Telaprevir (Incivek)

Prepared by: David Spach, MD & H. Nina Kim, MD
Last Updated: February 3, 2014
## Telaprevir
### Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Clinical Symptom with ≥ 5% Higher Frequency with Telaprevir</th>
<th>Telaprevir + PEG + RBV N = 1797</th>
<th>PEG + RBV N = 493</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash (any)</td>
<td>56%</td>
<td>34%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>56%</td>
<td>50%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>47%</td>
<td>28%</td>
</tr>
<tr>
<td>Nausea</td>
<td>39%</td>
<td>28%</td>
</tr>
<tr>
<td>Anemia</td>
<td>36%</td>
<td>17%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26%</td>
<td>17%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13%</td>
<td>8%</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>12%</td>
<td>3%</td>
</tr>
<tr>
<td>Anorectal Discomfort</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>Anal Pruritus</td>
<td>6%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Source: Telaprevir *(Incivek)* Prescribing Information and Vertex Pharmaceuticals.
Telaprevir
Mild Skin Rash

Source: Photograph Courtesy of John Scott, MD, University of Washington
Telaprevir
Mild Skin Rash

• **Assessment**
  - Localized rash and/or rash with limited distribution
  - With or without associated pruritus

• **Management**
  - Continue all medications for HCV therapy
  - Use good skin care practices
  - Consider oral antihistamine plus topical corticosteroid
  - Monitor and reassess if progression occurs*

---

*Stop telaprevir if becomes severe or systemic symptoms develop; OK to continue Peginterferon and Ribavirin, but if rash persists within 7 days of stopping Telaprevir, consider sequential or simultaneous discontinuation of Peginterferon and Ribavirin.

Source: Telaprevir (Incivek) Prescribing Information and Vertex Pharmaceuticals.
Telaprevir
Good Skin Care for Telaprevir-Associated Rash

- Apply skin moisturizers at least twice a day
- Avoid perfumes and other scented skin care products
- Use hypoallergenic products
- Keep hydrated
- Wear loose-fitted clothing
- Avoid scratching
- Use unscented and mild laundry detergent
- Avoid using dryer sheets with clothes in dryer
- Limit sun exposure and use sun screen when out in sun
- Avoid hot showers and hot baths
- Consider using a nonsoap cleanser
- Apply skin moisturizers after bathing (before drying off)

Source: Vertex Pharmaceuticals.
Telaprevir
Moderate Skin Rash

Source: Photograph Courtesy of John Scott, MD, University of Washington
Telaprevir
Moderate Skin Rash

• **Assessment**
  - Diffuse rash and/or rash with limited distribution
  - With or without superficial skin peeling, pruritus, or mucous membrane involvement with no ulceration

• **Management**
  - Continue all medications for HCV therapy
  - Use good skin care practices
  - Consider oral antihistamine plus topical corticosteroid
  - Monitor and reassess if progression occurs*

*Stop telaprevir if becomes severe or systemic symptoms develop; OK to continue Peginterferon and Ribavirin, but if does not improve within 7 days after stopping Telaprevir, consider sequential or simultaneous discontinuation of Peginterferon and Ribavirin

Source: Telaprevir (Incivek) Prescribing Information and Vertex Pharmaceuticals.
Telaprevir
Severe Skin Rash

Source: Photograph Courtesy of John Scott, MD, University of Washington
Telaprevir
Severe Skin Rash

• **Assessment**
  - Generalized rash with or without pruritus  
    *OR*
  - Rash with vesicles, bullae, or ulcerations (other than SJS)

• **Management**
  - Stop Telaprevir (do not restart)
  - May continue peginterferon plus ribavirin
  - Use good skin care practices
  - Consider oral antihistamine plus topical corticosteroid
  - Monitor and reassess*

*If rash does not improve within 7 days of stopping Telaprevir, consider sequential or simultaneous discontinuation of Peginterferon and Ribavirin

Source: Telaprevir (*Incivek*) Prescribing Information. Vertex Pharmaceuticals.
Telaprevir
Serious Skin Rash (DRESS or SJS)

• **Assessment**
  - **Stevens-Johnson Syndrome (SJS):** Generalized rash with symptoms that may include fever, target lesions, and mucosal erosions or ulcerations
  
  **OR**

  - **Drug Rash with Eosinophilia and Systemic Symptoms (DRESS):** Presenting signs and systemic symptoms may include rash, fever, facial edema, and evidence of internal organ involvement (e.g., hepatitis, nephritis). May occur with or without eosinophilia.

