HEPATITIS WEB STUDY HEPATITIS C ONLINE

Telaprevir (*Incivek*)

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Last Updated: February 3, 2014

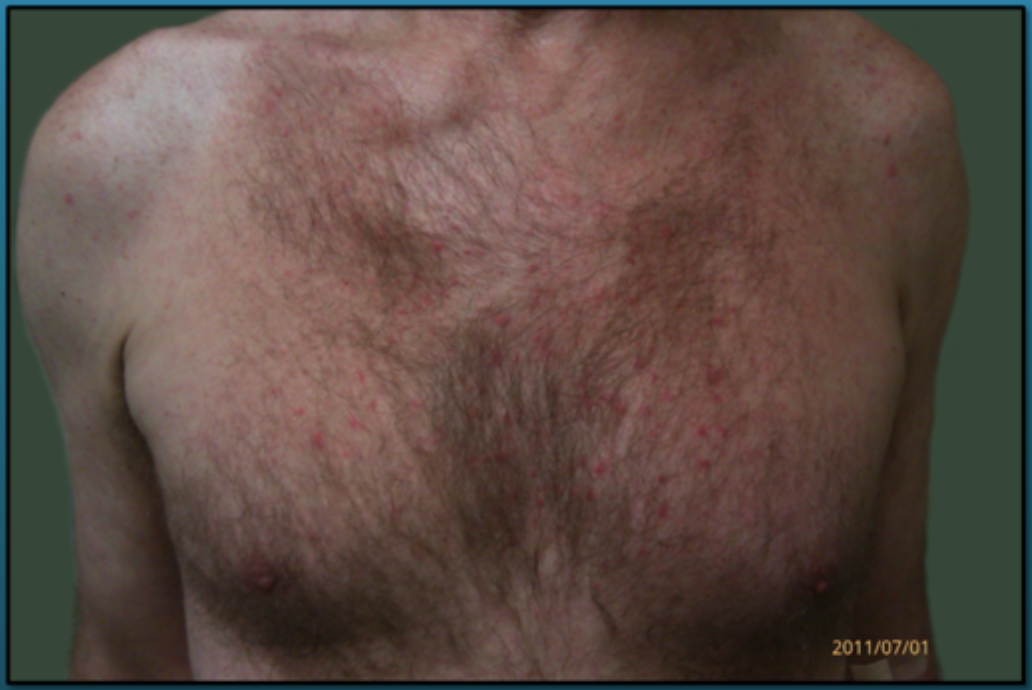
Hepatitis web study

Telaprevir
Adverse Effects

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

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

Telaprevir
Mild Skin Rash



Source: Photograph Courtesy of John Scott, MD, University of Washington

Hepatitis web study

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

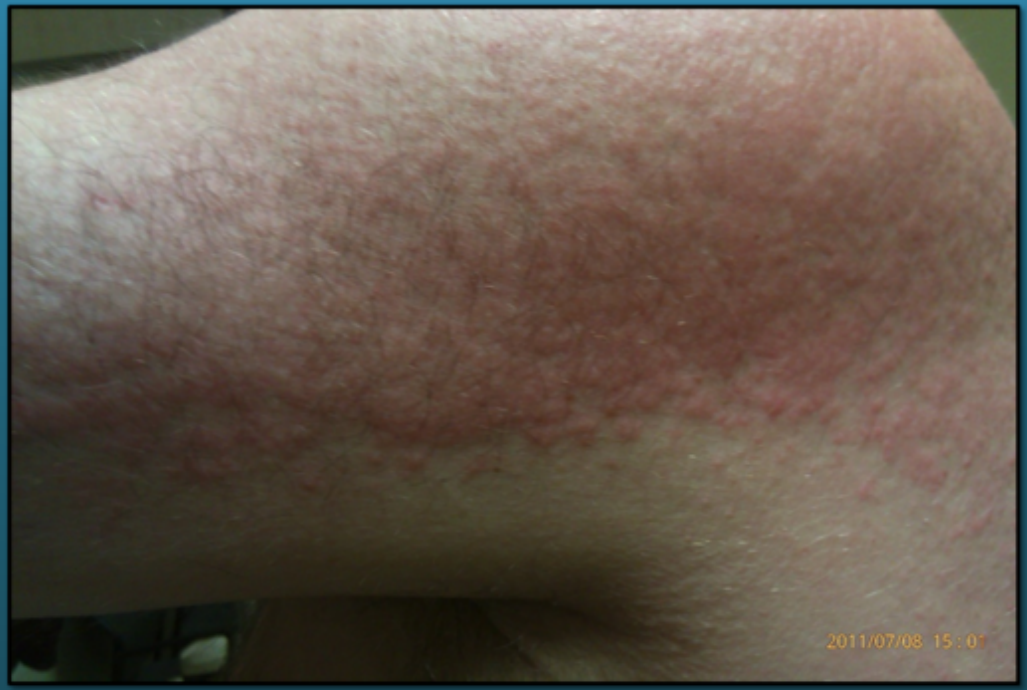
Source: Telaprevir (*Incivek*) Prescribing Information and Vertex Pharmaceuticals.

