Final Results From Phase 3 Portion in Phase 2/3 Study of Elbasvir/Grazoprevir in Hepatitis C Genotype 1-Infected Japanese Patients

Background

- Broad activity versus most hepatitis C virus (HCV) genotypes in vitro.
- Relates in vitro activity against many clinically relevant resistance-associated variants (RAAV).
- Efficacious in treatment-naive and treatment-experienced cohorts; and non-cirrhotic patients with HCV, in HCV/HCV-coinfected patients, and chronic kidney disease (CKD) stage 4-5 patients with HCV.
- All-oral, once-daily regimen.
- Received approval as ZEPATIER® for the treatment of chronic hepatitis C (HCV) genotype 1 or 4 infection in US and EU.

Aim

- The study was conducted as a Phase 2/3 design. The dose of grazoprevir (GZR) 100 mg was selected based on the results of the Phase 2 portion of the study.
- The aim of the Phase 2 portion of the Phase 2/3 study was to evaluate the efficacy and safety of this drug combination in genotype 1 (GT1) infected treatment-naive patients or previous treatment-experienced patients with compensated cirrhosis.
- In this report, we present Phase 3 results for a combined clinical and on-treatment response 12 weeks after completing therapy in the immediate-treatment group (ITT arm), the delayed-treatment group (DTG arm), and compensated cirrhosis arm.

Methods

Key inclusion criteria:

- GT1-infected, Japanese CHC subject
- Without cirrhosis or with compensated cirrhosis
- ≥20-35 years of age; male and female
- Treatment naïve or treatment experienced for interferon-based therapy without direct-acting antivirals
- HCV RNA at the time of screening ≥5 log IU/mL

Key exclusion criteria:

- Concomitant hepatitis B virus or HBV
- Crebogen clearance is less than 50 mL/min

Key endpoints:

- Efficacy (full analysis set [FAS]):
  - Primary endpoint: SVR12 (HCV RNA <15 IU/mL) at all follow-up week 12
  - Secondary endpoint: SVR24

- Safety:
  - All-cause and serious adverse events
  - Laboratory abnormalities

Table 1. Demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Overall Efficacy</th>
<th>ITG Arm</th>
<th>DTG Arm</th>
<th>ITG + GZR</th>
<th>DTG + GZR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male (%)</td>
<td>89/94</td>
<td>46/48</td>
<td>43/47</td>
<td>41/45</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>21-55</td>
<td>50/50</td>
<td>50/50</td>
<td>50/50</td>
<td>50/50</td>
</tr>
<tr>
<td>Baseline HCV RNA (IU/mL)</td>
<td>83 (21–160)</td>
<td>85 (22–160)</td>
<td>83 (21–160)</td>
<td>83 (21–160)</td>
<td></td>
</tr>
<tr>
<td>Prior treatment with peginterferon α-2b/ribavirin</td>
<td>16/16</td>
<td>12/12</td>
<td>12/12</td>
<td>12/12</td>
<td></td>
</tr>
<tr>
<td>Baseline NS5A RAVs</td>
<td>No</td>
<td>34/35</td>
<td>34/35</td>
<td>34/35</td>
<td>34/35</td>
</tr>
<tr>
<td>Baseline NS3 RAVs</td>
<td>No</td>
<td>34/35</td>
<td>34/35</td>
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<td>34/35</td>
</tr>
</tbody>
</table>

Table 2. Impact of NS5A RAVs at baseline

<table>
<thead>
<tr>
<th>NS5A RAVs</th>
<th>N (%)</th>
<th>ITG Arm</th>
<th>N (%)</th>
<th>DTG Arm</th>
<th>N (%)</th>
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</thead>
<tbody>
<tr>
<td>No NS5A RAVs</td>
<td>34/35</td>
<td>34/35</td>
<td>34/35</td>
<td>34/35</td>
<td></td>
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<tr>
<td>Any NS5A RAVs</td>
<td>9/6</td>
<td>9/6</td>
<td>9/6</td>
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</tbody>
</table>

Table 3. Adverse events (≥5%) through FU4 (ASaT)

<table>
<thead>
<tr>
<th>Event</th>
<th>ITG Arm</th>
<th>DTG Arm</th>
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</thead>
<tbody>
<tr>
<td>Rash</td>
<td>3/72</td>
<td>2/72</td>
</tr>
<tr>
<td>Headache</td>
<td>3/72</td>
<td>3/72</td>
</tr>
<tr>
<td>Constipation</td>
<td>3/72</td>
<td>3/72</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5/72</td>
<td>5/72</td>
</tr>
<tr>
<td>Nausea</td>
<td>3/72</td>
<td>3/72</td>
</tr>
<tr>
<td>Fats, lipids</td>
<td>3/72</td>
<td>3/72</td>
</tr>
</tbody>
</table>

Table 4. Subgroup analysis in Figure 5

- Subgroup analysis is shown in Figure 5

Results

- Overall SVR24 was 97.5% (the combined ITG and DTG) and combined population receiving EBR + GZR for 12 weeks (Figure 3).
- Overall SVR12 was 96% (Figure 4).
- One patient relapsed between follow-up weeks 12 and 24 (Figure 5).
- Safety: The frequency and nature of AEs were similar in patients receiving EBR + GZR (GT 1, GT 2, GT 3). As demonstrated in Table 3, drug-related AEs were slightly more frequent on EBR + GZR.
- Drug-related AEs were slightly more frequent on EBR + GZR.
- Table 4 shows the adverse events (≥5%) through FU4 (ASaT).

Conclusions

- SVR12 and SVR24 was achieved by 98% of patients.
- High efficacy for GT-1 infected Japanese CHC patients.
- High efficacy also in compensated cirrhosis.
- Low rates of AEs; comparable to placebo.
- High efficacy for GT1-infected Japanese CHC patients with or without cirrhosis.
- Table 2 shows the impact of NS5A RAVs at baseline.
- Table 3 shows the adverse events (≥5%) through FU4 (ASaT).
- Table 4 shows the subgroup analysis in Figure 5.

Disclosures

- Fujimaki Suzuki, Yoshinari Kariya, Kazuaki Chayama, Noritomi Kawada, Takeshi Okanoue, Yoshihito Itoh, Satoshi Morichi, Hidenori Toida, Hirotoshi Yoshih, Shintaro Takai, Naoiyo Yatsuzuka, Etsu Yodogawa, Go Fujimoto, Janice Wath, Michael Robertson, Stuart Black, Hiromitsu Kumada
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References