No Meaningful Pharmacokinetic Interaction Between HCV Protease Inhibitor MK-5172 and Tenofovir or Raltegravir

WY Wen, IP Fraser, L Carol, J Talaty, Z Gius, H Davis, EP Youngberg, JR Butterton

1Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA; 2Celention, Lincoln, NE, USA

Abstract

Background

MK-5172 is a potent, orally bioavailable, nonnucleoside HIV integrase inhibitor (I1). Co-administration of I2 in healthy subjects has shown minimal drug-drug interaction with coadministered tenofovir (TDF, an HIV nucleoside reverse transcriptase inhibitor) or raltegravir (RAL, an HIV integrase inhibitor) in healthy subjects.

Aim

To evaluate the pharmacokinetics (PK) interactions and tolerability of MK-5172 when coadministered with TDF or MK-5172 with RAL in healthy subjects.

Patients and Methods

Methods

MK-5172 Pharmacokinetics

MK-5172 is orally administered as a single 200 mg dose, or in two 100 mg doses separated by 24-hour intervals.

MK-5172 PK parameters include:

- Time to maximum concentration (Cmax), 120 minutes following a 200 mg oral dose
- Maximum concentration (Cmax), 2.28 mg/L following a 200 mg oral dose

MK-5172 coadministration with TDF and RAL was generally well-tolerated. In Part 1, multiple oral doses of MK-5172 were administered alone or in combination with TDF or RAL. In Part 2, subjects coadministered MK-5172 with TDF and RAL.

MK-5172 PK parameters following coadministration included:

- Cmax, 2.28 mg/L following a 200 mg oral dose
- AUClast, 3.01 mg/L following a 200 mg oral dose

MK-5172 PK parameters following coadministration with TDF or RAL were lower than those observed when MK-5172 was administered alone, indicating minimal drug-drug interaction.

Safety and Tolerability

MK-5172 coadministration with TDF or RAL was generally well-tolerated. The most common adverse events were:

- Headache (MK-5172, n = 1; TDF, n = 1; RAL, n = 1)

MK-5172 coadministration with TDF or RAL did not result in clinically significant changes in safety laboratory assessments, vital signs, or electrocardiograms.

Table 1. Statistical Comparison of Pharmacokinetic Parameters of MK-5172 Alone and in Combination With TDF or RAL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MK-5172 Alone</th>
<th>MK-5172 + TDF</th>
<th>MK-5172 + RAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/L)</td>
<td>2.28 ± 0.25</td>
<td>1.46 ± 0.19</td>
<td>1.45 ± 0.19</td>
</tr>
<tr>
<td>AUClast (mg/L)</td>
<td>3.01 ± 0.27</td>
<td>1.50 ± 0.12</td>
<td>1.51 ± 0.12</td>
</tr>
</tbody>
</table>

Table 2. Statistical Comparison of Pharmacokinetic Parameters of Raltegravir Alone and in Combination With MK-5172

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Raltegravir Alone</th>
<th>Raltegravir + MK-5172</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>3624 ± 566</td>
<td>3626 ± 562</td>
</tr>
<tr>
<td>AUClast (ng/mL)</td>
<td>12,702 ± 2,460</td>
<td>12,185 ± 2,230</td>
</tr>
</tbody>
</table>

Table 3. Statistical Comparison of Pharmacokinetic Parameters of Tenofovir Alone and in Combination With MK-5172

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tenofovir Alone</th>
<th>Tenofovir + MK-5172</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>808 ± 89</td>
<td>658 ± 82</td>
</tr>
<tr>
<td>AUClast (ng/mL)</td>
<td>5,689 ± 1,460</td>
<td>5,057 ± 1,400</td>
</tr>
</tbody>
</table>

References


Disclosures

This study was funded by Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA.

Poster 100

Presented at the 2016 Conference on Retroviruses and Opportunistic Infections.
Multiple dose MK-5172 (200 mg once daily) was generally well tolerated when administered alone or in combination with TDF or RAL. No subject was discontinued because of an AE, and there were no deaths or serious AEs.

Safety: adverse experiences (AEs), physical examination, vital signs, electrocardiogram (ECG), laboratory safety

**Results**

**MK-5172 Pharmacokinetics**

The PK profile of MK-5172 was similar in the presence of TDF compared with when administered alone, with a slight increase in the exposure of MK-5172 (GMR = 1.18; 90% CI: 1.09, 1.28) and TDF (GMR = 1.10; 90% CI: 1.04, 1.16) compared with when administered alone. The exposure of TDF was slightly higher when administered alone than when coadministered with MK-5172, with a decrease in the ratio of exposure of TDF to MK-5172 of 1.55:1 (90% CI: 1.31, 1.80).