• **Management**
  - Stop all drugs immediately
  - Promptly refer for urgent medical care
  - Do NOT restart telaprevir at any time in future

Source: Telaprevir (*Incivek*) Prescribing Information and Vertex Pharmaceuticals.
Telaprevir (Incivek)
Drug Interactions
TELAPREVIR (INCIVEK)
Background and Dosing
# Telaprevir

Drug-Drug Interactions: Contraindicated Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Medication and Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-1 Adrenoceptor Antagonist</td>
<td>Alfuzosin</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, phenobarbital, phenytoin</td>
</tr>
<tr>
<td>Antimycobacterials</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Ergot Derivatives</td>
<td>Dihydroergotamine, ergonovine, ergotamine, methylergonovine</td>
</tr>
<tr>
<td>Gastrointestinal Motility Agent</td>
<td>Cisapride</td>
</tr>
<tr>
<td>Herbal Products</td>
<td>St John’s wort (<em>Hypericum perforatum</em>)</td>
</tr>
<tr>
<td>HMG CoA-Reductase Inhibitors</td>
<td>Lovastatin, simvastatin</td>
</tr>
<tr>
<td>Neuroleptic</td>
<td>Pimozide</td>
</tr>
<tr>
<td>PDE5 Inhibitor</td>
<td>Sildenafil or Tadalafil (dose levels for treatment of pulmonary hypertension)</td>
</tr>
<tr>
<td>Sedatives/hypnotics</td>
<td>Orally administered midazolam, triazolam</td>
</tr>
</tbody>
</table>

Source: Vertex Pharmaceuticals.
Telaprevir (Incivek) Resistance
Viral Breakthrough & Telaprevir Resistance

- 14 (8.7%) viral breakthroughs were observed
- Half of these occurred before or at week 4
- Viral breakthroughs were more frequent in patients with HCV genotype 1a (11/14) than 1b (3/14).
- 11 (79%) of 14 patients with viral breakthrough had variants harboring mutations (V36M, V36M/R155K, or A156S) associated with decreased susceptibility to telaprevir
- No differences in number and type of mutations were observed across telaprevir arms
Telaprevir for Chronic HCV Infection
Resistance Among those who did not Achieve SVR

- Treatment-emergent resistance mutations occurred in 62% of subjects from ADVANCE, ILLUMINATE, and REALIZE trials who did not achieve SVR.
- Resistance mutations occurred in nearly 100% of subjects who failed during initial 12 weeks of triple therapy, and in most who failed after week 12 or who relapsed.
- On-treatment virologic failure was more frequent in subjects with genotype 1A compared with 1B.
- Most common mutations: R155K/T, V36M, and V36M + R155K/T

Source: Vertex Pharmaceuticals.
Telaprevir for Chronic HCV Infection
Resistance Among those who did not achieve SVR24

Treatment-emergent resistance mutations in 525 subjects from ADVANCE, ILLUMINATE, and REALIZE trials who did not achieve SVR.

Source: Vertex Pharmaceuticals.
<table>
<thead>
<tr>
<th>Mutation</th>
<th>Telaprevir</th>
<th>Boceprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>V36A/M</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>T54S/A</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>V55A</td>
<td>In vitro</td>
<td>+</td>
</tr>
<tr>
<td>Q80R/K</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>R155K/T/Q</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>A156S</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>A156T/V</td>
<td>+</td>
<td>In vitro</td>
</tr>
<tr>
<td>D168A/V/T/H</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>V170A/T</td>
<td>In vitro</td>
<td>+</td>
</tr>
</tbody>
</table>

Telaprevir (Incivek)

Treatment Data
Telaprevir: Summary of Key Studies

- **Telaprevir Studies in Treatment-Naïve**
  - PROVE-1: Phase 2b
  - PROVE-2: Phase 2b
  - ADVANCE (Study 108): Phase 3
  - ILLUMINATE (Study 111): Phase 3
  - OPTIMIZE (Study C211): Phase 3

- **Telaprevir Studies in Previously Treated**
  - PROVE-3: Phase 2b
  - REALIZE (Study C216): Phase 3
Telaprevir + Peginterferon + Ribavirin for GT1
PROVE1 Study

Telaprevir for Treatment-Naïve HCV Genotype 1

PROVE1: Study Feature

**PROVE1: Study Features**
- N = 236 randomized
- Randomized, double-blind, placebo-controlled
- Phase 2b trial
- Chronic HCV and treatment naïve
- All with Genotype 1
- Age = 18-65; HIV negative; HBsAg negative
- Setting: 37 centers in United States
- Randomized to one of four treatment groups

**Drug Dosing**
Telaprevir = 1250 mg on day 1, then 750 mg every 8 hours
Peginterferon alfa-2a = 180 µg weekly
Ribavirin = 1000 mg/day for wt < 75 kg; 1200 mg/day for wt ≥ 75 kg

Telaprevir (*Incivek*)

- **Approval**: FDA Approved May 23, 2011

- **Indications**
  - In combination with peginterferon-alfa and ribavirin (PR)
  - Chronic HCV genotype 1 infection
  - Adults ($\geq$ 18 years of age) with compensated liver disease, including cirrhosis
  - Treatment-naïve or prior interferon-based treatment

- **Dosing**
  - 1125 mg (three 375-mg tablets) twice daily (10-14 hours apart)
  - Take with food (not low fat)
  - Telaprevir + PR for 12 weeks, followed by 12 or 36 weeks PR alone
  - Patients with cirrhosis may benefit from total of 48 weeks of treatment

- **Adverse Effects**
  - Rash, anemia, nausea, fatigue, headache, diarrhea, pruritus, and anal or rectal irritation and pain

Source: Telaprevir (*Incivek*) Prescribing Information. Vertex Pharmaceuticals.
Telaprevir for Treatment-Naïve HCV Genotype 1