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

Hepatitis web study

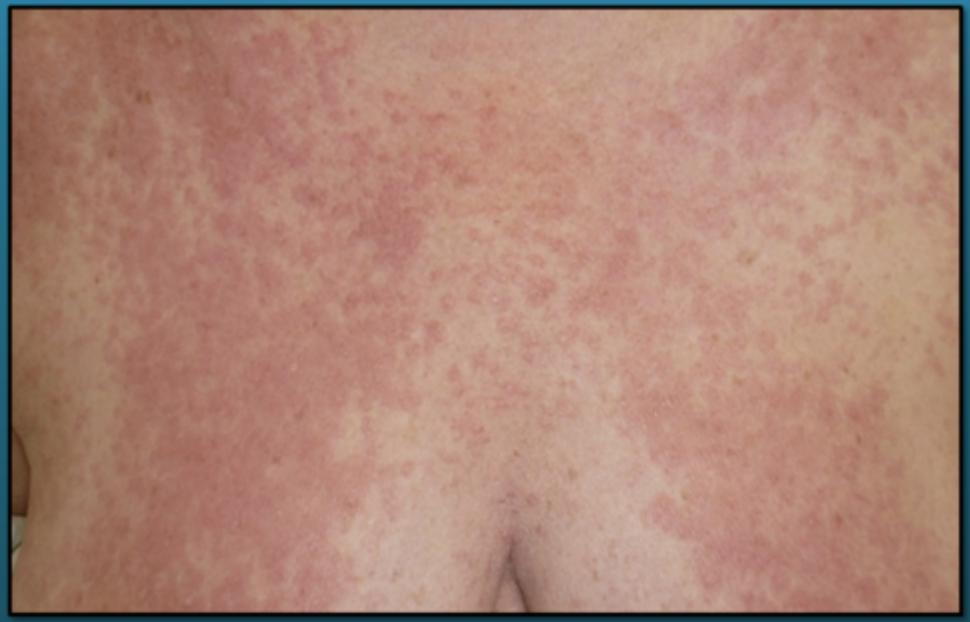
Telaprevir
Moderate Skin Rash

- **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

Hepatitis web study

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 (eg. 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

Medications Contraindicated for use with Telaprevir	
Drug Class	**Medication and Interaction**
Alpha-1 Adrenoreceptor Antagonist	Alfuzosin
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin
Antimycobacterials	Rifampin
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
Gastrointestinal Motility Agent	Cisapride
Herbal Products	St John's wort (*Hypericum perforatum*)
HMG CoA-Reductase Inhibitors	Lovastatin, simvastatin
Neuroleptic	Pimozide
PDE5 Inhibitor	Sildenafil or Tadalafil (dose levels for treatment of pulmonary hypertension)
Sedatives/hypnotics	Orally administered midazolam, triazolam

