Effect of Multiple-Dose Ketoconazole and the Effect of Multiple-Dose Rifampin on Pharmacokinetics (PK) of the HCV NS3 Protease Inhibitor Asunaprevir

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Disclosures

- Wenying Li is an employee of Bristol-Myers Squibb
- These studies were funded by Bristol-Myers Squibb, and this presentation includes discussion of investigational drugs not approved for use in humans
Introduction

- Asunaprevir (ASV) is a selective NS3 protease inhibitor with antiviral activity against genotypes 1, 4, 5, and 6 *in vitro*
  - Twice-daily dosing with no food restrictions with the phase 3 capsule formulation
  - Studied in > 2000 patients in various combinations in phase 2 and 3

- ASV is a substrate of OATP1B1 and OATP2B1 and undergoes active liver uptake at physiologically relevant plasma concentrations ($K_m = 0.68 \, \mu M$)
  - Liver concentrations in animals > 40× plasma levels
  - Single-dose rifampin (600 mg) increases plasma $AUC_{\infty}$ of single-dose ASV (200 mg) by 14.8-fold and $C_{\text{max}}$ by 21.1-fold

- ASV is a substrate of CYP 3A4 and P-glycoprotein

- The effects of multiple-dose ketoconazole (KTZ) and rifampin (RIF) on ASV plasma exposure were assessed in 2 studies in healthy volunteers
Study Designs

**Study AI447-014: effect of ketoconazole**

- **N = 19**
- **Screening Day -21**
- **ASV 200 mg BID**
  - Days 1–7
- **ASV 200 mg BID + KTZ 200 mg BID**
  - Days 8–14
- **Discharge Day 15**

**ASV: 12-h serial PK (AM + PM doses) Days 7 + 14**

**Study AI447-018: Effect of rifampin**

- **N = 20**
- **Screening Day -21**
- **Single-dose ASV/RIF**
  - Days 1–8
  - *Data previously presented*
- **ASV 600 mg BID**
  - Days 10–16
- **ASV 600 mg BID + RIF 600 mg QD**
  - Days 17–23
  - *RIF (PM dosing) on Days 17–22 only*
- **Discharge Day 24**

**ASV: 12-h serial PK (AM dose) Days 16 + 23**

- Healthy men and women not of childbearing potential, aged 18–49 years with BMI 18–30 (-018) or 18–32 (-014) kg/m²
- ASV phase 2 tablet formulation
- ASV was given with food; RIF was given 2 hours after the ASV PM dose
Noncompartmental PK were derived

GMR (90% CI) for ASV $C_{max}$ and $AUC_\tau$ were derived

Similar populations for each study
- All Asian/Indian men, mean age ≈ 30 years, mean BMI 23 kg/m$^2$

**AI447-014 (KTZ):** all subjects completed the study

**AI447-018 (RIF):** 1 discontinuation for moderate treatment-related diarrhea on Day 21 (ASV + RIF)

No serious or severe adverse events occurred in either study
AI447-014: Steady-State ASV Concentration-Time (200 mg BID ± KTZ 200 mg BID)

Post-AM dose on Days 7 (ASV) and 14 (ASV + KTZ)
**AI447-014: Steady-State ASV PK Parameters (200 mg BID ± KTZ 200 mg BID) and GMR**

<table>
<thead>
<tr>
<th>Geo. mean (%CV)</th>
<th>$C_{\text{max}}$ ng/mL</th>
<th>$\text{AUC}_\tau$ ng·h/mL</th>
<th>$C_{\text{min}}$ ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASV (N = 19)</strong></td>
<td>639 (35)</td>
<td>2023 (25)</td>
<td>24 (41)</td>
</tr>
<tr>
<td><strong>ASV + KTZ (N = 19)</strong></td>
<td>4423 (45)</td>
<td>19,515 (34)</td>
<td>229 (36)</td>
</tr>
</tbody>
</table>

- KTZ significantly increased all measures of ASV plasma exposure.
AI447-018: Steady-State ASV Concentration-Time
(600 mg BID ± RIF 600 mg QD)

Graph showing the ASV concentration (mean [SD] ng/mL) over time in hours. The graph compares ASV (600 mg BID) and ASV + RIF (600 mg QD). The concentration peaks around 4 hours and then decreases over time.
### AI447-018: Steady-State ASV PK Parameters (600 mg BID ± RIF 600 mg QD) and GMR

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<th>Geo mean (%CV)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>ASV ($N = 20$)</td>
<td>1409 (82)</td>
<td>4169 (74)</td>
<td>32 (43)</td>
</tr>
<tr>
<td>ASV + RIF ($N = 19$)</td>
<td>1325 (68)</td>
<td>3245 (51)</td>
<td>8 (53)</td>
</tr>
</tbody>
</table>

- **AUC$_\tau$ [90% CI]**
  - $0.79$ [0.56–1.09]
- **$C_{\text{max}}$ [90% CI]**
  - $0.95$ [0.60–1.50]

RIF had a modest effect on mean plasma ASV exposure measures, but 90% CIs were wide.
AI447-018: Individual Steady-State ASV Parameters
(600 mg BID ± RIF 600 mg QD)

Very broad range of effect of RIF on ASV exposure
As presented at last year’s workshop

- Single dose of RIF on single-dose ASV
  - $\text{AUC}_{\infty} \uparrow 14.8$-fold
  - $C_{\text{max}} \uparrow 21.1$-fold
- OATP1B1 and OATP2B1 inhibition by RIF
- Highly variable effects
Unchanged or elevated steady-state ASV exposure with multiple-dose RIF occurred mostly in subjects with the largest single-dose increase.

Metabolic induction was apparently confounded by inhibition of liver uptake.

Hepatic ASV is likely to be significantly reduced due to combined effects of RIF.

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Fold-change in ASV AUC

$\frac{\text{AUC}_{\infty}}{\text{AUC}_\tau}$

$\text{AUC}_{\infty}$

(200 mg single dose)

$\text{AUC}_\tau$

(600 mg BID steady state)
Conclusions

- Ketoconazole markedly increased plasma ASV exposure, consistent with inhibition of CYP 3A4 metabolism
  - P-gp inhibition likely contributed to the observed effects

- The expected reduction in steady-state ASV exposure under multidose RIF exposure was apparently confounded by OATP inhibition

- These data clearly demonstrate a significant interaction potential with agents that strongly influence activity of CYP 3A4 and P-gp

- Managing interactions for ASV with medications that significantly affect both CYP 3A4/P-gp activity and OATP transport may prove challenging