PROVE1 Study: Treatment Regimens

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>T12 PR12</td>
<td>N=17</td>
<td>Telaprevir</td>
<td>PEG + RBV</td>
<td></td>
</tr>
<tr>
<td>T12 PR24</td>
<td>N=79</td>
<td>Telaprevir</td>
<td>PEG + RBV</td>
<td></td>
</tr>
<tr>
<td>T12 PR48</td>
<td>N=79</td>
<td>Telaprevir</td>
<td>PEG + RBV</td>
<td></td>
</tr>
<tr>
<td>PR48</td>
<td>N=75</td>
<td>Placebo</td>
<td>PEG + RBV</td>
<td></td>
</tr>
</tbody>
</table>

Telaprevir for Treatment-Naïve HCV Genotype 1
PROVE1 Study: Results

PROVE1: SVR24 by Regimen

- **T12/PR12**: 35%
- **T12/PR24**: 61%
- **T12/PR48**: 67%
- **PR48**: 41%

Sustained Virologic Response (SVR) = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

Telaprevir for Treatment-Naïve HCV Genotype 1
PROVE1 Study: Results

PROVE1: Percentage of Patients with Relapse by Regimen

T12/PR12: 33%
T12/PR24: 2%
T12/PR48: 6%
PR48: 23%

T = Telaprevir; PR = Peginterferon + Ribavirin

Telaprevir for Treatment-Naïve HCV Genotype 1
PROVE1 Study: Results

PROVE1: Patients with SVR24 and Relapse by Regimen

SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

Conclusions: “Treatment with a telaprevir-based regimen significantly improved sustained virologic response rates in patients with genotype 1 HCV, albeit with higher rates of discontinuation because of adverse events.”

Treatment Naïve

Telaprevir in Treatment Naïve GT-1
PROVE2 Study

### PROVE2: Study Design

**PROVE2: Study Features**

- N = 334 enrolled and 323 received at least 1 dose
- Randomized, partially double-blind trial, placebo-controlled
- Phase 2b trial
- Chronic HCV and treatment naïve
- All with Genotype 1; 84% with HCV RNA ≥ 800,000 IU/ml
- Age = 18-65 and HIV-negative
- Setting: 28 sites in Europe
- Randomized to one of 4 arms

### Drug Dosing

Telaprevir = 1250 mg on day 1, then 750 mg every 8 hours

Peginterferon alfa-2a = 180 µg weekly

Ribavirin = 1000 mg/day for wt < 75 kg; 1200 mg/day for wt ≥ 75 kg

### Telaprevir for Treatment-Naïve HCV Genotype 1 PROVE2 Study: Treatment Regimens

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>T12</td>
<td></td>
<td></td>
<td>Telaprevir</td>
<td></td>
</tr>
<tr>
<td>PR12</td>
<td>Telaprevir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PEG + RBV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=82</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T12</td>
<td>Telaprevir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR24</td>
<td></td>
<td>PEG + RBV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=81</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T12</td>
<td>Telaprevir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P12</td>
<td></td>
<td>PEG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=78</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR48</td>
<td>Placebo</td>
<td></td>
<td>PEG + RBV</td>
<td></td>
</tr>
<tr>
<td>N=82</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Telaprevir for Treatment-Naïve HCV Genotype 1
PROVE2 Study: Results

PROVE2: SVR24 by Regimen

SVR = Sustained Virologic Response; T = Telaprevir; P = Peginterferon; PR = Peginterferon + Ribavirin

Telaprevir for Treatment-Naïve HCV Genotype 1 
PROVE2 Study: Results

PROVE2: Patients with Relapse by Regimen

- T12/PR12: 30
- T12/PR24: 14
- T12/P12: 48
- PR 48: 22

T = Telaprevir; P = Peginterferon; PR = Peginterferon + Ribavirin

HCV Protein Processing
Role of NS3/4A Serine Protease

Polyprotein Precursor

Signal Peptidase NS2/3 Protease NS3/4A Serine Protease

C E1 E2 p7 NS2 NS3 A NS4 A NS5 A B B

Proteins
C E1 E2 p7 NS2 NS3 NS4 A NS4B NS5A NS5B

Hepatitis web study
Telaprevir for Treatment-Naïve HCV Genotype 1
PROVE2 Study: Results

PROVE2: Patients with SVR and Relapse by Regimen

- T12/PR12: 60 SVR, 30 Relapse
- T12/PR24: 69 SVR, 14 Relapse
- T12/P12: 36 SVR, 48 Relapse
- PR 48: 46 SVR, 22 Relapse

SVR = Sustained Virologic Response; T = Telaprevir; P = Peginterferon; PR = Peginterferon + Ribavirin

Telaprevir for Treatment-Naïve HCV Genotype 1

PROVE2 Study: Results

PROVE2: Severe (Grade 3) Adverse Events by Regimen

- T12/PR12
- T12/PR24
- T12/P12
- PR 48

**Patients (%)**

<table>
<thead>
<tr>
<th>Any</th>
<th>Rash</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>3</td>
</tr>
</tbody>
</table>

T = Telaprevir; P = Peginterferon; PR = Peginterferon + Ribavirin

**Conclusions**: “In this phase 2 study of patients infected with HCV genotype 1 who had not been treated previously, one of the three telaprevir groups had a significantly higher rate of sustained virologic response than that with standard therapy. Response rates were lowest with the regimen that did not include ribavirin.”