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

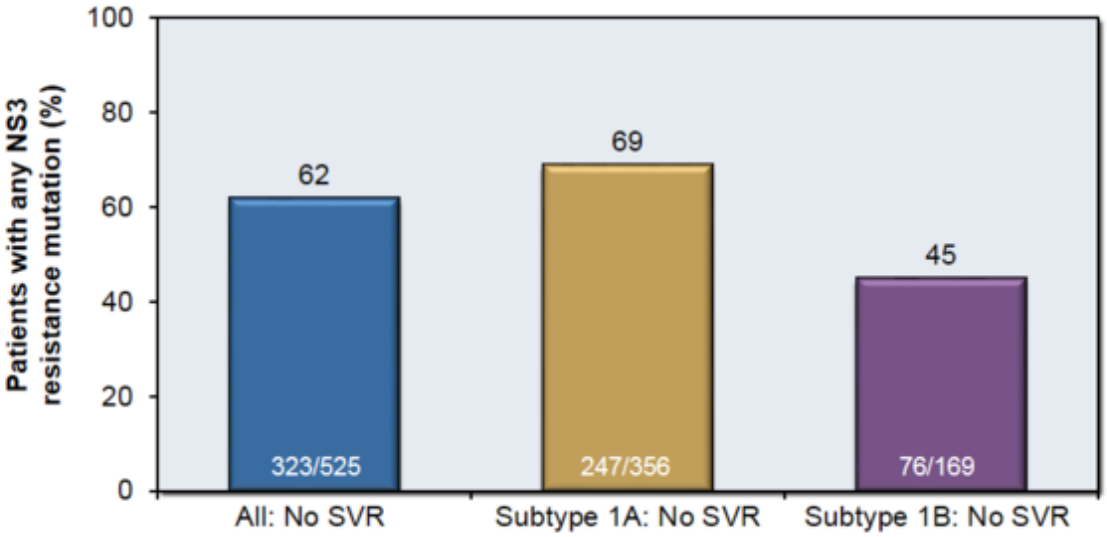
Source: Marcellin P, et. al. Gastroenterology. 2011;140:459-68.

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.

Telaprevir and Boceprevir Genotypic Resistance

Mutation	Telaprevir	Boceprevir
V36A/M	+	+
T54S/A	+	+
V55A	In vitro	+
Q80R/K	-	-
R155K/T/Q	+	+
A156S	+	+
A156T/V	+	In vitro
D168A/V/T/H	-	-
V170A/T	In vitro	+

Source: Sarrazin C, Zeuzem S. Gastroenterology. 2010;138:447-62.

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

Treatment Naïve

Telaprevir + Peginterferon + Ribavirin for GT1
PROVE1 Study

McHutchison JG, et. al. N Engl J Med. 2009;360:1827-38.

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

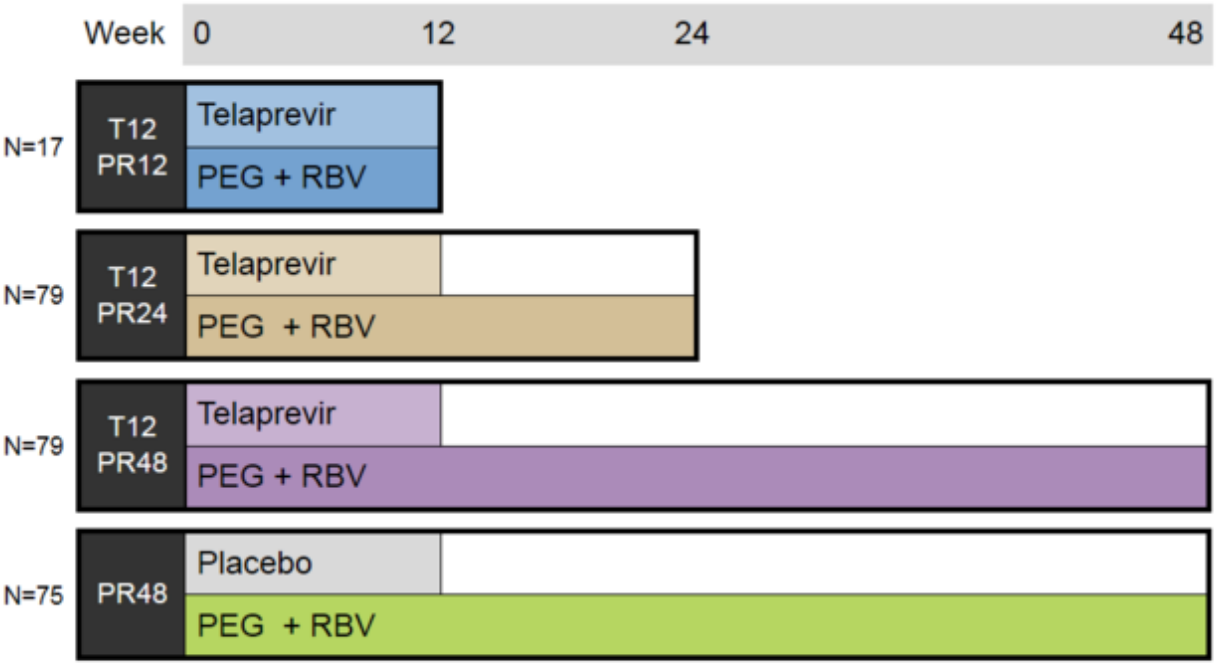
Source: McHutchison JG, et. al. N Engl J Med. 2009;360:1827-38.

