Peginterferon alfa-2b (PegIntron)

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Last Updated: February 3, 2014
Peginterferon alfa-2b + Ribavirin versus Interferon alfa-2b + Ribavirin
Study Design

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>511</td>
<td>514</td>
<td>505</td>
</tr>
</tbody>
</table>

- **Higher-Dose Peginterferon + Ribavirin**
  - Peginterferon alfa-2b: 1.5 μg/kg 1x/week + Ribavirin: 800 mg/day
  - SVR24

- **Lower-Dose Peginterferon + Ribavirin**
  - Peginterferon alfa-2b: 1.5 μg/kg 1x/week x 4 weeks, then 0.5 mcg/kg 1x/week + Ribavirin: 1000-1200 mg/day
  - SVR24

- **Interferon + Ribavirin**
  - Standard Interferon alfa-2b: 3 million U 3x/week + Ribavirin: 1000-1200 mg/day
  - SVR24

Peginterferon alfa-2b + Ribavirin versus Interferon alfa-2b + Ribavirin

Results

Response after 48 Weeks of Treatment

<table>
<thead>
<tr>
<th></th>
<th>Higher-dose Peginterferon + Ribavirin (low dose)</th>
<th>Lower-dose Peginterferon + Ribavirin (weight dose)</th>
<th>Interferon + Ribavirin (weight dose)</th>
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</thead>
<tbody>
<tr>
<td><strong>End of Treatment Response</strong></td>
<td>65/333</td>
<td>56/289</td>
<td>54/271</td>
</tr>
<tr>
<td><strong>Sustained Virologic Response</strong></td>
<td>54/274</td>
<td>47/244</td>
<td>47/235</td>
</tr>
</tbody>
</table>

Peginterferon alfa-2b + Ribavirin versus Interferon alfa-2b + Ribavirin Results

SVR24, Based on Genotype

Peginterferon alfa-2b + Ribavirin versus Interferon alfa-2b + Ribavirin
IDEAL Study: Conclusions

**Interpretation**: “In patients with chronic hepatitis C, the most effective therapy is the combination of peginterferon alfa-2b 1.5 μg/kg per week plus ribavirin. The benefit is mostly achieved in patients with HCV genotype 1 infections.”

Phase 3

Treatment Naïve, Chronic HCV

Peginterferon alfa-2b + Ribavirin in GT 1-6
(Flat versus Weight-Based Ribavirin Dosing)

WINR Study

Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose)
WIN-R Study: Design

- **Study**
  - Prospective, randomized, open-label trial

- **Subjects**
  - N = 5027 with chronic hepatitis C (4913 analyzed)
  - Treatment naïve adult patients (Age 18-70)

- **Treatment Regimens**
  - Peginterferon alfa-2b: 1.5 µg/kg/wk + Wt-based* Ribavirin: 800-1400 mg/d
  - Peginterferon alfa-2b: 1.5 µg/kg/wk + Flat-dose Ribavirin: 800 mg/d

- **Treatment Duration**
  - Genotypes 1,4,5,6: duration of 48 weeks
  - Genotypes 2,3: duration of 24 or 48 weeks

- **Primary Endpoint**
  - Undetectable serum HCV RNA at end of treatment (ETR)
  - Undetectable serum HCV RNA 24 weeks after cessation of treatment (SVR)

*Weight-based ribavirin dosing: < 65 kg: 800 mg/d; 65-85 kg: 1000 mg/d; >85-105 kg: 1200 mg/d; >105 kg: 1400 mg/d

Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose) WIN-R Study: Design

Week 0

PEG + Ribavirin (weight-based) (n = 2111)

Week 24

PEG + Ribavirin (flat dose) (n = 2144)

Week 48

SVR24

Week 72

GT 1-6

PEG + Ribavirin (weight-based) (n = 333)

Drug Dosing

Peginterferon alfa-2b: 180 μg once weekly
Weight-based Ribavirin (in 2 divided doses):
- 800 mg/d if < 65 kg; 1000 mg/d if 65-85 kg; 1200 mg/d if >85-105 kg; 1400 mg/d if >105 kg
Flat-dose Ribavirin (in 2 divided doses): 800 mg/day

GT 2, 3

PEG + Ribavirin (flat dose) (n = 335)

