 and at follow-up to assess safety and tolerability of study therapy. All clinical adverse events and laboratory abnormalities were graded according to the AIDS Clinical Trials Group (ACTG) severity grading scale. Clinical adverse events, whether related to study medications or not, and cardiovascular parameters were monitored and recorded over the study period.

**Statistical methods.** The intent-to-treat (ITT) population was defined as those volunteers who received at least one dose of trial medication, and was the primary population for the safety analyses. No formal sample size calculation was performed for this explorative, cross-over, phase I study. A total of between 14 and 18 volunteers was considered sufficient to allow relevant conclusions to be drawn.

Pharmacokinetic parameters were determined by non-compartmental methods and included: minimum ($C_{\text{min}}$) and maximum ($C_{\text{max}}$) plasma concentrations; area under the curve from 0 to 12 h ($\text{AUC}_{0-12\text{h}}$) and time to maximum plasma concentration ($t_{\text{max}}$). Descriptive statistics for the plasma concentrations of TMC114 and RTV were calculated using WinNonlin Professional™ (version 3.3; Pharsight Corporation, Mountain View,
California, USA.) and Microsoft Excel® (version 2000; Microsoft, Redmond, Washington, USA).

The least square (LS) means of $C_{\text{min}}$, $C_{\text{max}}$ and AUC$_{0-12h}$ for each treatment group were estimated with a linear mixed effects model, controlling for treatment, sequence and period as fixed effects and volunteer as a random effect. Period effects were considered significant at the 5% level and sequence effects were considered significant at the 10% level. If period and sequence effects were not significant, they were removed from the model. The LS mean ratio and 90% confidence intervals (CI) were calculated by comparison of TMC114/r plus omeprazole or ranitidine (test) with TMC114/r alone (reference). Only paired observations for the compared regimens were included in the statistical analysis. $T_{\text{max}}$ of TMC114/r plus omeprazole or ranitidine (test) was compared with TMC114/r alone (reference) by non-parametric Koch test, using the crossover design tool of WinNonlin Professional™.

RESULTS

Study population. Of 18 volunteers initially randomized, 17 received at least one dose of study medication and one was considered by the investigator to be unsuitable for study entry. Of the 17 evaluable volunteers, median (range) age was 26 years (19–53), weight was 69 kg (46–101), height was 169 cm (150–183) and body mass index was 25 kg/m$^2$ (18–30), and eight (47%) subjects were male. These 17 volunteers comprised the ITT population, which was used for all analyses. One volunteer discontinued treatment due to an adverse event (grade 2 maculopapular rash) prior to study completion. No major protocol deviations were reported and there were no major differences in demographic parameters between the randomization groups.
**Pharmacokinetic data.** Mean plasma concentration versus time curves for TMC114 were similar between the regimens, as shown in Fig. 1. This was also true for RTV, as shown in Fig. 2. The mean pharmacokinetic parameters for TMC114 and RTV are described in Table 1.

There were no differences in TMC114 plasma $C_{\text{min}}$, $C_{\text{max}}$ and $\text{AUC}_{0-12h}$ when TMC114/r was co-administered with ranitidine, compared with TMC114/r alone. As shown in Table 2, the LS mean ratios (90% CI) for this interaction were as follows: $C_{\text{min}}$ 0.94 (0.90–0.99); $C_{\text{max}}$ 0.96 (0.89–1.05) and $\text{AUC}_{0-12h}$ 0.95 (0.90–1.01). Similarly, co-administration of ranitidine had no effect on $t_{\text{max}}$ of TMC114.

In the presence of omeprazole, there was a slight increase in TMC114 $C_{\text{min}}$, $C_{\text{max}}$ and $\text{AUC}_{0-12h}$ compared with TMC114/r alone. The LS mean ratios (90% CI) for this interaction were as follows: $C_{\text{min}}$ 1.08 (0.93–1.25); $C_{\text{max}}$ 1.02 (0.95–1.09) and $\text{AUC}_{0-12h}$ 1.04 (0.96–1.13). Co-administration of omeprazole had no effect on $t_{\text{max}}$ of TMC114.

No changes in RTV exposure was observed in the presence of ranitidine or omeprazole (Table 2).