Telaprevir in Treatment Naïve GT-1 ADVANCE (Study 108)

Telaprevir for Treatment-Naïve HCV Genotype 1

ADVANCE: Study Design

ADVANCE: Study Features

- N = 1,088 enrolled
- Randomized, double-blind, placebo-controlled, Phase 3 trial
- Genotype 1 HCV and treatment naïve
- 77% with HCV RNA ≥ 800,000 IU/ml
- Randomized to one of 3 arms
- RVR = HCV RNA undetectable at week 4
- eRVR = HCV RNA undetectable at weeks 4 & 12
- Erythroid stimulating agents not allowed
- Telaprevir-treated patients without eRVR received PR up to week 48

Drug Dosing

- Telaprevir = 750 mg every 8 hours
- Peginterferon alfa-2a = 180 µg weekly
- Ribavirin = 1000 mg/day for wt < 75 kg; 1200 mg/day for wt ≥ 75 kg

Telaprevir for Treatment-Naïve HCV Genotype 1 ADVANCE Study: Treatment Regimens

**Week 0**: T8 PR 24 or 48, T12 PR 24 or 48, PR48

**Week 8**: Telaprevir + PEG + RBV, Telaprevir + PEG + RBV, Placebo + PEG + RBV

**Week 12**: Telaprevir + PEG + RBV, Telaprevir + PEG + RBV, Placebo + PEG + RBV

**Week 24**: eRVR: PEG + RBV, eRVR: PEG + RBV, PEG + RBV

**Week 48**: No eRVR: PEG + RBV, No eRVR: PEG + RBV, PEG + RBV

Telaprevir for Treatment-Naïve HCV Genotype 1

ADVANCE Study: Results

ADVANCE: SVR24 by Regimen

Patients with SVR (%)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients with SVR (%)</th>
<th>Total Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>T8/PR24 or 48</td>
<td>69</td>
<td>250/364</td>
</tr>
<tr>
<td>T12/PR24 or 48</td>
<td>75</td>
<td>271/363</td>
</tr>
<tr>
<td>PR 48</td>
<td>44</td>
<td>158/361</td>
</tr>
</tbody>
</table>

SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

Telaprevir for Treatment-Naïve HCV Genotype 1
ADVANCE Study: RVR and eRVR Rates

ADVANCE: Patients with RVR and eRVR

<table>
<thead>
<tr>
<th></th>
<th>RVR (week 4)</th>
<th>eRVR (week 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T8/PR24 or 48</td>
<td>66/364</td>
<td>57/364</td>
</tr>
<tr>
<td>T12/PR24 or 48</td>
<td>68/363</td>
<td>58/363</td>
</tr>
<tr>
<td>PR48</td>
<td>34/361</td>
<td>29/361</td>
</tr>
</tbody>
</table>

T = Telaprevir; PR = Peginterferon + Ribavirin; RVR = rapid virologic response; eRVR = extended rapid virologic response

Telaprevir for Treatment-Naïve HCV Genotype 1
ADVANCE Study: Results According to eRVR

ADVANCE: SVR24 by eRVR Status

- **With eRVR**
  - T8/PR24 or 48: 171/207 (83%)
  - T12/PR24 or 48: 189/212 (89%)
  - PR48: 28/29 (97%)

- **Without eRVR**
  - T8/PR24 or 48: 79/157 (50%)
  - T12/PR24 or 48: 82/151 (54%)
  - PR48: 130/342 (39%)

T = Telaprevir; PR = Peginterferon + Ribavirin; SVR = Sustained Virologic Response
eRVR = extended rapid virologic response (undetectable HCV RNA at weeks 4 and 12)

Telaprevir for Treatment-Naïve HCV Genotype 1
ADVANCE Study: Results According to eRVR

ADVANCE: SVR24 by eRVR Status

<table>
<thead>
<tr>
<th>Condition</th>
<th>With eRVR</th>
<th>Without eRVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>T8/PR24 or 48</td>
<td>83/207</td>
<td>50/157</td>
</tr>
<tr>
<td>T12/PR24 or 48</td>
<td>89/212</td>
<td>54/151</td>
</tr>
<tr>
<td>PR 48</td>
<td>97/29</td>
<td>39/342</td>
</tr>
</tbody>
</table>

SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin; eRVR = extended rapid virologic response (undetectable HCV RNA at weeks 4 and 12)

Telaprevir: Mechanism of Action
NS3/4A Serine Protease Inhibition
Telaprevir for Treatment-Naïve HCV Genotype 1
ADVANCE Study: Results According to Race

ADVANCE: SVR24 by Race

<table>
<thead>
<tr>
<th>Race</th>
<th>T8/PR 24 or 48</th>
<th>T12/PR24 or 48</th>
<th>PR48</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>70</td>
<td>75</td>
<td>46</td>
</tr>
<tr>
<td>Black</td>
<td>58</td>
<td>62</td>
<td>25</td>
</tr>
<tr>
<td>Hispanic</td>
<td>66</td>
<td>74</td>
<td>39</td>
</tr>
</tbody>
</table>