SVR24

Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose) WIN-R Study: Results

SVR 24, by Genotype and Treatment Regimen

Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose) WIN-R Study: Results

All Treated: SVR24 by Weight Distribution

Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose) WIN-R Study: Results

Sustained Virologic Response (SVR) by Weight Distribution

African American Genotype 1

<table>
<thead>
<tr>
<th>Weight Distribution</th>
<th>SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight-Based Ribavirin</td>
<td>13.1, 22.2, 31.3</td>
</tr>
<tr>
<td>Flat-Dose Ribavirin</td>
<td>11.7, 9.9, 6.7</td>
</tr>
</tbody>
</table>

Peginterferon alfa-2b (PegIntron)
Background and Dosing
**Conclusion**: “Peginterferon alfa-2b plus weight-based ribavirin is more effective than flat-dose ribavirin, particularly in genotype 1 patients, providing equivalent efficacy across all weight groups. Ribavirin 1400 mg/day is appropriate for patients 105 to 125 kg. For genotype 2/3 patients, 24 weeks of treatment with flat-dose ribavirin is adequate; no evidence of additional benefit of extending treatment to 48 weeks was demonstrated.”

Treatment Naïve, Chronic HCV

Peginterferon alfa-2b + Weight-based Ribavirin in HCV GT 2,3

Peginterferon alfa-2b + Ribavirin for GT 2 or 3
Study Design

- **Study**
  - Single arm, open-label, historical-control, phase 4 study
  - Conducted in 39 centers in Europe

- **Subjects**
  - N = 224 with chronic hepatitis C enrolled (223 treated)
  - Treatment naïve adult patients with genotype 2 or 3 HCV

- **Regimens**
  - Peginterferon alfa-2b: 1.5 µg/kg/wk + Ribavirin*: 800-1400 mg/d x 24 wks

- **Primary Endpoint**
  - Undetectable serum HCV RNA at end of treatment (ETR)
  - Undetectable serum HCV RNA 24 wks after cessation of treatment (SVR)

*Ribavirin dosing: <65 kg = 800 mg/d; 65-85 kg = 1000 mg/d; >85-105 kg = 1200 mg/d; >105 kg = 1400 mg/d

Peginterferon alfa-2b + RBV for 12 or 24 Weeks in GT 2 or 3

Treatment Duration and Ribavirin Dose

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>24</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 224</td>
<td>Peginterferon alfa-2a + Ribavirin</td>
<td>SVR24</td>
<td></td>
</tr>
</tbody>
</table>

Drug Dosing
- Peginterferon alfa-2b: 1.5 μg/kg 1x/week
- Ribavirin (divided bid): 800-1400 mg/day
- Ribavirin dosing: <65 kg = 800 mg/d; 65-85 kg = 1000 mg/d; >85-105 kg = 1200 mg/d; >105 kg = 1400 mg/d

Peginterferon alfa-2b + Ribavirin for GT 2 or 3

Results

SVR24 Rates, by Genotype

- **All**: 81% (182/224)
- **Genotype 2**: 93% (39/42)
- **Genotype 3**: 79% (143/182)

**Conclusions**: “Treatment for 24 weeks with peginterferon alfa-2b and ribavirin is sufficient in HCV 2 or 3 infected patients. The lower SVR in patients infected with HCV-3 compared with HCV-2 infected patients may be related to higher levels of steatosis in this population.”

Treatment Naïve, Chronic HCV

Peginterferon alfa-2b + Ribavirin for 12 or 24 Weeks in GT 2,3

Peginterferon alfa-2b + RBV for 12 or 24 Weeks in GT 2 or 3 Study Design

- **Study**
  - Randomized, open-label trial
  - Conducted in 12 centers in Italy

- **Subjects**
  - N = 283 with chronic hepatitis C
  - Treatment naïve adult patients
  - Genotype 2 or 3

- **Regimens**
  - Peginterferon alfa-2b: 1.0 μg/kg/wk + Ribavirin: 1000-1200 mg/d x 24 wks
  - Peginterferon alfa-2b: 1.0 μg/kg/wk + Ribavirin: 1000-1200 mg/d x 12 or 24 wks*

- **Primary Endpoint**
  - Undetectable serum HCV RNA at end of treatment (ETR)
  - Undetectable serum HCV RNA 24 wks after cessation of treatment (SVR)

*Duration based on whether week 4 HCV RNA negative (12 weeks) or positive (24 weeks)

Peginterferon alfa-2b + RBV for 12 or 24 Weeks in GT 2 or 3
Treatment Duration and Ribavirin Dose

