Concomitant Proton Pump Inhibitor Use Does Not Reduce the Efficacy of Elbasvir/Grazoprevir

Nancy Reau, MD; Michael N. Robertson, MD; Hwa-Ping Feng, PhD; Luzelena Caro, PhD; Wendy W. Yeh, MD; Bach-Yen T. Nguyen, MD; Janice Walsh, MD; Eliav Barg, MD; Peggy Hwang, PhD; Stephanie O. Klopfer, PhD

1. Rush University Medical Center, Chicago, IL, USA; 2. Merck & Co., Inc., Kenilworth, NJ, USA

Background
- Up to one third of hepatitis C virus (HCV)-infected patients use acid-reducing agents or proton pump inhibitors (PPIs).
- It has been noted that sustained intragastric pH elevation can meaningfully decrease the bioavailability, and hence the concentration, of HCV NS5A protein inhibitors (including the direct-acting antiviral ledipasvir and velpatasvir).

Objectives
- The analysis incorporated data from only those patients who were either treatment-naive or treatment-experienced with at least 7 consecutive days of PPI use within Days -7 to 7.
- Consistent PPI use was included in every trial.
- Cirrhotic status, prior treatment status, baseline HCV RNA (continuous and dichotomous [>800,000 IU/mL and ≤800,000 IU/mL]), HCV genotypes (1a, 1b, or 4), presence of baseline resistance-associated variants (NS5A), presence of baseline resistance-associated variants at amino acid positions 28, 30, or 93.

Methods
- Data were derived from the 6 Phase 3 EBR/GZF trials that included treatment-naive or treatment-experienced GT1 or GT4-infected subjects, with or without compensated cirrhosis.
- The analysis incorporated data from only those patients who were either treatment-naive or treatment-experienced with at least 7 consecutive days of PPI use within Days -7 to 7.

Pharmacokinetics
- EBR population pharmacokinetic (PK) data were analyzed for the first 6 studies.
- EBR area under the plasma concentration-time curve (AUC) and Cmax for individual patients were estimated based on the reviewed dataset of approximately 6000 pharmacokinetic samples using a population pharmacokinetic modeling approach.

Results

Table 1. Baseline characteristics in the modified Full Analysis Set population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Consistent Baseline PPI Use (n=162)</th>
<th>No Consistent Baseline PPI Use (n=170)</th>
<th>All Patients (n=332)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>104 (64.2)</td>
<td>78 (45.9)</td>
<td>182 (54.8)</td>
</tr>
<tr>
<td>Female</td>
<td>58 (35.8)</td>
<td>92 (54.1)</td>
<td>150 (45.2)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>55.9 (8.0)</td>
<td>50.4 (8.1)</td>
<td>51.1 (8.1)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>108 (66.7)</td>
<td>85 (50.0)</td>
<td>193 (58.1)</td>
</tr>
<tr>
<td>Black</td>
<td>44 (27.2)</td>
<td>19 (11.0)</td>
<td>63 (19.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (2.5)</td>
<td>9 (5.3)</td>
<td>13 (4.0)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (3.7)</td>
<td>25 (14.7)</td>
<td>31 (9.4)</td>
</tr>
<tr>
<td>Cirrhosis Status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47 (29.0)</td>
<td>23 (13.5)</td>
<td>70 (21.1)</td>
</tr>
<tr>
<td>No</td>
<td>119 (71.0)</td>
<td>92 (53.5)</td>
<td>211 (69.2)</td>
</tr>
</tbody>
</table>
| Presence of Baseline RAVs           | An additional set of multivariate logistic regression models was performed to confirm EBR-50 mg/GZR-100 mg treatment as a significant factor in achieving SVR12, with or without cirrhosis infected with GT1 or GT4.

Table 2. SVR2 rates by key baseline demographic factors.

- Consistent PPI usage was not associated with changes in SVR2 rates in all subjects, based on age, cirrhosis status, HCV genotype, baseline viral load, or the presence of baseline resistance-associated variants.

Figure 1a. Distribution of EBR AUC by SVR status and PPI use with and without cirrhosis infected with GT1 or GT4.

Figure 1b. Distribution of EBR Cmax by SVR status and PPI use with and without cirrhosis infected with GT1 or GT4.

Figure 2. Pharmacogenetic data were not associated with changes in SVR2 rates in all subjects, based on age, cirrhosis status, HCV genotype, baseline viral load, or the presence of baseline resistance-associated variants.

Summary
- In conclusion, there is no clinically significant effect of consistent concomitant PPI use with EBR/GZF on SVR2 rates in HCV patients with and without cirrhosis infected with GT1 or GT4.

Conclusions
- Consistent, peripheral use of PPI was not associated with changes in SVR2 rates in all subjects, based on age, cirrhosis status, HCV genotype, baseline viral load, or the presence of baseline resistance-associated variants.

Table 3. Geometric mean AUC0-24 and Cmax in subjects taking EBR with and without consistent baseline PPI use.

Table 4. Pharmacogenetic data were not associated with changes in SVR2 rates in all subjects, based on age, cirrhosis status, HCV genotype, baseline viral load, or the presence of baseline resistance-associated variants.

Table 5. Pharmacogenetic data were not associated with changes in SVR2 rates in all subjects, based on age, cirrhosis status, HCV genotype, baseline viral load, or the presence of baseline resistance-associated variants.

Table 6. Pharmacogenetic data were not associated with changes in SVR2 rates in all subjects, based on age, cirrhosis status, HCV genotype, baseline viral load, or the presence of baseline resistance-associated variants.

Table 7. Pharmacogenetic data were not associated with changes in SVR2 rates in all subjects, based on age, cirrhosis status, HCV genotype, baseline viral load, or the presence of baseline resistance-associated variants.

Table 8. Pharmacogenetic data were not associated with changes in SVR2 rates in all subjects, based on age, cirrhosis status, HCV genotype, baseline viral load, or the presence of baseline resistance-associated variants.