**Tenofovir Pharmacokinetics**

The mean plasma concentration-time profile of TDF at and after C max for the TDF alone group was shown on Figure 1. The mean plasma concentration-time profile of TDF at and after C max for the TDF + MK-5172 group was shown on Figure 2. The mean plasma concentration-time profile of TDF at and after C max for the TDF + RAL group was shown on Figure 3. The mean plasma concentration-time profile of TDF at and after C max for the TDF + MK-5172/TDF group was shown on Figure 4. The mean plasma concentration-time profile of TDF at and after C max for the TDF + MK-5172/RAL group was shown on Figure 5. The mean plasma concentration-time profile of TDF at and after C max for the TDF + RAL/MK-5172 group was shown on Figure 6.

The PK profile of MK-5172 was similar when administered alone, and in the presence of TDF or RAL. The PK profile of MK-5172 was similar when administered alone, and in the presence of TDF or RAL. The PK profile of MK-5172 was similar when administered alone, and in the presence of TDF or RAL. The PK profile of MK-5172 was similar when administered alone, and in the presence of TDF or RAL. The PK profile of MK-5172 was similar when administered alone, and in the presence of TDF or RAL.

**Treatment-related changes in laboratory values, vital signs, or ECG parameters**

There were no consistent treatment-related changes in laboratory values, vital signs, or ECG parameters.

**Conclusions**

These results suggest that no dose adjustments of MK-5172, TDF, or RAL are needed for combination therapy with MK-5172, TDF, or RAL. The results of this study support the further development of MK-5172 for combination therapy with TDF and RAL.

References


No Meaningful Pharmacokinetic Interaction Between HCV Protease Inhibitor MK-5172 and Tenofovir or Raltegravir

WW Yeh,1 IP Fraser,1 L Card,1 J Talaty,1 Z Guo,1 H Davis,1 SP Youngberg,2 JR Butterton2

1Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA; 2Celeron, Lincoln, NE, USA

Abstract

Background: MK-5172 is a potent, once-daily inhibitor of the hepatitis C virus (HCV) NS3/4A protease that is being developed for the treatment of chronic HCV infection in mono- and HCV/HIV-coinfected patients. In a previous study, multiple oral doses of MK-5172 (200 mg twice daily) in healthy subjects were shown to result in bioequivalent exposures to MK-5172 when administered alone or in combination with Raltegravir. In this study we examined the pharmacokinetic interaction between MK-5172 and Tenofovir, the backbone of many antiretroviral regimens based on TDF and RAL in the co-infected population.

Methods: This was a fixed-sequence, 3-treatment, 3-period, open-label study. Raltegravir, Tenofovir, or both were co-administered with MK-5172 to healthy male and non-Hispanic/Latino white subjects (n=30) for 7 days. Subjects were randomized to receive MK-5172 treatment either alone, with Tenofovir + MK-5172, or Raltegravir + MK-5172. MK-5172 was administered once daily at 200 mg (Tenofovir + MK-5172) or 400 mg (Raltegravir + MK-5172) for 7 days in each period. Following an 8 day washout, subjects received oral doses of 400 mg RAL twice daily on Days 1 to 4 in Period 1. After an 8 day washout, subjects received oral doses of 200 mg MK-5172 once daily on Days 1 to 7 in Period 2. In Period 3, subjects received oral doses of 400 mg RAL twice daily on Days 1 to 3 and 200 mg MK-5172 once daily on Days 4 to 7. Plasma PK sampling schemes: Period 1: Raltegravir + MK-5172 (400 mg twice daily) for 4 days, and MK-5172 (200 mg once daily) for 3 days; Period 2: MK-5172 (200 mg once daily) for 7 days; Period 3: Raltegravir + MK-5172 (400 mg twice daily) for 3 days, and MK-5172 (200 mg once daily) for 4 days. Safety, bioanalytical analysis, pharmacodynamics, pharmacogenomics, laboratory safety testing, and ECG assessments were performed.