Telaprevir (*Incivek*)

- **Approval**: FDA Approved May 23, 2011
- **Indications**
  - In combination with peginterferon-alfa and ribavirin (PR)
  - Chronic HCV genotype 1 infection
  - Adults (≥ 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.

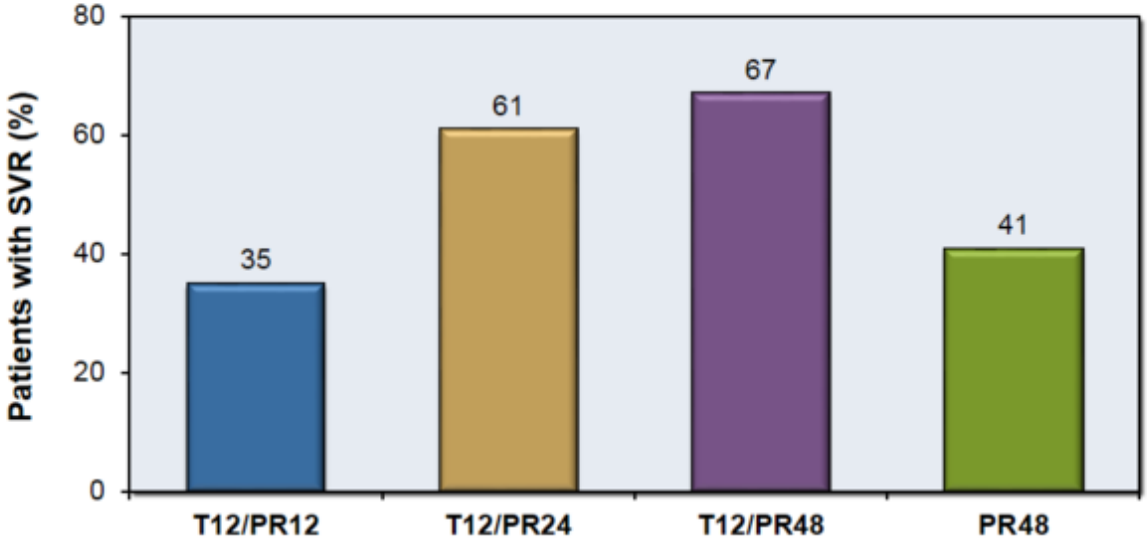
Telaprevir for Treatment-Naïve HCV Genotype 1
PROVE1 Study: Treatment Regimens



Source: McHutchison JG, et. al. N Engl J Med. 2009;360:1827-38.

