Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1
QUEST-2 Trial

### QUEST-2 Trial: Features

- **Design**: Randomized, double-blind, placebo-controlled, phase 3 trial of simeprevir + PEG + RBV versus PEG + RBV in HCV GT1

- **Setting**: Multicenter at 76 sites in 14 countries

- **Entry Criteria**
  - Treatment-naïve, chronic HCV monoinfection
  - HCV Genotypes 1a or 1b

- **Patient Characteristics**
  - N = 391
  - HCV Subtype: 1a (41%); 1b (58%); other (<1%)
  - IL28B Genotype: 30% CC
  - Age and Sex: median age 46; 55% male
  - Race: 92% white
  - Liver disease: 14% with F3; 6% with F4

- **Primary end-points**: Efficacy (SVR12) and safety
Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1

**QUEST-2 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>
</table>

N = 257

<table>
<thead>
<tr>
<th>N = 257</th>
<th>Simeprevir + PEG + RBV</th>
<th>PEG + RBV</th>
<th>PEG + RBV</th>
</tr>
</thead>
</table>

N = 134

<table>
<thead>
<tr>
<th>N = 134</th>
<th>Placebo + PEG + RBV</th>
<th>PEG + RBV</th>
</tr>
</thead>
</table>

**Study Notes**
- Randomized 2:1, stratified on IL28B and HCV subtype
- 63% in each arm randomized to receive PEG alfa-2a or PEG alfa-2b; remainder assigned PEG alfa-2a
- Response-guided therapy (RGT): 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

**Drug Dosing**
- Simeprevir: 150 mg once daily
- Peginterferon alfa-2a (PEG): 180 mcg/week OR Peginterferon alfa-2b: 1.5 mcg/kg/week
- Ribavirin (RBV) weight-based (in 2 divided doses): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1
QUEST-2 Trial: Results

**QUEST 2: Proportion of Patients with SVR12**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (%) with SVR12</th>
<th>Patients (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir + PEG + RBV</td>
<td>81</td>
<td>209/257</td>
</tr>
<tr>
<td>PEG + RBV</td>
<td>50</td>
<td>67/134</td>
</tr>
</tbody>
</table>

P < 0.0001

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

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1

QUEST-2 Trial: Results

**QUEST 2: SVR12 by HCV Genotype 1 Subtype**

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

**Graph:**
- Patients (%) with SVR 12 by HCV Genotype
- **1a:**
  - Simeprevir + PEG + RBV: 86/107 (79.7%)
  - PEG + RBV: 26/57 (45.6%)
  - *P* < 0.0001
- **1b:**
  - Simeprevir + PEG + RBV: 123/150 (82.0%)
  - PEG + RBV: 41/77 (53.3%)
  - *P* < 0.0001

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1a (with baseline Q80K) and (without baseline Q80K) QUEST-2 Trial: Results

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

**HCV Genotype**

<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>18/24</td>
<td>7/14</td>
</tr>
<tr>
<td>1a (without baseline Q80K)</td>
<td>65/79</td>
<td>17/40</td>
</tr>
</tbody>
</table>

**Patients (%) with SVR 12**

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

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 
QUEST-2 Trial: Results

QUEST 2: SVR12 Response in Simeprevir Arm Based on RGT Criteria

Patients (%) who Met RGT Criteria

- Met RGT Criteria: 91%
- Did Not Meet RGT Criteria: 6%
- Unclassified: 3%

N = 257

SVR 12 Based on Meeting RGT

- Met RGT: 202/235 (86 patients)
- Did Not Meet RGT: 5/16 (31 patients)

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 in Treatment-Naïve Genotype 1

QUEST-2 Trial: Results

QUEST 2: SVR12 by Host *IL28B* Genotype

<table>
<thead>
<tr>
<th>IL28B Genotype</th>
<th>Simeprevir + PEG + RBV</th>
<th>PEG + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CC</strong></td>
<td>72/75</td>
<td>34/42</td>
</tr>
<tr>
<td><strong>CT</strong></td>
<td>114/142</td>
<td>29/71</td>
</tr>
<tr>
<td><strong>TT</strong></td>
<td>23/40</td>
<td>4/21</td>
</tr>
</tbody>
</table>

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

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

**QUEST 2: SVR12 by Liver Fibrosis (Metavir Score)**

<table>
<thead>
<tr>
<th>Liver Fibrosis</th>
<th>Simeprevir + PEG + RBV</th>
<th>PEG + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0-F2</td>
<td>85/195 (P &lt; 0.0001)</td>
<td>51/102</td>
</tr>
<tr>
<td>F3</td>
<td>67/36 (P &lt; 0.0001)</td>
<td>53/17</td>
</tr>
<tr>
<td>F4 (Cirrhosis)</td>
<td>65/17 (P &lt; 0.0001)</td>
<td>40/15</td>
</tr>
</tbody>
</table>

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

Simeprevir + PEG + RBV in Treatment-Naïve Genotype 1 QUEST-2 Trial: Results

SVR12 by Type of Peginterferon

<table>
<thead>
<tr>
<th>Type of Peginterferon</th>
<th>Simeprevir + PEG + RBV</th>
<th>PEG + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG alfa-2a (randomized)</td>
<td>68/77 (88)</td>
<td>28/45 (62)</td>
</tr>
<tr>
<td>PEG alfa-2b (randomized)</td>
<td>62/80 (78)</td>
<td>18/43 (42)</td>
</tr>
<tr>
<td>PEG alfa-2a (assigned)</td>
<td>79/100 (79)</td>
<td>21/46 (46)</td>
</tr>
</tbody>
</table>

Type of PEG: 63% of patients randomized to receive PEG alfa-2a versus alfa-2b; remainder assigned PEG alfa-2a
Abbreviations: SVR12 = sustained virologic response at 12 weeks; PEG = peginterferon; RBV = ribavirin

QUEST 2: Patients Who Had On-Treatment Failure or Relapse

**Abbreviations:** PEG = Peginterferon; RBV = Ribavirin
On-Treatment Failure: Detectable HCV RNA at end of treatment.

### QUEST 2: Event

<table>
<thead>
<tr>
<th>Event</th>
<th>Simeprevir + PEG/RBV (n=257)</th>
<th>Placebo + PEG/RBV (n=134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation (due to adverse event)</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Grade 3 adverse event</td>
<td>27%</td>
<td>31%</td>
</tr>
<tr>
<td>Grade 4 adverse event</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Headache</td>
<td>39%</td>
<td>37%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37%</td>
<td>42%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>31%</td>
<td>40%</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Rash (any type)</td>
<td>27%</td>
<td>20%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>26%</td>
<td>27%</td>
</tr>
<tr>
<td>Photosensitivity reactions</td>
<td>4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Anemia</td>
<td>21%</td>
<td>28%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>21%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Among simeprevir-treated patients who failed to achieve SVR12, emergent mutations in NS3 protease domain detected in 98%

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

- Genotype 1B: Most common mutation = D168V and Q80R + D168E

Interpretation: “Addition of simeprevir to either peginterferon alfa 2a or peginterferon alfa 2b plus ribavirin improved SVR in treatment-naive patients with HCV genotype 1 infection, without worsening the known adverse events associated with peginterferon alfa 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

Funded by a grant from the Centers for Disease Control and Prevention.