Background: MK-5172 is a potent, once-daily inhibitor of the hepatitis C virus (HCV) NS3/4A protease with improved potency compared with the approved first generation protease inhibitors, and deacetylated (DCV), an HCV NS5A replication complex inhibitor with pan-genotypic activity in vitro. The results of MK-5172 in healthy volunteers demonstrated 2-fold higher exposure compared with healthy subjects, a 200 mg dose of MK-5172 in healthy subjects was used in the study, which demonstrated a 100 mg dose (the intended clinical dose) in HCV-infected patients. Period 1, subjects received oral doses of 60 mg DCV once daily on Days 1 to 7, a 4-day washout, subjects received oral doses of 200 mg MK-5172 once daily on Day 1, 7 in Period 2. In Period 3, which commenced immediately after Period 2, subjects were co-administered once daily oral doses of 200 mg MK-5172 and 60 mg DCV on Day 1 to 8. Plasma pharmacokinetic samples were obtained for DCV on Day 7 in Period 1 and Day 8 in Period 3, as well as MK-5172 on Day 1 in Period 3. Safety assessments included laboratory tests, vital signs, clinical laboratory tests, physical examination, and adverse event monitoring.

Aims:
- To assess the effect of multiple oral doses of MK-5172 on the steady-state pharmacokinetics (e.g., AUC0-24h, Cmax, C0-24h, C0) of MK-5172 with MK-5172+DCV/DCV pharmacokinetic parameter mean ratios (GMRs) with 90% confidence intervals (CIs) for AUC0-24h, Cmax, C0 and C0-24h.
- To evaluate the safety and tolerability of multiple doses of MK-5172 alone, multiple doses of DCV alone, and multiple doses of MK-5172 co-administered with multiple doses of DCV in healthy volunteers.

Methods:

Study Design: This was a single-center, open-label, fixed-sequence, multiple-dose study.

Subjects: Twenty (20) healthy male and female volunteers were included in the study. Subjects were excluded if they had a history of drug or alcohol abuse within the past year, or if they were taking any concomitant medications that could affect the pharmacokinetics of MK-5172 or DCV.

Treatments:
- Session MK-5172 in HCV-infected patients demonstrated 2-fold higher exposure compared with healthy subjects, a 200 mg dose of MK-5172 in healthy subjects was used in this study to match the exposure of a 100 mg dose (the intended clinical dose) in HCV-infected patients.
- DCV 60 mg QD, the clinical dose, was used in this study.
- Period 1: oral doses of 60 mg DCV once daily on Days 1 to 7 followed by a 4-day washout.
- Period 2: oral doses of 200 mg MK-5172 QD on Days 1 to 7, a 4-day washout followed this period.

Assessments:
- Plasma pharmacokinetic samples were obtained for DCV on Day 7 in Period 1 and Day 8 in Period 3, as well as MK-5172 on Day 7 in Period 2. Safety assessments included laboratory tests, vital signs, clinical laboratory tests, physical examination, and adverse event monitoring.

Safety and Tolerability:
- Co-administration of MK-5172 with DCV was safe and well tolerated in the healthy adult male and female subjects. No deaths, serious adverse experiences, or laboratory abnormalities were reported during the study.
- The investigator discontinued 1 subject on Day 7 of Period 3 due to moderate drug-related adverse events.
- All adverse experiences that were mild to moderate intensity. The most common adverse experiences were headache, nausea, and constipation.
- The only drug-related adverse event reported in the study was diarrhea reported by 1 subject on 5 occasions following DCV alone. There were no consistent treatment-related changes in laboratory tests, vital signs, or ECG safety parameters.

Results:

Table 1. Pharmacokinetics of MK-5172 alone and in combination with DCV

<table>
<thead>
<tr>
<th>Subject</th>
<th>Pharmacokinetic Parameter</th>
<th>MK-5172 Alone</th>
<th>MK-5172+DCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-24h</td>
<td>10.010 (8.87, 12.42)</td>
<td>10.010 (8.87, 12.42)</td>
<td>10.010 (8.87, 12.42)</td>
</tr>
<tr>
<td>Cmax</td>
<td>1.50 (1.10, 2.00)</td>
<td>1.50 (1.10, 2.00)</td>
<td>1.50 (1.10, 2.00)</td>
</tr>
<tr>
<td>C0</td>
<td>0.80 (0.67, 1.00)</td>
<td>0.80 (0.67, 1.00)</td>
<td>0.80 (0.67, 1.00)</td>
</tr>
<tr>
<td>C0-24h</td>
<td>0.80 (0.67, 1.00)</td>
<td>0.80 (0.67, 1.00)</td>
<td>0.80 (0.67, 1.00)</td>
</tr>
</tbody>
</table>

Table 2. Pharmacokinetics of DCV alone and in combination with MK-5172

<table>
<thead>
<tr>
<th>Subject</th>
<th>Pharmacokinetic Parameter</th>
<th>DCV Alone</th>
<th>MK-5172+DCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-24h</td>
<td>10.010 (8.87, 12.42)</td>
<td>10.010 (8.87, 12.42)</td>
<td>10.010 (8.87, 12.42)</td>
</tr>
<tr>
<td>Cmax</td>
<td>1.50 (1.10, 2.00)</td>
<td>1.50 (1.10, 2.00)</td>
<td>1.50 (1.10, 2.00)</td>
</tr>
<tr>
<td>C0</td>
<td>0.80 (0.67, 1.00)</td>
<td>0.80 (0.67, 1.00)</td>
<td>0.80 (0.67, 1.00)</td>
</tr>
<tr>
<td>C0-24h</td>
<td>0.80 (0.67, 1.00)</td>
<td>0.80 (0.67, 1.00)</td>
<td>0.80 (0.67, 1.00)</td>
</tr>
</tbody>
</table>

Discussion and Conclusions:

- The mean steady-state AUC0-24h, Cmax, and C0 of MK-5172 were unchanged when daily doses of 200 mg MK-5172 were co-administered with daily doses of 60 mg DCV compared with daily doses of 200 mg MK-5172 administered alone.
- The mean steady state AUC0-24h, of DCV was unchanged when daily doses of 60 mg DCV were administered with daily doses of 200 mg MK-5172 compared with daily doses of 60 mg DCV administered alone.
- The mean steady state Cmax of DCV decreased by ~20% and mean C0 increased by ~20%.
- Multiple oral doses of MK-5172 co-administered with DCV were generally safe and well tolerated in the healthy adult male and female subjects.

Conclusions:

- Co-administration of MK-5172 and DCV in healthy volunteers did not result in clinically significant drug-drug interactions.
- Co-administration of MK-5172 and DCV resulted in no dose-adjustment or dose-reduction needs for either co-administered drugs with other drugs without other direct acting antiviral agents in interferon-free, combination regimens in HCV-infected patients.