Patients with SVR (%)

SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

Telaprevir for Treatment-Naïve HCV Genotype 1
ADVANCE Study: Results by Fibrosis Stage

ADVANCE: SVR24 by Fibrosis Stage

Patients with SVR (%)

No or Minimal Fibrosis: 79/128, 81/134, 46/147
Portal Fibrosis: 69/151, 75/156, 48/141
Bridging Fibrosis: 58/59, 62/52, 33/52
Cirrhosis: 42/26, 62/21, 33/21

SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

Telaprevir for Treatment-Naïve HCV Genotype 1
ADVANCE Study: Adverse Effects

ADVANCE: Percentage of Patients with Anemia

Hemoglobin (Hb) Nadir Through Week 12

T = Telaprevir; PR = Peginterferon + Ribavirin

Telaprevir for Treatment-Naïve HCV Genotype 1
ADVANCE Study: Adverse Effects

ADVANCE: Percentage of Patients with Rash

T = Telaprevir; PR = Peginterferon + Ribavirin

Telaprevir for Treatment-Naïve HCV Genotype 1
SVR Rates by *IL28B* rs12979860 Genotype

ADVANCE: SVR24 by rs12979860 Genotype

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>T/T</th>
<th>C/T</th>
<th>C/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR48</td>
<td>6/26</td>
<td>25/80</td>
<td>35/55</td>
</tr>
<tr>
<td>T12/PR24 or 48</td>
<td>16/22</td>
<td>48/68</td>
<td>45/50</td>
</tr>
</tbody>
</table>

PR48 = Peginteron/Ribavirin x 48 weeks
PR/T12 = Peginteron/Ribavirin + Telaprevir x 12 weeks

Source: Telaprevir (*Incivek*) Prescribing Information. Vertex Pharmaceuticals.
Conclusions: “Telaprevir with peginterferon–ribavirin, as compared with peginterferon–ribavirin alone, was associated with significantly improved rates of sustained virologic response in patients with HCV genotype 1 infection who had not received previous treatment, with only 24 weeks of therapy administered in the majority of patients.”

Telaprevir in Treatment Naïve GT-1 ILLUMINATE (Study 111)

Telaprevir for Treatment-Naïve HCV Genotype 1

ILLUMINATE: Study Design

ILLUMINATE: Study Features

- Randomized, open label, Phase 3 trial
- Genotype 1 HCV and treatment naïve, with or without cirrhosis
- N = 540 enrolled
- RVR = HCV RNA undetectable at week 4
- eRVR = HCV RNA undetectable at weeks 4 & 12
- Erythroid stimulating agents not allowed
- All received telaprevir x 12 weeks
- Patients with eRVR randomized to PR for 24 or 48 weeks
- Patients without eRVR received PR x 48 weeks

Drug Dosing

Telaprevir = 750 mg every 8 hours
Peginterferon alfa-2a = 180 µg per week
Ribavirin = 1000 mg/day for wt < 75 kg; 1200 mg/day for wt ≥ 75 kg

Telaprevir for Treatment-Naïve HCV Genotype 1
ILLUMINATE Study: Design

Week 0  12  20  24  48

With eRVR

PR

Without eRVR

PR

T12 PR 24 or 48

Telaprevir

PEG + Ribavirin (PR)

eRVR (+) T12/PR24

eRVR (+) T12/PR48

eRVR (-) T12/PR48

T = Telaprevir
PR = Peginterferon + Ribavirin
eRVR = extended rapid virologic response (undetectable HCV RNA at weeks 4 and 12)

# Telaprevir Response Guided Therapy

## Treatment-Naïve and Prior Relapse Patients

<table>
<thead>
<tr>
<th>HCV RNA*</th>
<th>Regimen</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 4 &amp; 12: Undetectable</td>
<td>Telaprevir 12 weeks</td>
<td>24 Weeks</td>
</tr>
<tr>
<td></td>
<td>Peginterferon + Ribavirin 24 weeks</td>
<td></td>
</tr>
<tr>
<td>Weeks 4 and/or 12: Detectable at Low-level (\leq 1000) IU/ml</td>
<td>Telaprevir 12 weeks</td>
<td>48 Weeks</td>
</tr>
<tr>
<td></td>
<td>Peginterferon + Ribavirin 48 weeks</td>
<td></td>
</tr>
</tbody>
</table>

## Prior Partial and Null Responders

<table>
<thead>
<tr>
<th>All Patients</th>
<th>Telaprevir 12 weeks</th>
<th>48 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peginterferon + Ribavirin 48 weeks</td>
<td></td>
</tr>
</tbody>
</table>

*In clinical trials, HCV-RNA in plasma was measured using a COBAS® TaqMan® assay with a lower limit of quantification of 25 IU/mL and a limit of detection of 10 IU/mL.

*^Treatment-naïve patients with cirrhosis who have undetectable HCV RNA levels at weeks 4 and 12 may benefit from total treatment duration of 48 weeks.