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

PROVE1: SVR24 by Regimen

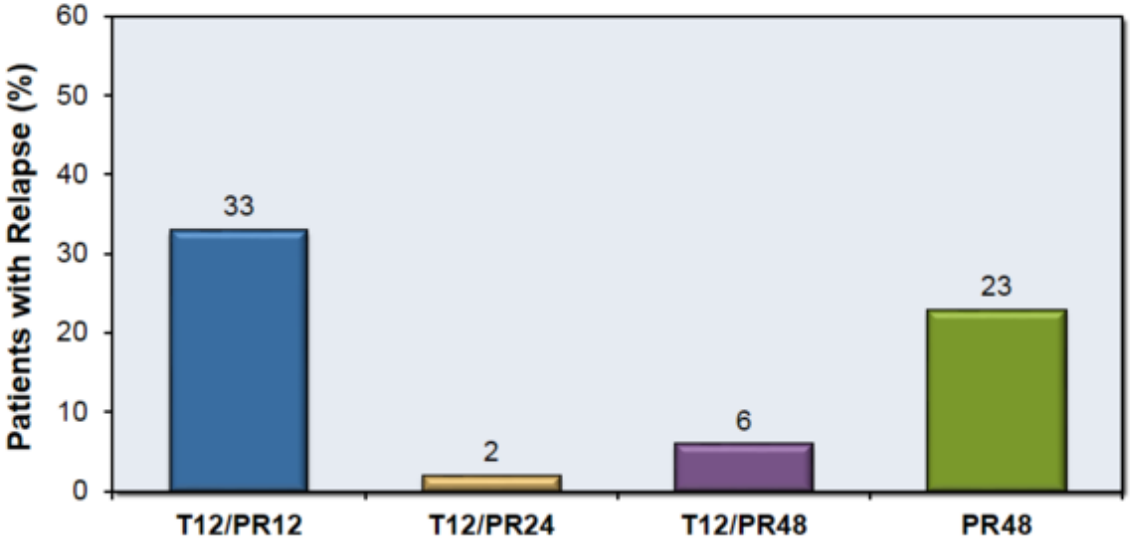


SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

Source: McHutchison JG, et. al. N Engl J Med. 2009;360:1827-38.

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

PROVE1: Percentage of Patients with Relapse by Regimen

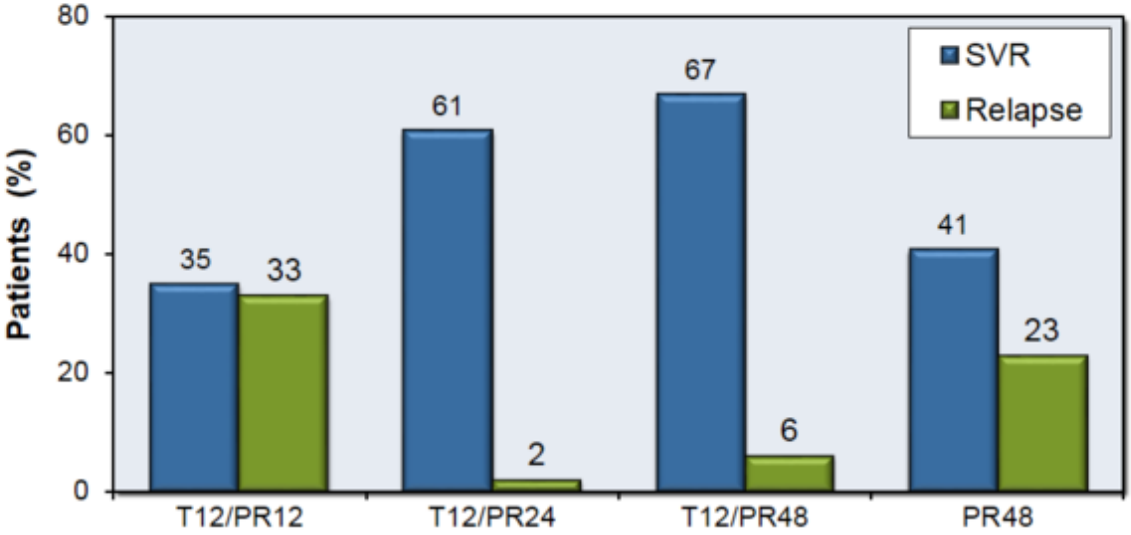


T = Telaprevir; PR = Peginterferon + Ribavirin

Source: McHutchison JG, et. al. N Engl J Med. 2009;360:1827-38.

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

Source: McHutchison JG, et. al. N Engl J Med. 2009;360:1827-38.

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

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."

Source:McHutchison JG, et. al. N Engl J Med. 2009;360:1827-38.

Treatment Naïve

Telaprevir in Treatment Naïve GT-1 PROVE2 Study

Hézode C, et al. N Engl J Med. 2009;360:1839-50.

Telaprevir for Treatment-Naïve HCV Genotype 1
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