- **Week 0**: Standard: All received 24 week of treatment (N = 70)
  - Peginterferon alfa-2b + Ribavirin
  - SVR24

- **Variable: Duration based on Week 4 HCV RNA (negative = 12 week Rx; positive = 24 week Rx)**
  - N = 76
    - Peginterferon alfa-2b + Ribavirin
    - SVR24
  - N = 132
    - Peginterferon alfa-2b + Ribavirin
    - SVR24

**Drug Dosing**
- Peginterferon alfa-2b: 1.5 µg/kg 1x/week
- Ribavirin (divided bid): <75 kg (1000 mg/day); ≥75 kg (1200 mg/day)

Peginterferon alfa-2b + RBV for 12 or 24 Weeks in GT 2 or 3 Treatment Duration and Ribavirin Dose

SVR24 Rates, by Regimen

<table>
<thead>
<tr>
<th></th>
<th>Standard 24-Weeks</th>
<th>Variable 12-Weeks</th>
<th>Variable 24-Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>53/70</td>
<td>113/133</td>
<td>51/80</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>40/53</td>
<td>89/102</td>
<td>51/80</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>13/17</td>
<td>24/31</td>
<td>9/22</td>
</tr>
</tbody>
</table>

Peginterferon alfa-2b (PegIntron) Summary

- **Approval Status:** FDA approved in 2001
- **Indications:**
  - In combination with ribavirin for all genotypes
  - In combination with ribavirin plus protease inhibitor for GT1
- **Class & Mechanism**
  - Complex mechanism based on altering immune response to HCV infection
- **Dosing:**
  - 1.5 mcg/kg subcutaneously once per week
  - Duration dependent on genotype and remaining components of regimen
- **Adverse Effects (AE)**
  - Extensive adverse effects
  - Influenza-like symptoms
  - Depression
  - Hematologic (leukopenia and thrombocytopenia)
  - Thyroid dysfunction

Source: Peginterferon alfa-2b (PegIntron) Prescribing Information. Merck & Co.
Conclusions: “A shorter course of therapy over 12 weeks with peginterferon alfa-2b and ribavirin is as effective as a 24-week course for patients with HCV genotype 2 or 3 who have a response to treatment at 4 weeks.”

Treatment Naïve, Chronic HCV

Peginterferon alfa-2b + RBV vs. Peginterferon alfa-2a + RBV
IDEAL STUDY

Peginterferon alfa-2b + Ribavirin vs Peginterferon alfa-2a + Ribavirin

IDEAL Study: Design

• Study
  - Randomized comparative trial
  - 118 centers in United States

• Subjects
  - N = 3070 with chronic hepatitis C
  - All genotype 1 (other genotypes excluded)
  - Treatment naïve
  - Subjects were 18 years of age or older

• Regimens (Ribavirin Dosed by Weight)
  - Peginterferon alfa-2b: 1.5 μg/kg 1x/week + Ribavirin 800-1400 mg/day*
  - Peginterferon alfa-2b: 1.0 μg/kg 1x/week + Ribavirin 800-1400 mg/day*
  - Peginterferon alfa-2a: 180 μg 1x/week + Ribavirin 1000-1200 mg/day^*

• Primary Endpoint (Sustained Virologic Response [SVR])
  - SVR = Undetectable serum HCV RNA 24 weeks after 48-week treatments

*Ribavirin dosing: 40-65 kg: 800 mg/d; >65-85 kg: 1000 mg/d; >85-105 kg: 1200 mg/d; >105-120 kg: 1400 mg/d
^Ribavirin dosing: < 75 kg: 1000 mg/d; ≥75 kg: 1200 mg/d

Peginterferon alfa-2b + Ribavirin vs Peginterferon alfa-2a + Ribavirin

IDEAL Study: Design

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard-Dose Peginterferon alfa-2b + Ribavirin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 1019</td>
<td></td>
<td></td>
<td>SVR24</td>
</tr>
<tr>
<td>Peginterferon alfa-2b: 1.5 µg/kg 1x/week + Ribavirin: 800-1400 mg/d (by weight)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Low-Dose Peginterferon alfa-2b + Ribavirin</strong></td>
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<tr>
<td>N = 1016</td>
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<td>SVR24</td>
</tr>
<tr>
<td>Peginterferon alfa-2b: 1.0 µg/kg 1x/week + Ribavirin: 800-1400 mg/d (by weight)</td>
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<tr>
<td><strong>Peginterferon alfa-2a + Ribavirin</strong></td>
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<tr>
<td>N = 1035</td>
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<td>SVR24</td>
</tr>
<tr>
<td>Peginterferon alfa-2a: 180 µg 1x/week + Ribavirin: 1000-1200 mg/d (by weight)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Peginterferon alfa-2b + Ribavirin vs Peginterferon alfa-2a + Ribavirin
IDEAL Study: Results

