The effect of food and different meal types on the bioavailability of simeprevir (TMC435), an HCV protease inhibitor in clinical development

Sivi Ouwerkerk-Mahadevan,¹ Alexandru Simion,² Steven Mortier,² Monika Peeters,² Maria Beumont-Mauviel²

¹Janssen Research and Development, Beerse, Belgium
²Janssen Infectious Diseases BVBA, Beerse, Belgium
Simeprevir (SMV, TMC435)

- Potent, oral, once-daily, investigational, HCV NS3/4A protease inhibitor currently in Phase III clinical development for the treatment of HCV genotypes 1 and 4

- Results from the QUEST-1, QUEST-2 and PROMISE Phase III international trials in genotype 1, naïve patients showed SVR12 rates of 80%, 81%, and 79% respectively\(^1\)–\(^3\)

- Readily absorbed when formulated as an oral solution or a capsule

---

SMV, simeprevir
SVR12, sustained virologic response 12 weeks after end of treatment

\(^1\)Manns M et al. Oral presentation at EASL 2013
\(^2\)Jacobson I et al. Poster presented at EASL 2013
\(^3\)Lawitz E et al. Oral presentation at DDW 2013
Pharmacokinetic characteristics of SMV

- In healthy volunteers, $t_{\text{max}}$ was 4–8 h after repeated dosing\(^1\)
- Food type has no effect on the pharmacokinetics of the SMV oral solution\(^2\)

**AIM:** To assess, in healthy subjects, the effect of food and different meal types on the pharmacokinetics of the SMV gelatin capsule formulation used in Phase III trials

---

SMV, simeprevir; $t_{\text{max}}$, time to reach maximum plasma concentration

\(^1\)Reesink H et al. Gastroenterology 2010;138:913–921

\(^2\)Verloes R et al. Poster presented at AASLD 2007
Methods: Subjects (N=24)

- Key inclusion criteria:
  - Healthy male or female
  - Aged 18–55 years
  - Body mass index of 18–30 kg/m²
  - Non-smokers for ≥3 months prior to screening

- Key exclusion criteria:
  - HIV type 1 or 2, or hepatitis A, B or C infection present at screening
  - History of liver or renal insufficiency
  - Use of disallowed therapies (incl. over-the-counter pharmaceuticals and dietary supplements)
  - Platelet count ≤99 × 10⁹/L

- Restrictions:
  - Consumption of alcohol, quinine-containing substances, grapefruit, grapefruit juice, and xanthenes (tea, coffee, cola, chocolate) was prohibited until the last pharmacokinetic blood sample was taken
Methods: Trial design

- Phase I, open-label, randomized, cross-over design study

Example group (n=4)

<table>
<thead>
<tr>
<th>Session I</th>
<th>Session II</th>
<th>Session III</th>
</tr>
</thead>
</table>
| **Fasted conditions**  
No food until 4 h post-dose  
150 mg SMV | **Standard breakfast†**  
Kcal: 533  
Fat: 21 g  
Carbohydrates: 67 g  
Proteins: 19 g  
150 mg SMV | **High-fat breakfast†**  
Kcal: 928  
Fat: 56 g  
Carbohydrates: 65 g  
Protein: 41 g  
150 mg SMV |

- Following an overnight fasting period of ≥10 h SMV was administered with or without breakfast
- Next meal provided 4 h post-dose and subjects could resume their regular diet 8 h post-dose

*a*Treatments were randomized according to a classical 6-sequence, 3-period Williams design

*Day 1 of a treatment session is the first day of the washout period

†Served 30 min pre-dose

SMV, simeprevir
**Methods: Pharmacokinetic and safety assessments**

- Venous blood samples were collected to analyze plasma SMV concentration:
  - Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48 and 72 h post-dose
- Samples were analyzed using LC-MS/MS
- Pharmacokinetic measurements assessed: $C_{\text{max}}$, $t_{\text{max}}$, $AUC_{\infty}$, $t_{\frac{1}{2}\text{term}}$
- Safety and tolerability were evaluated:
  - Adverse events reported by the subject for the duration of the study
  - Vital signs and safety electrocardiogram recordings
  - Physical examination and clinical laboratory tests

SMV, simeprevir; LC-MS/MS, liquid chromatography tandem mass spectrometry; $C_{\text{max}}$, maximum plasma concentration; $t_{\text{max}}$, time to reach $C_{\text{max}}$; $AUC_{\infty}$, area under the curve extrapolated to infinity; $t_{\frac{1}{2}\text{term}}$, terminal elimination half-life
Results: SMV plasma concentration-time curves (mean ± SD)

- $t_{\text{\textfrac{1}{2}}}$ term was unchanged between fasted and fed conditions
- There was a longer absorption phase in fed conditions compared with fasted conditions