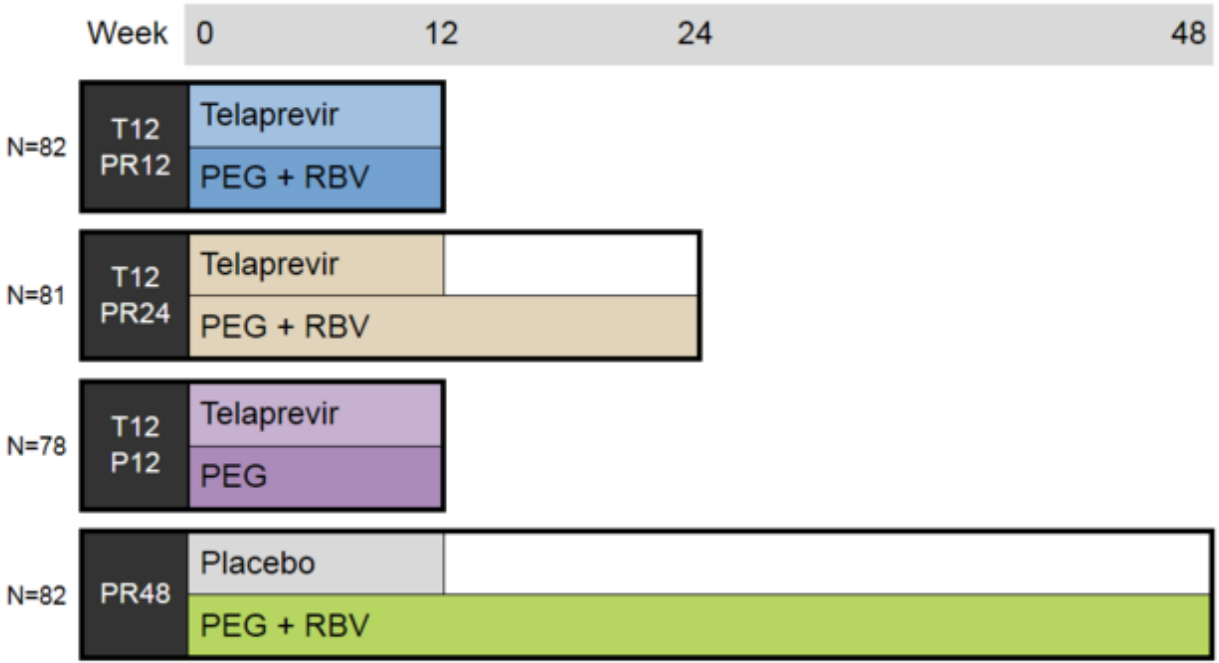
Telaprevir = 1250 mg on day 1, then 750 mg every 8 hours

Peginterferon alfa-2a = 180 µg weekly

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

Source: Hézode C, et al. N Engl J Med. 2009;360:1839-50.

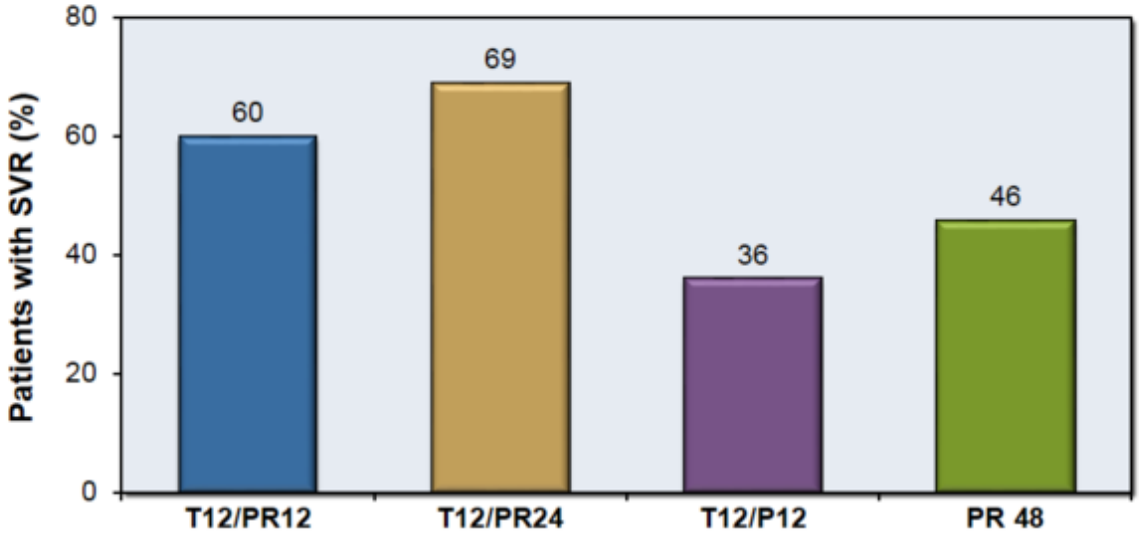
Telaprevir for Treatment-Naïve HCV Genotype 1
PROVE2 Study: Treatment Regimens



Source: Hézode C, et al. N Engl J Med. 2009;360:1839-50.