Source: Telaprevir (Incivek) Prescribing Information. Vertex Pharmaceuticals.
Telaprevir for Treatment-Naïve HCV Genotype 1
ILLUMINATE Study: Results

ILLUMINATE: SVR 24 by Regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients with SVR (%)</th>
<th>Count (SVR/Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>72</td>
<td>388/540</td>
</tr>
<tr>
<td>eRVR (+) T12/PR24</td>
<td>92</td>
<td>149/162</td>
</tr>
<tr>
<td>eRVR (+) T12/PR48</td>
<td>88</td>
<td>140/160</td>
</tr>
<tr>
<td>eRVR (-) T12/PR48</td>
<td>64</td>
<td>76/118</td>
</tr>
</tbody>
</table>

SVR = Sustained virologic response; T = Telaprevir; PR = Peginterferon + Ribavirin
eRVR = extended rapid virologic response (undetectable HCV RNA at weeks 4 and 12)

Telaprevir for Treatment-Naïve HCV Genotype 1
ILLUMINATE Study: Key Findings

- 24 weeks of Peg-IFN non-inferior to 48 weeks in patients with eRVR
- Overall SVR 72%
- SVR in 60% of blacks
- SVR of 63% in patients with cirrhosis
- 65% of patients had eRVR
- 88-92% of those who achieved eRVR achieved SVR
- 7% stopped treatment early due to virologic failure
- 17% stopped early due to fatigue or anemia

**Conclusions**: “In this study, among patients with chronic HCV infection who had not received treatment previously, a regimen of peginterferon–ribavirin for 24 weeks, with telaprevir for the first 12 weeks, was noninferior to the same regimen for 48 weeks in patients with undetectable HCV RNA at weeks 4 and 12, with an extended rapid virologic response achieved in nearly two thirds of patients.”

Telaprevir BID versus q8 in Treatment Naïve GT-1
OPTIMIZE (Study C211)

# Twice Daily Telaprevir for Treatment-Naïve HCV Genotype 1

**OPTIMIZE: Study Design**

<table>
<thead>
<tr>
<th>Study Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 740 enrolled</td>
</tr>
<tr>
<td>Randomized, double-blind, placebo-controlled, Phase 3 trial</td>
</tr>
<tr>
<td>Genotype 1 HCV and treatment naïve</td>
</tr>
<tr>
<td>85% with HCV RNA ≥ 800,000 IU/ml</td>
</tr>
<tr>
<td>Randomized to one of 2 arms to compare bid and q8h telaprevir</td>
</tr>
<tr>
<td>RVR = HCV RNA undetectable (&lt;25 IU/ml) at week 4</td>
</tr>
<tr>
<td>All patients received telaprevir for 12 weeks (bid or q8h)</td>
</tr>
<tr>
<td>Patients with RVR received PR for 24 weeks</td>
</tr>
<tr>
<td>Patients without RVR received PR for 48 weeks</td>
</tr>
</tbody>
</table>

**Drug Dosing**

- Telaprevir = 1125 mg bid or 750 mg q8h
- Peginterferon alfa-2a = 180 µg weekly
- Ribavirin = 1000 mg/day for wt < 75 kg; 1200 mg/day for wt ≥ 75 kg

# Twice Daily Telaprevir for Treatment-Naïve HCV Genotype 1

**OPTIMIZE Study: Treatment Regimens**

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>T12 bid PR 24 or 48 (n = 369)</td>
<td>Telaprevir (bid)</td>
<td>PEG + RBV</td>
<td>If (-) RVR continue PEG + RBV</td>
<td></td>
</tr>
<tr>
<td>T12 q8h PR 24 or 48 (n = 371)</td>
<td>Telaprevir (q8h)</td>
<td>PEG + RBV</td>
<td>If (-) RVR continue PEG + RBV</td>
<td></td>
</tr>
</tbody>
</table>

RVR = week 4 HCV RNA undetectable
PEG = peginterferon; RBV = ribavirin
Therapy stopped if HCV RNA > 1000 IU/mL at week 4 or HCV RNA > 25 IU/mL at weeks 12, 24, 32, or 40

Twice Daily Telaprevir for Treatment-Naïve HCV Genotype 1

OPTIMIZE Study: Results

OPTIMIZE: SVR12 by Regimen

Patients with SVR 12 (%)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients with SVR12 (%)</th>
<th>Total Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir bid + PR</td>
<td>74</td>
<td>274/369</td>
</tr>
<tr>
<td>Telaprevir q8h + PR</td>
<td>73</td>
<td>270/371</td>
</tr>
</tbody>
</table>

SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

Twice Daily Telaprevir for Treatment-Naïve HCV Genotype 1 OPTIMIZE Study: Results

OPTIMIZE: SVR12 by Week 4 Virologic Response

RVR = rapid virologic response (undetectable HCV RNA at week 4)
Abbreviations: SVR = sustained virologic response; PR = peginterferon + ribavirin

Twice Daily Telaprevir for Treatment-Naïve HCV Genotype 1

OPTIMIZE Study: Results

OPTIMIZE: SVR12 by Genotype 1 Subtype

<table>
<thead>
<tr>
<th>Genotype 1a</th>
<th>Telaprevir bid + PR</th>
<th>Telaprevir q8h + PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%) with SVR12</td>
<td>70</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>146/210</td>
<td>145/209</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype 1b</th>
<th>Telaprevir bid + PR</th>
<th>Telaprevir q8h + PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%) with SVR12</td>
<td>80</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>126/157</td>
<td>123/160</td>
</tr>
</tbody>
</table>

