**Introduction**

- Elbasvir (EBR) is a potent hepatitis C virus (HCV) NS5A inhibitor, and grazoprevir (GZR) is a potent NS3/4A inhibitor.
- The Phase 3 portion of a Phase 2/3 study evaluated the efficacy and safety of the combination of EBR/GZR given once daily in genotype 1 (GT1)-infected, mostly GT1b-infected treatment-naive or -experienced Japanese chronic hepatitis C (CHC) patients with or without cirrhosis.
- The full analysis set (FAS) population for GT1b patients, coadministration of EBR/GZR for 12 weeks resulted in SVR24 of 94.4%.
- Only 1.8% (6/335) of GT1a patients were included, and all of them achieved SVR24.
- EBR/GZR was largely safe and well tolerated.

**Objectives**

In Japanese GT1b-infected patients with CHC, with or without cirrhosis, in the Phase 3 portion of a Japanese Phase 2/3 study:

- To evaluate the prevalence and types of NS3 and NS5A variants at baseline.
- To determine the impact of baseline variants on treatment response in subjects treated with EBR/GZR.
- To identify and characterize the post-treatment-resistance-associated variants (RAVs) in virologic failures (VFAs).

**Methods**

- Resistance analyses were conducted on the resistance analysis population (RAP), which included all subjects from the FAS population who either achieved SVR24 or met the criteria for VFI (Figure 1).
- Four patients excluded from the RAP: 2 patients discontinued due to adverse events (AEs) and 2 patients died before follow-up week 12.
- Plasma samples from all patients at day 1, pre-dosing, and at follow-up visits in patients with confirmed VF were evaluated by population sequencing (Pop seq) of NS3 and NS5A genes.
- These samples were further analyzed by whole-genome next-generation sequencing (NGS), also called deep sequencing in duplicate.

**Results**

**Table 1. Demographics**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Noncirrhotic</th>
<th>Cirrhotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median years (range)</td>
<td>64 (21-80)</td>
</tr>
<tr>
<td>HCV subtype, n (%)</td>
<td>GT1b</td>
<td>223 (100%)</td>
</tr>
<tr>
<td>Prior treatment, n (%)</td>
<td>Monotherapy</td>
<td>115 (52%)</td>
</tr>
<tr>
<td>NS3 variants</td>
<td>1% to 20%</td>
<td>20 (9%)</td>
</tr>
<tr>
<td>NS5A variants</td>
<td>1% to 20%</td>
<td>20 (9%)</td>
</tr>
</tbody>
</table>

**Figure 2. Prevalence and impact of baseline NS3 variants on efficacy**

- Of 325 patients with baseline NS3 variants, 317 (97.5%) achieved SVR24.
- SVR24 rates in GT1b subjects without or with baseline NS3 variants were 97.5% (317/325) and 97.2% (8/8), respectively (Table 2).

**Table 2. Prevalence and impact of baseline NS5A variants on efficacy**

<table>
<thead>
<tr>
<th>Number of sequences</th>
<th>325</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS5A variants by amino acid position</td>
<td>100% (40/40)</td>
</tr>
</tbody>
</table>

**Figure 3. Table 3. Prevalence and impact of baseline NS5A variants on efficacy**

- Of 325 patients with baseline NS5A variants, 317 (97.5%) achieved SVR24.
- SVR24 rates in GT1b subjects without or with baseline NS5A variants were 97.5% (317/325) and 97.2% (8/8), respectively (Table 2).

**Figure 4. Individual patients with Y93H at baseline (1% or more by NGS)**

- Y93H was detected in all 8 failures at failure point by Pop seq (Table 4).
- Y93H was detected in 4 patients at baseline, and the remaining 4 failures had Y93H as a treatment-emergent RAV.
- All L31M and all Y93H detected at failure point persisted through F24 (Table 4).

**Next-Generation Sequencing Results**

- All 325 baseline sequences were available.
- The SVR24 rates were 87% (273/315), 100% (262/262), and 82% (18/22) when Y93H was present at a detection rate of 1% to 20%, >20% to 40%, and >40%, respectively (Table 5).
- The SVR24 rates by detection rate of baseline L31M showed the same tendency (Table 5).
- The detection rates of baseline Y93H in individual patients had no impact to SVR24 rates (Figure 4).

**Conclusion**

- The prevalence of NS3 baseline variants was low, and there was no impact on treatment response.
- No NS3 post-treatment RAVs were observed.
- L31M and Y93H were the most prevalent baseline RAVs.
- Regardless of presence of baseline NS3 variants, the SVR24 in GT1b patients was >90%.
- The increased detection of baseline Y93H in individual patients by NGS revealed no impact on SVR24 rates.
- The most prevalent post-treatment NS5A RAVs was Y93H.

**Disclosures**

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**Figure 1. Resistance analysis population (RAP)**

329 GT1b patients enrolled in Part 2: Arm 1: 223 patients (immediate treatment group) Arm 2: 72 patients (delayed treatment group) Arm 3: 34 patients (corticosteroid arm)

- 4 patients excluded: - 2 patients discontinued due to adverse events - 2 patients died