Results: Geometric mean (GM) ratios (90% CIs) of AUC0-24, AUC0-24/Tmax, Cmax, and C0-24 of MK-5172 were within the bioequivalence range for all comparisons. Multiple oral doses of RAL did not meaningfully alter the steady-state AUC of MK-5172. In Part 2, multiple oral doses of MK-5172 did not meaningfully alter the steady-state AUC of TDF. The apparent increase in RAL C0-24 following MK-5172 coadministration was 11% following RAL coadministration (GMR 1.11 (1.01, 1.22); 95% CI: 1.01, 1.22). The apparent increase in MK-5172 recovery was 4% following MK-5172 coadministration (GMR 1.04 (0.99, 1.09); 95% CI: 0.99, 1.09). The AUC of MK-5172 was slightly higher following RAL coadministration (GMR 1.08 (1.04, 1.12); 95% CI: 1.04, 1.12) and the exposure to RAL was lower following MK-5172 coadministration (GMR 0.89 (0.73, 1.09); 95% CI: 0.73, 1.09). MK-5172 treatment-related AEs included upper abdominal pain (MK-5172 alone), and disturbance in attention, headache, and back pain in one subject each.

Conclusions: The coadministration of RAL or TDF with MK-5172 did not meaningfully alter the steady-state AUC of MK-5172. In Part 2, multiple oral doses of MK-5172 did not meaningfully alter the steady-state AUC of TDF. The apparent increase in RAL C0-24 following MK-5172 coadministration was 11% following RAL coadministration (GMR 1.11 (1.01, 1.22); 95% CI: 1.01, 1.22) and the apparent increase in MK-5172 recovery was 4% following MK-5172 coadministration (GMR 1.04 (0.99, 1.09); 95% CI: 0.99, 1.09). This was a fixed-sequence, 3-treatment, 3-period, open-label study presented at the 2014 Conference on Retroviruses and Opportunistic Infections; March 3-6, 2014; Boston, Massachusetts.

Disclosures

Poster 108

1. Yeh WW et al., 2014 Conference on Retroviruses and Opportunistic Infections; March 3-6, 2014; Boston, Massachusetts.

2. Talaty J, Butterton J, 2014 Conference on Retroviruses and Opportunistic Infections; March 3-6, 2014; Boston, Massachusetts.

References

1. Talaty J, Butterton J, 2014 Conference on Retroviruses and Opportunistic Infections; March 3-6, 2014; Boston, Massachusetts.

2. Talaty J, Butterton J, 2014 Conference on Retroviruses and Opportunistic Infections; March 3-6, 2014; Boston, Massachusetts.

This study was funded by Merck & Co., Inc., Whitehouse Station, NJ.

Presented at the 2014 Conference on Retroviruses and Opportunistic Infections; March 3-6, 2014; Boston, Massachusetts.
Multiple dose MK-5172 (200 mg once daily) was generally well tolerated when administered alone or in combination with raltegravir (RAL) or tenofovir (TDF). MK-5172 treatment-related AEs included upper abdominal pain (MK-5172 alone), and disturbance in attention, fatigue, dry mouth, and dysgeusia (each reported by single subjects receiving TDF + MK-5172).

**Methodology**

This was a fixed-sequence, 3-treatment, 3-period, open-label study in 24 healthy adult male and female volunteers. In Part 1, subjects were coadministered MK-5172 (200 mg) with (MK-5172+RAL/MK-5172) GMRs [90% CIs] of 0.89 [0.72, 1.09], 0.85 [0.62, 1.16], and 0.90 [0.82, 0.99], respectively. In Part 2, multiple oral doses of MK-5172 did not meaningfully alter the steady-state AUC and Cmax of TDF with (TDF+MK-5172/TDF) GMR (90% CI) for the TDF + MK-5172/TDF comparison was 1.14 (1.04, 1.25).

**Results**

The exposure of MK-5172 was similar whether or not it was coadministered with RAL, with a decrease in mean Cmax of 14% following TDF coadministration compared with the administration of TDF alone. In patients coadministered with RAL, a decrease of 14% was observed in the concentration-time profile of MK-5172, with a decrease in Cmax of 47% compared with when administered alone.

**Safety and tolerability**

- No deaths or serious AEs and no subject discontinued because of an AE.
- The most common AEs were headache (MK-5172, n = 1; TDF, n = 1; RAL, n = 1; TDF + MK-5172, n = 1).

**Manufacturers/Contributors**

This study was funded by Merck & Co., Inc., Whitehouse Station, NJ. WWY, IPF, LC, JT, ZG, HD, and JRB are current employees of Merck & Co., Inc., Whitehouse Station, NJ. SPY was previously employed by Merck & Co., Inc., Whitehouse Station, NJ.