Abbreviations: SVR = sustained virologic response; PR = peginterferon + ribavirin

Twice Daily Telaprevir for Treatment-Naïve HCV Genotype 1
OPTIMIZE Study: Results

OPTIMIZE: SVR12 by Host *IL28B* Genotype

<table>
<thead>
<tr>
<th>IL28B Genotype</th>
<th>Telaprevir bid + PR</th>
<th>Telaprevir q8h + PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>92/105</td>
<td>92/106</td>
</tr>
<tr>
<td>CT</td>
<td>67/139</td>
<td>68/141</td>
</tr>
<tr>
<td>TT</td>
<td>66/38</td>
<td>65/37</td>
</tr>
</tbody>
</table>

Abbreviations: SVR = sustained virologic response; PR = peginterferon + ribavirin

Telaprevir Response-Guided Therapy
Treatment Naïve and Prior Relapse Patients

Telaprevir: Response Guided Therapy (RGT) for Treatment Naïve and Prior Relapse Patients

RGT
- Telaprevir-12 wks
- Peginterferon + Ribavirin-24 wks
- Telaprevir-12 wks
- Peginterferon + Ribavirin-48 wks

HCV RNA IU/ml

Telaprevir: Response-Guided Therapy
Duration of therapy based on response at weeks 4 and 12

Treatment Week

-8 -4 0 4 8 12 16 20 24 28 32 36 40 44 48

Undetectable
Twice Daily Telaprevir for Treatment-Naïve HCV Genotype 1

OPTIMIZE Study: Results

OPTIMIZE: SVR12 by Fibrosis Stage

<table>
<thead>
<tr>
<th>Fibrosis Stage</th>
<th>Telaprevir bid + PR</th>
<th>Telaprevir q8h + PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No or Minimal Fibrosis</td>
<td>80/172</td>
<td>79/177</td>
</tr>
<tr>
<td>Portal Fibrosis</td>
<td>79/95</td>
<td>80/85</td>
</tr>
<tr>
<td>Bridging Fibrosis</td>
<td>67/48</td>
<td>64/59</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>54/54</td>
<td>49/49</td>
</tr>
</tbody>
</table>

Patients (%) with SVR 12

Abbreviations: SVR = sustained virologic response; PR = peginterferon + ribavirin

Conclusions: “Based on a phase 3 trial, telaprevir twice daily is noninferior to every 8 hours in producing SVR12, with similar levels of safety and tolerability. These results support use of telaprevir twice-daily in patients with chronic HCV genotype 1 infection, including those with cirrhosis.”

Telaprevir in Treatment Experienced GT-1
PROVE3

# Telaprevir for Treatment-Experienced HCV Genotype 1

## PROVE3 Study: Study Design

<table>
<thead>
<tr>
<th>PROVE3: Study Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, partially double-blind trial, placebo-controlled</td>
</tr>
<tr>
<td>Phase 2b trial</td>
</tr>
<tr>
<td>All with HCV and lack of SVR with Peginterferon + Ribavirin</td>
</tr>
<tr>
<td>Eligible if 18 to 70 years of age</td>
</tr>
<tr>
<td>All with Genotype 1; 92% with HCV RNA ≥ 800,000 IU/ml</td>
</tr>
<tr>
<td>N = 465 enrolled and 453 received at least 1 dose</td>
</tr>
<tr>
<td>Setting: 53 international sites (41 in US)</td>
</tr>
<tr>
<td>Randomized to one of 4 arms</td>
</tr>
</tbody>
</table>

## Drug Dosing

- Telaprevir = 1125 mg loading dose, then 750 mg every 8 hours
- Peginterferon alfa-2a = 180 µg weekly
- Ribavirin = 1000 mg/d for wt < 75 kg; 1200 mg/d for wt ≥ 75 kg

Telaprevir for Treatment-Experienced HCV Genotype 1
PROVE3 Study: Results

PROVE3: SVR24 by Regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients with SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T12/PR24</td>
<td>51</td>
</tr>
<tr>
<td>T24/PR48</td>
<td>53</td>
</tr>
<tr>
<td>T24/P24</td>
<td>24</td>
</tr>
<tr>
<td>PR 48</td>
<td>14</td>
</tr>
</tbody>
</table>

SVR = sustained virologic response; T = Telaprevir; P = Peginterferon; PR = Peginterferon + Ribavirin

Telaprevir for Treatment-Experienced HCV Genotype 1
PROVE3 Study: Results Based on Prior History

PROVE3: SVR24 by Prior Response Status

SVR = sustained virologic response; T = Telaprevir; P = Peginterferon; PR = Peginterferon + Ribavirin

Telaprevir for Treatment-Experienced HCV Genotype 1
PROVE3 Study: Results

PROVE3: Adverse Events

- **Any Rash-Related Event**
  - T12/PR24: 50%
  - T24/PR48: 60%
  - T24/P24: 41%
  - PR 48: 20%

- **Anemia**
  - T12/PR24: 26%
  - T24/PR48: 27%
  - T24/P24: 8%
  - PR 48: 8%

T = Telaprevir; P = Peginterferon; PR = Peginterferon + Ribavirin

Conclusions: “In HCV-infected patients in whom initial peginterferon alfa and ribavirin treatment failed, retreatment with telaprevir in combination with peginterferon alfa-2a and ribavirin was more effective than retreatment with peginterferon alfa-2a and ribavirin alone.”