IDEAL Study: Virologic Responses by Treatment Regimen

Peginterferon alfa-2b + Ribavirin vs Interferon alfa-2a + Ribavirin

IDEAL Study: Results

IDEAL Study: Serious Adverse Event Rates

**Conclusions:** “In patients infected with HCV genotype 1, the rates of sustained virologic response and tolerability did not differ significantly between the two available peginterferon-ribavirin regimens or between the two doses of peginterferon alfa-2b.”

Phase 3

Treatment Naïve, Chronic HCV and HIV

Peginterferon alfa-2b + RBV *versus* Interferon alfa-2b

**RIBAVIC STUDY**

Peginterferon + RBV versus Interferon + RBV in HCV & HIV
RIBAVIC Study: Design

• Study
  - Randomized, phase 3, open-label, parallel group trial
  - Conducted at 71 French centers

• Subjects
  - N = 412 chronically infected with both HCV and HIV
  - Treatment naïve; 48% genotype 1
  - CD4 >200 cells/mm³

• Regimens (48 Week Treatment)
  - Peginterferon alfa-2b 1.5 μg 1x/week + Ribavirin 800 mg/day
  - Interferon alfa-2b: 3 million IU 3x/week + Ribavirin 800 mg/day

• Primary Endpoint
  - Undetectable serum HCV RNA 24 weeks after stopping treatment

Peginterferon + RBV versus Interferon + RBV in HCV & HIV

RIBAVIC Study: Design

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 205</td>
<td>Peginterferon alfa-2b + Ribavirin</td>
<td>SVR24</td>
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</tr>
<tr>
<td>N = 207</td>
<td>Interferon alfa-2b + Ribavirin</td>
<td>SVR24</td>
<td></td>
</tr>
</tbody>
</table>

**Drug Dosing**
- Peginterferon alfa-2b: 1.5 μg/kg 1x/week
- Standard Interferon alfa-2b 3 million units 3x/week
- Ribavirin (divided bid): 800 mg/day

Interferon alfa engages receptors on the surface of the hepatocyte, initiating intracellular signal transduction that prompts the transcription of multiple interferon-stimulated genes (ISGs). These ISGs encode proteins that can interfere at various stages of the hepatitis C viral life cycle.

Peginterferon + RBV versus Interferon + RBV in HCV & HIV

RIBAVIC Study: Design

RIBAVIC Study: SVR24 by Treatment Regimen and Genotype

Conclusion: “In combination with ribavirin, treatment with peginterferon alfa-2b is more effective than standard interferon alfa-2b for HCV infection in HIV-infected patients.”

Treatment Naïve, Chronic HCV

Peginterferon alfa-2b + Ribavirin in Blacks & Non-Hispanic Whites

Peginterferon alfa-2b + Ribavirin in Blacks & Non-Hispanic Whites

Design

• Study
  - Prospective, multicenter, phase 3 trial
  - 16 centers in Southeastern United States

• Subjects
  - N = 200 adults with chronic HCV (100 blacks and 100 non-Hispanic whites)
  - Treatment naïve
  - HCV genotype (98% with genotype 1)

• Regimens (Ribavirin Dosed by Weight)
  - Peginterferon alfa-2b: 1.5 μg/kg 1x/week x 48 weeks +
    Ribavirin 1000 mg/day for weeks 1-12, then 800 mg/day for weeks 13-48

• Primary Endpoint (Sustained Virologic Response [SVR])
  - SVR = Undetectable serum HCV RNA 24 weeks after 48-week treatments

### Peginterferon alfa-2b + Ribavirin in Blacks and Non-Hispanic Whites

#### Results

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>48</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>100</td>
<td></td>
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</tr>
<tr>
<td>Peginterferon alfa-2b + Ribavirin</td>
<td>Blacks</td>
<td>SVR24</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peginterferon alfa-2b + Ribavirin</td>
<td>Non-Hispanic Whites</td>
<td>SVR24</td>
<td></td>
</tr>
</tbody>
</table>

### Drug Dosing

Peginterferon alfa-2b: 1.5 μg/kg 1x/week
Ribavirin (divided bid): 1000 mg/day x weeks 1-12, then 800 mg/day for weeks 13-48

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Peginterferon alfa-2b + Ribavirin in Blacks and Non-Hispanic Whites

Results

Virologic Responses by Race

**Conclusions**: “Black patients with chronic hepatitis C have a lower rate of response to treatment with peginterferon alfa-2b and ribavirin than non-Hispanic white patients, a difference that is not explained by differences in the viral genotype.”