SMV, simeprevir; $t_{\text{\textfrac{1}{2}}}$ term, terminal elimination half-life
# Results: Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Pharmacokinetics of SMV (mean ± SD, $t_{max}$: median [range])</th>
<th>SMV 150 mg, fasted</th>
<th>SMV 150 mg, standard breakfast</th>
<th>SMV 150 mg, high-fat breakfast</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>24</td>
<td>24&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>$C_{max}$, ng/mL</td>
<td>817.9 ± 423.5</td>
<td>1286 ± 593.7</td>
<td>1162 ± 456.7</td>
</tr>
<tr>
<td>$t_{max}$, h</td>
<td>4.0 (3.0–8.0)</td>
<td>6.0 (3.0–24.0)</td>
<td>6.0 (2.0–24.0)</td>
</tr>
<tr>
<td>$AUC_{\infty}$, ng.h/mL</td>
<td>11 460 ± 5724</td>
<td>19 450 ± 9311</td>
<td>17 840 ± 6726</td>
</tr>
<tr>
<td>$t_{\frac{1}{2} \text{term}}$, h</td>
<td>10.17 ± 2.245</td>
<td>10.25 ± 1.673</td>
<td>9.819 ± 1.433</td>
</tr>
</tbody>
</table>

<sup>a</sup>n=23 for $AUC_{\infty}$, $t_{\frac{1}{2} \text{term}}$

- Mean $C_{max}$ and $AUC_{\infty}$ were higher following a standard or high-fat breakfast compared with fasted conditions.
- Mean $C_{max}$ and $AUC_{\infty}$ were similar following a standard or high-fat breakfast.
- $t_{max}$ was longer in fed conditions compared with fasted conditions.

$C_{max}$, maximum plasma concentration; $t_{max}$, time to reach $C_{max}$; $AUC_{\infty}$, area under the plasma concentration-time curve extrapolated to infinity; $t_{\frac{1}{2} \text{term}}$, terminal elimination half life.
Results: Statistical analyses

<table>
<thead>
<tr>
<th></th>
<th>Least squares means ratioa (90% CI)</th>
<th>Treatment difference mediana (90% CI, h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard breakfast vs fasting</td>
<td>High-fat breakfast vs fasting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>1.60 (1.3–1.96)</td>
<td>1.49 (1.22–1.82)</td>
</tr>
<tr>
<td>$\text{AUC}_{\infty}$</td>
<td>1.69 (1.36–2.08)</td>
<td>1.61 (1.33–1.93)</td>
</tr>
<tr>
<td>$t_{\text{max}}$</td>
<td>1.50 (1.00–2.00)</td>
<td>1.00 (0.00–2.00)</td>
</tr>
</tbody>
</table>

*a n=24 for reference, b n=23 for test

- $C_{\text{max}}$ and $\text{AUC}_{\infty}$ were ~1.6-fold higher in fed conditions compared with fasted conditions
- $t_{\text{max}}$ was longer in fed than fasted conditions
  - Treatment difference of 1 h after a high-fat breakfast and 1.5 h after a standard breakfast

$C_{\text{max}}$, maximum plasma concentration; $\text{AUC}_{\infty}$, area under the plasma concentration-time curve extrapolated to infinity; $t_{\text{max}}$, time to reach $C_{\text{max}}$
Results: AEs and safety

No serious AEs, no Grade ≥3 AEs, and no withdrawals due to an AE occurred.

There were no relevant differences in AEs between treatment conditions — Exception: headache occurred less frequently when SMV was administered with food.

There were no clinically relevant changes in any other laboratory parameters and no clinically significant changes in vital signs or electrocardiogram recordings during the study period.

**Table: System Organ Class Preferred Term n (%)**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>SMV 150 mg, fasted N=24</th>
<th>SMV 150 mg, standard breakfast N=24</th>
<th>SMV 150 mg, high-fat breakfast N=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>9 (37.5)</td>
<td>7 (29.2)</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>7 (29.2)</td>
<td>5 (20.8)</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td></td>
<td>6 (25.0)</td>
<td>4 (16.7)</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (4.2)</td>
<td>0</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td></td>
<td>1 (4.2)</td>
<td></td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (8.3)</td>
<td>1 (4.2)</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td></td>
<td>1 (4.2)</td>
<td></td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>1 (4.2)</td>
<td>1 (4.2)</td>
</tr>
</tbody>
</table>

N = number of subjects with data, n = number of subjects with that observation.

AE, adverse event; SMV, simeprevir
Conclusions

- When administered with food, SMV absorption was delayed by up to 1.5 h, compared with that in the fasted state.
- Administration with food increased the relative bioavailability of SMV (61–69% increase in $AUC_{\infty}$ after high-fat and normal caloric breakfasts).
- Food type (high-fat versus standard) had no effect on SMV exposure following administration.
- SMV was generally safe and well tolerated.
- It is recommended that SMV is administered with food.
Acknowledgements

- The volunteers and their families
- The study investigators and their teams
- Medical writing support was provided by Suzanne McAllister PhD of Complete Medical Communications, and was funded by Janssen