**Safety and tolerability.** Treatments were generally well tolerated and no serious adverse events were reported. The most commonly reported adverse events were headache and loose stools, reported in 9 and 4 volunteers, respectively. All adverse events were of grade 1 or 2 severity, with the exception of 1 volunteer who showed grade 3 increases in lipase and amylase during the follow-up period. Of the 16 individuals who reported one or more adverse event during treatment, 6 (38%) received TMC114/r, 8 (50%) received TMC114/r plus ranitidine and 9 (53%) received TMC114/r plus omeprazole. As requested by protocol, 1 volunteer withdrew from the trial following the occurrence of a grade 2 maculopapular rash on Day 3 of the washout period after receiving Treatment C.
(TMC114/r plus omeprazole). No clinically relevant changes in laboratory or cardiovascular variables were reported during the study and no treatment-emergent grade 3 or 4 laboratory abnormalities were observed.

**DISCUSSION**

We report here the steady-state pharmacokinetics, safety and tolerability of the co-administration of TMC114/r and ranitidine or omeprazole. No significant change in TMC114 plasma exposure was observed during co-administration of TMC114/r and ranitidine or omeprazole, compared with TMC114/r alone. TMC114/r with or without ranitidine or omeprazole was well tolerated. The most frequently reported adverse events were headache and loose stools. No grade 3 or 4 adverse events or laboratory abnormalities were observed during treatment.

Ranitidine and omeprazole have the potential to reduce the absorption of pH-sensitive PIs by increasing gastric pH. Both ranitidine and omeprazole reduce gastric acid secretion, but achieve this by different mechanisms. Ranitidine specifically binds and antagonizes H₂ receptors in the stomach, while omeprazole irreversibly inhibits the proton pump in actively-secreting gastric parietal cells (8). PI elimination could be reduced by drugs that inhibit hepatic metabolism and result in an increased plasma PI concentration. Ranitidine does not interact with hepatic drug metabolizing enzymes, but omeprazole has been shown to inhibit the hepatic enzyme CYP2C19 both in vitro and in vivo (9), however no relevant increase in TMC114 exposure was observed in the presence of omeprazole in this study.

The solubility of the PI atazanavir (ATV) decreases as pH increases, causing ATV absorption to be significantly reduced when given with drugs that increase gastric pH (4). Significant decreases in ATV exposure were seen following co-administration with
omeprazole or ranitidine in healthy volunteers (2). Similarly, co-administration of the H₂ receptor antagonist famotidine with ATV (400 mg) or ATV/r (300/100 mg qd) considerably reduced plasma ATV AUC, compared with ATV alone (1). For volunteers who received 400 mg ATV, the 41% reduction in ATV AUC was almost abolished by giving ATV 10 h after one dose of famotidine and 2 h before the next. Volunteers who received ATV/r with famotidine showed a reduction in ATV AUC of only 18%, which was corrected by increasing the dose of ATV to 400 mg. ATV should not be used in patients receiving PPIs (4,6).

Decreases in amprenavir (APV) exposure were seen following co-administration of fosamprenavir (FPV) with ranitidine in healthy volunteers, thus caution is recommended when these drugs are co-administered (7). Conversely, significant increases in saquinavir (SQV) exposure were observed (82% increase in AUC) when omeprazole and SQV/r were co-administered, although no short-term toxicities were observed (16). Co-administration of esomeprazole with FPV or FPV/r had no effect on steady-state APV pharmacokinetics, although the impact of staggered administration of PPIs on plasma APV exposure is as yet unknown (14).

Unlike ATV, and to a lesser extent APV, co-administration of TMC114/r with either ranitidine or omeprazole had no significant impact on the pharmacokinetics of TMC114 in our study. Moreover, TMC114 t_max was similar when TMC114/r was administered alone or in conjunction with either ranitidine or omeprazole, suggesting that co-administration of these drugs did not delay absorption of TMC114. RTV C_min was reduced when TMC114/r was co-administered with omeprazole, which may be caused by changes in solubility due to increased gastric pH. Important, however, this did not alter the pharmacokinetics of TMC114. Since no impact on TMC114 pharmacokinetics occurred in this study evaluating
the TMC114/r 400/100 mg bid dose, none is expected with the approved 600/100 mg bid
dose (15).

This study provides clinically relevant information to physicians and patients regarding
the appropriate co-administration of TMC114/r and ranitidine or omeprazole. No
significant interaction was observed between TMC114/r and either ranitidine or
omeprazole, therefore no dose adjustments are required when these agents are co-
administered.