Telaprevir in Treatment Experienced GT-1
REALIZE (Study 216)

## Telaprevir Treatment Futility Rules for All Patients

<table>
<thead>
<tr>
<th>Stopping Criteria*</th>
<th>Regimen and Treatment Duration (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Week 4 HCV RNA &gt; 1000 IU</td>
<td>Telaprevir</td>
</tr>
<tr>
<td>Week 12 HCV RNA &gt; 1000 IU</td>
<td>Telaprevir</td>
</tr>
<tr>
<td>Week 24 Detectable HCV RNA</td>
<td>Telaprevir</td>
</tr>
</tbody>
</table>

PR = Peginterferon + Ribavirin

*In clinical trials, HCV-RNA in plasma was measured using a COBAS® TaqMan® assay with a lower limit of quantification of 25 IU/mL and a limit of detection of 10 IU/mL.

Source: Telaprevir (Incivek) Prescribing Information. Vertex Pharmaceuticals.
# Telaprevir for Treatment-Experienced HCV Genotype 1

## REALIZE Study: Study Design

### REALIZE: Study Features

- Phase 3 trial
- Randomized, double-blind, placebo-controlled
- Eligible if 18 to 70 years of age
- All with genotype 1 chronic HCV infection
- Lack of SVR with prior peginterferon + ribavirin treatment
- N = 663 enrolled
- Setting: 100 international sites (most in Europe and US)
- Randomized to one of 3 arms (2:2:1 ratio)

### Drug Dosing

- Telaprevir = 750 mg q8h
- Peginterferon alfa-2a = 180 µg weekly
- Ribavirin = 1000 mg/day for wt < 75 kg; 1200 mg/day for wt ≥ 75 kg

---

Telaprevir for Treatment-Experienced HCV Genotype 1
REALIZE Study: Definitions for Prior Response

• **No Response**: Reduction of less than $2 \log_{10}$ in HCV RNA after 12 weeks of therapy

• **Partial Response**: Reduction of $2 \log_{10}$ or more in HCV RNA after 12 weeks of therapy, but with detectable HCV RNA

• **Relapse**: undetectable HCV RNA at the end of a previous course of therapy but HCV RNA positivity thereafter

# Telaprevir for Treatment-Experienced HCV Genotype 1

## REALIZE: Treatment Regimens

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>4</th>
<th>12</th>
<th>16</th>
<th>24</th>
<th>36</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=266</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T12</strong></td>
<td>Telaprevir</td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PR48</strong></td>
<td>Peginterferon + Ribavirin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **N=264** |     |     |     |     |     |     |     |
| **Lead-In** | Placebo | Telaprevir |     |     |     |     |     |
| **T12** | Peginterferon + Ribavirin |           |     |     |     |     |     |
| **PR48** |           |           |     |     |     |     |     |

| **N=132** |     |     |     |     |     |     |     |
| **PR48** | Placebo |             |     |     |     |     |     |
|**Peginterferon + Ribavirin** |           |           |     |     |     |     |     |

Telaprevir for Treatment-Experienced HCV Genotype 1
REALIZE Study: Results

REALIZE: SVR24 by Regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients with SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T12/PR48 (no lead in)</td>
<td>64/266</td>
</tr>
<tr>
<td>T12/PR48 (with lead in)</td>
<td>66/264</td>
</tr>
<tr>
<td>PR48</td>
<td>17/132</td>
</tr>
</tbody>
</table>

SVR = Sustained Virologic Response; T = Telaprevir, PR = Peginterferon + Ribavirin

Telaprevir for Treatment-Experience HCV Genotype 1

REALIZE: Results Based on Prior History

REALIZE: SVR24 by Prior Response

- T12/PR48 (no lead in)
- T12/PR48 (with lead in)
- PR 48

Patients with SVR (%)

<table>
<thead>
<tr>
<th>Previous Type of Response</th>
<th>No Response</th>
<th>Partial Response</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21/72</td>
<td>59/99</td>
<td>121/145</td>
</tr>
<tr>
<td></td>
<td>25/75</td>
<td>54/81</td>
<td>124/141</td>
</tr>
<tr>
<td></td>
<td>2/37</td>
<td>15/27</td>
<td>16/68</td>
</tr>
</tbody>
</table>

SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

Telaprevir for Treatment-Experience HCV Genotype 1

REALIZE: Adverse Effects

REALIZE: Anemia

T = Telaprevir; P = Peginterferon + Ribavirin

**Conclusions:** “Telaprevir combined with peginterferon plus ribavirin significantly improved rates of sustained virologic response in patients with previously treated HCV infection, regardless of whether there was a lead-in phase.”

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.
Telaprevir (Incivek)

Adverse Effects