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.
Peginterferon alfa-2b (*PegIntron*)
Contraindications

- Known hypersensitivity reaction
- Autoimmune hepatitis
- Hepatic decompensation (Child-Pugh score > 6) in cirrhotic patients
- Additional contraindications when used with ribavirin
  - Pregnant women and men whose female partners are pregnant
  - Hemoglobinopathies
  - Coadministration with didanosine

Source: Peginterferon alfa-2b (*PegIntron*) Prescribing Information. Merck & Co.
# Peginterferon alfa-2b Hematologic Dose Modification Guidelines for Adults

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Value</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>1.0 to &lt;1.5 $\times 10^9$/L</td>
<td>Reduce dose*</td>
</tr>
<tr>
<td></td>
<td>&lt;1.0 $\times 10^9$/L</td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>0.5 to &lt;0.75 $\times 10^9$/L</td>
<td>Reduce dose*</td>
</tr>
<tr>
<td></td>
<td>&lt;0.5 $\times 10^9$/L</td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td>Platelets</td>
<td>25 to &lt;50 $\times 10^9$/L</td>
<td>Reduce dose*</td>
</tr>
<tr>
<td></td>
<td>&lt; 25 $\times 10^9$/L</td>
<td>Discontinue treatment</td>
</tr>
</tbody>
</table>

*Adult patients on combination therapy: 1st dose reduction is to 1 mcg/kg/week. If needed, 2nd dose reduction is to 0.5 mcg/kg/week.

Source: Peginterferon alfa-2b (PegIntron) Prescribing Information. Merck & Co.
## Peginterferon alfa-2b Dose Modification Guidelines for Adults with Depression

<table>
<thead>
<tr>
<th>Depression Severity</th>
<th>Initial Management (4-8 weeks)</th>
<th>Depression Status</th>
<th>Worsens</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Dose Modification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>No change</td>
<td>Remains Stable</td>
<td>(See Moderate or Severe depression)</td>
</tr>
<tr>
<td></td>
<td>Evaluate once weekly by visit and/or phone</td>
<td>Improves</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Adjust dose. With combination therapy: 1st dose reduction is to 1 mcg/kg/week, 2nd dose reduction (if needed) is to 0.5 mcg/kg/week.</td>
<td>Consider psychiatric Consultation. Continue reduced dosing</td>
<td>Psychiatric therapy necessary</td>
</tr>
<tr>
<td></td>
<td>Evaluate once weekly (office visit at least every other week)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Discontinue peginterferon alfa-2b permanently</td>
<td>Obtain immediate psychiatric consultation</td>
<td></td>
</tr>
</tbody>
</table>
Treatment Naïve, Chronic HCV

Peginterferon alfa-2b + Ribavirin

versus

Interferon alfa-2b + Ribavirin

Peginterferon alfa-2b + Ribavirin versus Interferon alfa-2b + Ribavirin

Study Design

• Study
  - Open-label, randomized controlled trial
  - 62 sites in Europe, North America, & Argentina

• Subjects
  - N = 1530 with chronic hepatitis C
  - Treatment naïve
  - Genotype 1: 68%; Genotype 2 or 3: 29%; Genotype 4,5, or 6: 3%
  - Serum ALT >34 IU/L for women, >43 IU/L for men

• Regimens
  - Higher Dose Peginterferon alfa-2b: 1.5 µg/kg 1x/week + ribavirin 800 mg/day
  - Lower Dose Peginterferon alfa-2b: 1.5 µg/kg 1x/week x 4 weeks then 0.5 µg/kg 1x/week + ribavirin 1000-1200 mg/day*
  - Standard interferon alfa-2b: 3 million U 3x/week + ribavirin 1000-1200 mg/day*

• Primary Endpoint (Sustained Virologic Response [SVR])
  - SVR = Undetectable serum HCV RNA 24 weeks after 48-week treatments

*Ribavirin dosing: <75 kg: 1000 mg/day; ≥75 kg: 1200 mg/day