Simeprevir in Genotype 1 (Viral Relapsers) PROMISE Trial

# Simeprevir + PEG + Ribavirin for Chronic HCV

## PROMISE Trial

### Design
Randomized, double-blind, placebo-controlled phase 3 trial of triple therapy with simeprevir, peginterferon alfa-2a, and ribavirin

### Entry Criteria
- Treatment-experienced, chronic HCV monoinfection
- Viral relapse with prior (≥ 24 weeks) of peginterferon-based therapy
- HCV Genotype 1

### Patient Characteristics
- N = 393
- HCV Genotype: 1a (42%); 1b (58%)
- IL28B Genotype: 76% non-CC
- Age and Sex: median age 52; 66% male
- Race: 94% white
- Liver disease: 15% had METAVIR F3; 15% F4

### Primary end-points
Efficacy (SVR12)

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### Study Notes
- Randomized 2:1, stratified on IL28B and HCV subtype
- 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
- Ribavirin (RBV) weight-based (in 2 divided doses): 1000 mg if < 75kg or 1200 mg/day if ≥ 75kg

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Simeprevir and Peginterferon plus Ribavirin for Chronic HCV:

PROMISE Trial: Results

PROMISE Trial: Proportion of Patients with SVR12

![Bar chart showing the proportion of patients with SVR12 for Simeprevir + PEG + RBV versus PEG + RBV.]

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

PROMISE Trial: SVR12 by HCV Genotype 1 Subtype

Patients (%) with SVR 12

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>Simeprevir + PEG + RBV</th>
<th>PEG + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>70/111</td>
<td>15/54</td>
</tr>
<tr>
<td>1B</td>
<td>86/149</td>
<td>43/79</td>
</tr>
</tbody>
</table>

P < 0.001

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

Simeprevir and Peginterferon plus Ribavirin for Chronic HCV
PROMISE Results

PROMISE Trial: SVR12 Response in Simeprevir Arm Based on RGT Criteria

Patients (%) who Met RGT Criteria

<table>
<thead>
<tr>
<th>Met RGT Criteria</th>
<th>Did Not Meet RGT Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>93%</td>
<td>7%</td>
</tr>
</tbody>
</table>

n = 260

Patient (%) with SVR 12 Response

<table>
<thead>
<tr>
<th>Met RGT Criteria</th>
<th>Did Not Meet RGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>83</td>
<td>40</td>
</tr>
</tbody>
</table>

200/241

6/15

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 and Peginterferon plus Ribavirin for Chronic HCV PROMISE Trial: Results

PROMISE TRIAL: SVR12 by Host *IL28B* Genotype

**Patients (%) with SVR12**

<table>
<thead>
<tr>
<th>IL28B Genotype</th>
<th>Simeprevir + PEG + RBV</th>
<th>PEG + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>89/55 (82.8%)</td>
<td>53/18 (29.4%)</td>
</tr>
<tr>
<td>CT</td>
<td>78/131 (59.4%)</td>
<td>34/28 (12.1%)</td>
</tr>
<tr>
<td>TT</td>
<td>65/20 (32.5%)</td>
<td>19/3 (6.5%)</td>
</tr>
</tbody>
</table>

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

Simeprevir and Peginterferon plus Ribavirin for Chronic HCV
PROMISE Trial: Results

PROMISE Trial: SVR12 by Liver Fibrosis (METAVIR Fibrosis Score)

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

Patients Who Had On-Treatment Failure or Relapse

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

# Simeprevir

## Adverse Effects in PROMISE Trial


<table>
<thead>
<tr>
<th>PROMISE Trial: Event</th>
<th>Simeprevir + PR (n=260)</th>
<th>Placebo + PR (n=133)</th>
<th>Simeprevir + PR (n=260)</th>
<th>Placebo + PR (n=133)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First 12 Weeks</td>
<td>Entire Treatment Phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE leading to permanent discontinuation of ≥ 1 drug</td>
<td>1.2%</td>
<td>1.5</td>
<td>2.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Grade 3 event</td>
<td>18.1%</td>
<td>18.0%</td>
<td>24.2%</td>
<td>25.6%</td>
</tr>
<tr>
<td>Grade 4 event</td>
<td>1.9%</td>
<td>3.0%</td>
<td>3.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31.9%</td>
<td>42.1%</td>
<td>32.3%</td>
<td>43.6%</td>
</tr>
<tr>
<td>Headache</td>
<td>31.9%</td>
<td>36.1%</td>
<td>33.1%</td>
<td>36.1%</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>29.6%</td>
<td>20.3%</td>
<td>30.0%</td>
<td>20.3%</td>
</tr>
<tr>
<td>Rash (any type)</td>
<td>18.5%</td>
<td>14.3%</td>
<td>23.1%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>23.5%</td>
<td>16.5%</td>
<td>27.7%</td>
<td>27.8%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14.6%</td>
<td>16.5%</td>
<td>17.7%</td>
<td>21.8%</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>3.5%</td>
<td>0%</td>
<td>3.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Anemia</td>
<td>10.8%</td>
<td>6.0%</td>
<td>16.9%</td>
<td>20.3%</td>
</tr>
</tbody>
</table>
Most (90.4%) of simeprevir-treated patients who failed to achieve SVR12 developed emerging mutations in the NS3 protease domain.

- Genotype 1A: Most common mutation = R155K or D168E, or combination of R155K and mutations at codons 80 and/or 168
- Genotype 1B: Most common mutations = D168V or D168A, E, T or E/V or the combinations Q80R + D168E/V, or Q80R + S122T + D168E

**Conclusions**: “In a Phase 3 trial of patients who had relapsed following interferon-based therapy, addition of simeprevir to PR was generally well tolerated, with an SVR12 rate of 79.2%. Most patients (92.7%) receiving simeprevir were able to shorten therapy to 24 weeks.”
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.