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

PROVE2: SVR24 by Regimen

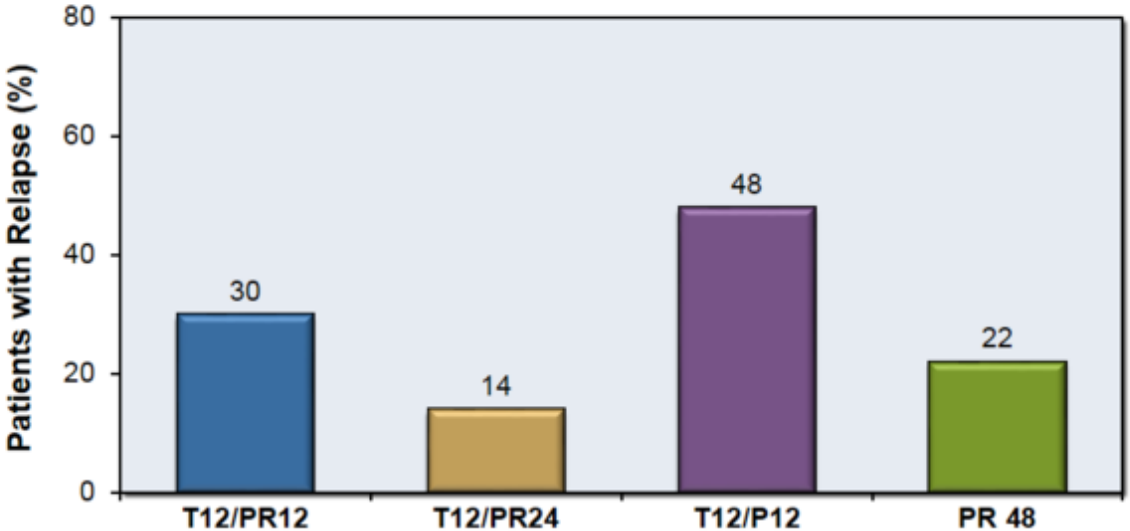


SVR = Sustained Virologic Response; T = Telaprevir; P = Peginterferon; PR = Peginterferon + Ribavirin

Source: Hézode C, et al. N Engl J Med. 2009;360:1839-50.

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

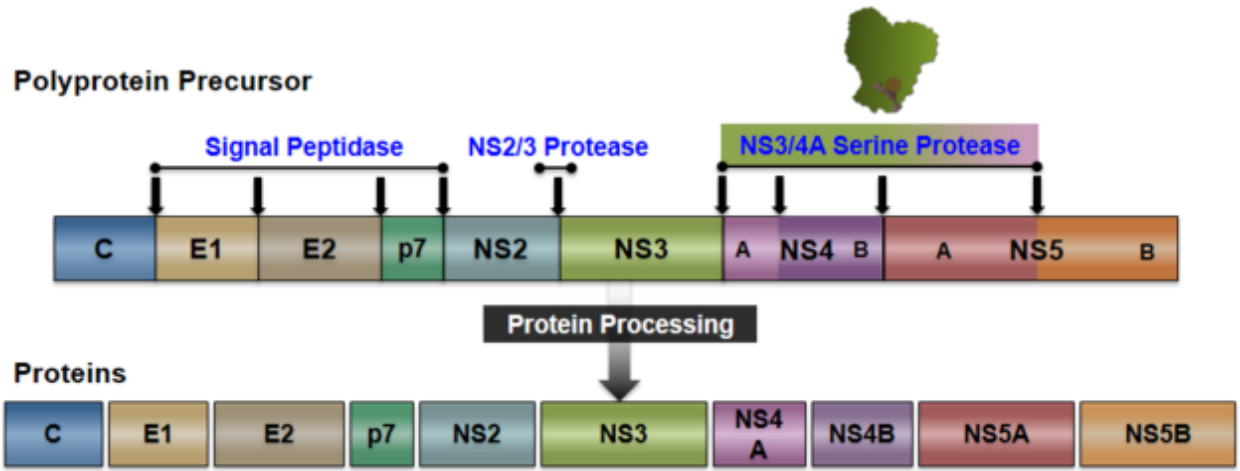
PROVE2: Patients with Relapse by Regimen



