Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-1 Trial

Simeprevir + PEG + Ribavirin for Treatment-Naïve HCV GT1

QUEST-1 Trial

**QUEST-1 Trial: Features**

- **Design**: Randomized, double-blind, placebo-controlled, phase 3 trial with simeprevir + PEG + RBV versus PEG + RBV in treatment-naïve GT 1
- **Setting**: Multicenter at 71 sites in 13 countries
- **Entry Criteria**
  - Treatment-naïve, chronic HCV monoinfection
  - HCV Genotype 1 (1a or 1b)
- **Patient Characteristics**
  - N = 394
  - HCV Genotype: 1a (56%); 1b (44%)
  - IL28B Genotype: 71% non-CC
  - Age: median age 48
  - Sex: 56% male
  - Race: 89% white, 8% black
  - Liver disease: F3 = 18%; F4 = 12%
- **Primary end-points**: Efficacy (SVR12) and safety
### Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1

**QUEST-1 Trial: Design**

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized 2:1; stratified on IL28B and HCV1 subtype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 264</td>
<td>Simeprevir + PEG + RBV</td>
<td>PEG + RBV</td>
<td>PEG + RBV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 130</td>
<td>Placebo + PEG + RBV</td>
<td>PEG + RBV</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Response-Guided Therapy**
- Patients with HCV RNA <25 IU/ml at week 4 and <15 IU/ml at week 12 completed treatment after 24 weeks.

**Drug Dosing**
- Simeprevir: 150 mg once daily
- Peginterferon alfa-2a (PEG): 180 mcg/week
- Ribavirin (RBV) weight-based (in 2 divided doses): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75kg

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1

QUEST-1 Trial: Results

QUEST-1: Proportion of Patients with SVR12

Abbreviations: SVR12 = sustained virologic response at 12 weeks; PEG = peginterferon; RBV = ribavirin

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1
QUEST-1 Trial: Results

SVR12 by HCV Genotype 1 Subtype

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>Simeprevir + PEG + RBV</th>
<th>PEG + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>71/147</td>
<td>49/74</td>
</tr>
<tr>
<td>1b</td>
<td>90/117</td>
<td>52/56</td>
</tr>
</tbody>
</table>

Abbreviations: PEG = Peginterferon; RBV = Ribavirin

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1

QUEST-1 Trial: Results

QUEST 2: SVR12 for HCV 1a by Baseline Q80K Status

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>Simeprevir + PEG + RBV</th>
<th>PEG + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a (with baseline Q80K)</td>
<td>52/60</td>
<td>16/30</td>
</tr>
<tr>
<td>1a (without baseline Q80K)</td>
<td>85/86</td>
<td>44/43</td>
</tr>
</tbody>
</table>

Patients (%) with SVR 12

Abbreviations: PEG = Peginterferon; RBV = Ribavirin

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1
QUEST-1 Trial: Results

SVR12 Response in Simeprevir Arm Based on Achievement of RGT Criteria

Patients (%) who Met RGT Criteria

- Met RGT Criteria: 85%
- Did Not Meet RGT Criteria: 11%
- Unclassified: 4%

N = 264

SVR12 Based on Meeting RGT

- Met RGT: 203/224 (91%)
- Did Not Meet RGT: 6/28 (21%)

RGT= response-guided therapy: in simeprevir study arm, patients with HCV RNA<25 IU/ml at week 4 (undetectable or detectable) and <25 IU/ml at week 12 (undetectable) stopped treatment after 24 weeks

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1

QUEST-1 Trial: Results

### QUEST 1: SVR12 by Host IL28B Genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Simeprevir + PEG + RBV</th>
<th>PEG + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>94/77 (72/77)</td>
<td>78/37 (29/37)</td>
</tr>
<tr>
<td>CT</td>
<td>76/50 (114/50)</td>
<td>42/76 (32/76)</td>
</tr>
<tr>
<td>TT</td>
<td>65/37 (24/37)</td>
<td>24/17 (4/17)</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- PEG = Peginterferon
- RBV = Ribavirin

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1
QUEST-1 Trial: Results

QUEST 1: SVR12 by Liver Fibrosis (Metavir Score)

Abreviations: PEG = Peginterferon ; RBV = Ribavirin

Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1

QUEST-1 Trial: Results

On-Treatment Failure or Relapse

Stopping rules: (1) Stop simeprevir or placebo if HCV RNA > 1000 at week 4; (2) Stop all therapy if HCV RNA < $2 \log_{10}$ IU/mL reduction at week 12; (3) Stop all therapy if HCV RNA ≥25 IU/mL at week 24 or 36.


Emergent Protease Resistance in Patients who Failed to Achieve SVR12

- Among simeprevir-treated patients who failed to achieve SVR12, emergent mutations in NS3 protease domain detected in 35 (92%) of 38

- Genotype 1A: Most common mutation = R155K alone or in combination with mutations at codons 80 and/or 168

- Genotype 1B: Most common mutation = D168V

### Simeprevir + PEG + RBV for Treatment-Naïve HCV GT1 QUEST-1 Trial: Adverse Effects

<table>
<thead>
<tr>
<th>QUEST 1: Event</th>
<th>Simeprevir + PEG + RBV (n=264)</th>
<th>Placebo + PEG + RBV (n=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation (due to adverse event)</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Grade 3 adverse event</td>
<td>25%</td>
<td>33%</td>
</tr>
<tr>
<td>Grade 4 adverse event</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>42%</td>
<td>41%</td>
</tr>
<tr>
<td>Headache</td>
<td>33%</td>
<td>39%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>Rash (any type)</td>
<td>34%</td>
<td>32%</td>
</tr>
<tr>
<td>Anemia</td>
<td>20%</td>
<td>21%</td>
</tr>
<tr>
<td>Photosensitivity condition</td>
<td>3%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>24%</td>
<td>18%</td>
</tr>
<tr>
<td>Bilirubin increase</td>
<td>9%</td>
<td>5%</td>
</tr>
</tbody>
</table>

**Interpretation**: “Simeprevir once daily with peginterferon alfa 2a and ribavirin shortens therapy in treatment-naive patients with HCV genotype 1 infection without worsening the adverse event profiles associated with peginterferon alfa 2a plus ribavirin.”
This slide deck is from the University of Washington’s *Hepatitis C Online* and *Hepatitis Web Study* projects.

**Hepatitis C Online**

[www.hepatitisc.uw.edu](http://www.hepatitisc.uw.edu)

**Hepatitis Web Study**


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