Evaluation of Drug-Drug Interaction Between Sofosbuvir/Velpatasvir and Rifaximin in HCV-Infected Subjects with Moderate Hepatic Impairment

Erik Mogalian, Brian Kirby, Liyun Ni, Shu-Min Chuang, John McNally, and Anita Mathias

Gilead Sciences, Foster City, CA
Disclosures

Erik Mogalian is an employee of Gilead Sciences, Inc.
Background: Sofosbuvir/Velpatasvir

- **Sofosbuvir (SOF)**\(^1,2\)
  - Potent antiviral activity against HCV GT 1–6
  - GS-331007, predominant circulating metabolite

- **Velpatasvir (VEL; GS-5816)**\(^3\)
  - Picomolar potency against GT 1–6
  - PK supports once-daily dosing

- **SOF/VEL (400/100 mg) FDC**
  - Treatment with SOF/VEL for 12 weeks in Phase 3 studies resulted in high SVR in patients with HCV GT 1–6 \(^4-6\)
  - SOF/VEL + RBV in subjects with moderate hepatic impairment
  - Currently under regulatory review

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FDC, fixed-dose combination.
Background: ASTRAL-4 Study Design

- Open-label, randomized (1:1:1) US study
- HCV GT 1–6 treatment-naïve or -experienced patients with Child-Pugh-Turcotte (CPT) B cirrhosis

RBV, ribavirin; SVR12, sustained virologic response 12 weeks after treatment end.
Background: Potential for SOF/VEL DDIs

- **Sofosbuvir**
  - Substrate of P-gp, BCRP

- **Velpatasvir**
  - Substrate of P-gp, BCRP, OATP1B, CYP2B6, CYP2C8, CYP3A4
  - Inhibitor of P-gp, BCRP, OATP
Background: Rifaximin

- Indicated for use in hepatic encephalopathy
- Structural analog of rifampin
  - Induces CYP3A4 in vitro
  - Limited induction potential in healthy individuals
    - Midazolam AUC ↓8.8% following 14 days with rifaximin
- Low bioavailability (<0.4%)
- PK in Special Populations
  - Exposure in subjects with hepatic impairment increase up to 20-fold
  - “In patients with normal liver function, rifaximin at the recommended dosing regimen is not expected to induce CYP3A4. It is unknown whether rifaximin can have a significant effect on the pharmacokinetics of concomitant CYP3A4 substrates in patients with reduced liver function who have elevated rifaximin concentrations.”

<table>
<thead>
<tr>
<th>Rifaximin PK Parameter</th>
<th>Healthy Subjects n=14</th>
<th>A n=18</th>
<th>B n=7</th>
<th>C n=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;τ&lt;/sub&gt; (ng∙h/mL)</td>
<td>12.3 ± 4.8</td>
<td>118 ± 67.8</td>
<td>161 ± 101</td>
<td>246 ± 120</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>3.4 ± 1.6</td>
<td>19.5 ± 11.4</td>
<td>25.1 ± 12.6</td>
<td>35.5 ± 12.5</td>
</tr>
</tbody>
</table>

Background: Rifaximin

♦ Drug Interaction Potential
  – “An in vitro study suggested that rifaximin is a substrate of P-glycoprotein. It is unknown whether concomitant drugs that inhibit P-glycoprotein can increase the systemic exposure of rifaximin”¹
    • CACO-2 Monolayer²
      – $P_{app}$ A→B: $1 \times 10^{-6}$ cm/sec
      – Efflux ratio: 45-135 (reference ER: digoxin 11-12)
  – “In the presence of P-glycoprotein (P-gp) inhibitors, the efflux ratio (ER) of rifaximin decreased by 2-12 fold. Other transporters may be involved in efflux transport of rifaximin (e.g., BCRP).”

♦ Question: Can rifaximin act as a clinically relevant inducer of drug transporters and metabolizing enzymes in situations where high exposure can be expected?

Objectives

♦ To evaluate the effect of concomitant rifaximin use on the PK of SOF/VEL (400/100 mg) in HCV-infected subjects with decompensated cirrhosis from ASTRAL-4

  – Assess the inductive potential of rifaximin where systemic exposure is expected to be high
Methods

♦ Concomitant medication use was recorded throughout the study
♦ Samples to assess PK of SOF, GS-331007, and VEL PK were drawn at each on-treatment study visit
♦ SOF, GS-331007, and VEL exposure parameters ($\text{AUC}_{\text{tau}}, \text{C}_{\text{max}}, \text{and } \text{C}_{\text{tau}}$) were estimated using population PK models for each analyte
♦ Post hoc analysis compared PK of SOF/VEL in the presence/absence of rifaximin
### Results: Subject Enrollment and Demographics

<table>
<thead>
<tr>
<th></th>
<th>SOF/VEL ± RBV</th>
<th>No Rifaximin n=175</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rifaximin n=80</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, y (range)</td>
<td>58 (41, 70)</td>
<td>58 (40, 73)</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (range)</td>
<td>31 (18, 56)</td>
<td>30 (17, 50)</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>58 (73)</td>
<td>120 (69)</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>73 (91)</td>
<td>155 (89)</td>
</tr>
<tr>
<td>Hispanic/Latino, n (%)</td>
<td>14 (18)</td>
<td>25 (14)</td>
</tr>
<tr>
<td>CPT B, n (%)</td>
<td>74 (93)</td>
<td>154 (88)</td>
</tr>
</tbody>
</table>

n=13 listed rifaximin as concomitant medication, but not for the entire treatment duration.
Results: SOF Pharmacokinetics

Concomitant use of rifaximin does not affect the PK of P-gp substrate SOF
Results: GS-331007 Pharmacokinetics

Concomitant use of rifaximin does not affect the PK of GS-331007

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Rifaximin n=80</th>
<th>No Rifaximin n=174</th>
<th>%GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC\text{\textsubscript{tau}} (ng\textperiodcentered h/mL)</td>
<td>13900 (39.8)</td>
<td>13800 (38.3)</td>
<td>101 (93.0, 110)</td>
</tr>
<tr>
<td>C\text{\textsubscript{max}} (ng/mL)</td>
<td>834 (39.9)</td>
<td>811 (35.4)</td>
<td>102 (94.2, 111)</td>
</tr>
</tbody>
</table>
Concomitant use of rifaximin does not significantly affect the PK of P-gp and CYP substrate VEL

- ~10% decrease in VEL exposure similar to that observed with rifaximin + midazolam in healthy subjects.

### PK Parameter

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Rifaximin n=79</th>
<th>No Rifaximin n=175</th>
<th>%GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;τ&lt;/sub&gt; (ng•h/mL)</td>
<td>1966 (51.5)</td>
<td>2285 (57.0)</td>
<td>88.4 (78.3, 99.8)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>130 (55.4)</td>
<td>153 (60.3)</td>
<td>87.4 (76.7, 99.4)</td>
</tr>
<tr>
<td>C&lt;sub&gt;τ&lt;/sub&gt; (ng/mL)</td>
<td>40 (51.9)</td>
<td>46 (58.6)</td>
<td>89.4 (79.2, 101)</td>
</tr>
</tbody>
</table>
Conclusions

♦ Concomitant use of rifaximin with SOF/VEL ± RBV in HCV-infected subjects with moderate HI did not significantly impact the PK of SOF/VEL.

♦ Clinically relevant induction of P-gp or CYPs by rifaximin is not expected, even in the context of high exposure situations such as in those with hepatic impairment and/or using a P-gp inhibitor.
We extend our thanks to the participants and the study team. This study was funded by Gilead Sciences, Inc.