ACKNOWLEDGEMENTS

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FIGURE LEGENDS

FIG. 1. Mean TMC114 plasma concentration-time curves on Day 5 of each evaluated regimen. The three regimens were TMC114/r 400/100 mg bid, TMC114/r 400/100 mg bid plus ranitidine 150 mg bid and TMC114/r 400/100 mg bid plus omeprazole 20 mg qd.

FIG. 2. Mean RTV plasma concentration-time curves on Day 5 of each evaluated regimen. The three regimens were TMC114/r 400/100 mg bid, TMC114/r 400/100 mg bid plus ranitidine 150 mg bid and TMC114/r 400/100 mg bid plus omeprazole 20 mg qd.
TABLE 1. Pharmacokinetics of TMC114 (Co-Administered With Low-Dose Ritonavir) on Day 5 in the Absence or Presence of Ranitidine or Omeprazole

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference</th>
<th>Test</th>
<th>Ratio (Test:Reference)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment A:</td>
<td>TMC114/r</td>
<td>400/100 mg bid</td>
<td>Treatment B:</td>
<td>TMC114/r</td>
</tr>
<tr>
<td>N</td>
<td>16</td>
<td>16</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;, h</td>
<td>4.0 (1.5 - 4.0)</td>
<td>3.5 (3.0 - 5.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt;, ng/mL</td>
<td>2851 ± 1172</td>
<td>2696 ± 1151</td>
<td>0.94</td>
<td>0.90-0.99</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;, ng/mL</td>
<td>5834 ± 1415</td>
<td>5743 ± 1878</td>
<td>0.96</td>
<td>0.89-1.05</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-12h&lt;/sub&gt;, ng·h/mL</td>
<td>48905 ± 14352</td>
<td>47258 ± 16340</td>
<td>0.95</td>
<td>0.90-1.01</td>
</tr>
</tbody>
</table>

| Treatment A: | TMC114/r | 400/100 mg bid | Treatment C: | TMC114/r | 400/100 mg bid + omeprazole 20 mg qd |
| N | 16 | 17 | - | - |
| t<sub>max</sub>, h | 4.0 (1.5 - 4.0) | 4.0 (2.0 - 5.0) | - | - |
| C<sub>min</sub>, ng/mL | 2851 ± 1172 | 3121 ± 1416 | 1.08 | 0.93-1.25 |
| C<sub>max</sub>, ng/mL | 5834 ± 1415 | 6009 ± 1844 | 1.02 | 0.95-1.09 |
| AUC<sub>0-12h</sub>, ng·h/mL | 48905 ± 14352 | 51505 ± 18930 | 1.04 | 0.96-1.13 |

N = number of subjects with data.

<sup>a</sup> Ratio based on LS means.
TABLE 2. Pharmacokinetics of Ritonavir (Co-Administered With TMC114) on Day 5 in the Absence or Presence of Ranitidine or Omeprazole

<table>
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<tr>
<th>Parameter</th>
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<th>Test</th>
<th>Ratio $^a$</th>
<th>90% CI</th>
</tr>
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<tbody>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;, h</td>
<td>4.0 (1.0 - 5.0)</td>
<td>4.0 (0.0 - 6.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt;, ng/mL</td>
<td>437 ± 184</td>
<td>442 ± 209</td>
<td>0.98</td>
<td>0.86-1.13</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;, ng/mL</td>
<td>1906 ± 560</td>
<td>2395 ± 1040</td>
<td>1.19</td>
<td>1.03-1.39</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-12h&lt;/sub&gt;, ng.h/mL</td>
<td>11670 ± 3039</td>
<td>12922 ± 4439</td>
<td>1.06</td>
<td>0.99-1.13</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Test</th>
<th>Ratio $^a$</th>
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<tbody>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;, h</td>
<td>4.0 (1.0 - 5.0)</td>
<td>4.0 (4.0 - 6.0)</td>
<td>-</td>
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</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt;, ng/mL</td>
<td>437 ± 184</td>
<td>351 ± 199</td>
<td>0.74</td>
<td>0.61-0.90</td>
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<td>C&lt;sub&gt;max&lt;/sub&gt;, ng/mL</td>
<td>1906 ± 560</td>
<td>2031 ± 987</td>
<td>1.03</td>
<td>0.88-1.20</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-12h&lt;/sub&gt;, ng.h/mL</td>
<td>11670 ± 3039</td>
<td>10945 ± 4009</td>
<td>0.92</td>
<td>0.83-1.02</td>
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</table>

N = number of subjects with data.

$^a$ Ratio based on LS means.