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

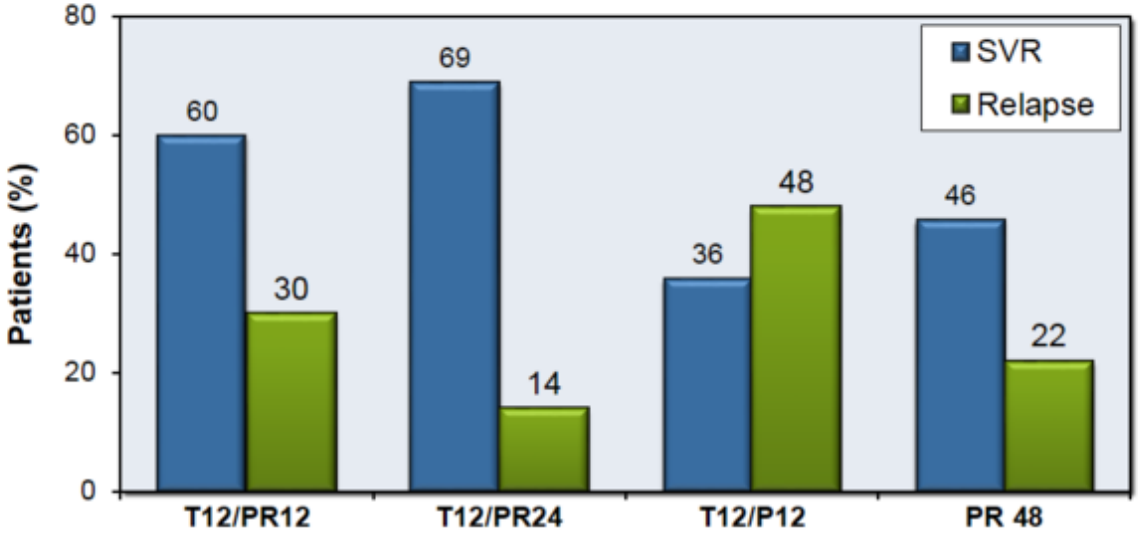
Source: Hézode C, et al. N Engl J Med. 2009;360:1839-50.

HCV Protein Processing
Role of Role of NS3/4A Serine Protease



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

PROVE2: Patients with SVR and Relapse by Regimen

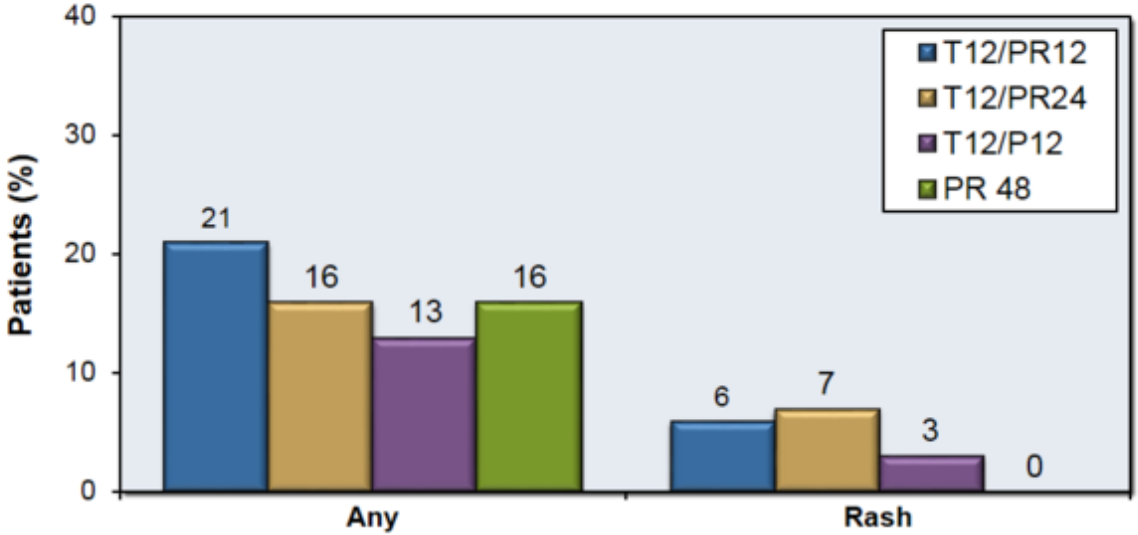


SVR = Sustained Virologic Response; T = Telaprevir; P = Peginterferon; PR = Peginterferon + Ribavirin

Source: Hézode C, et al. N Engl J Med. 2009;360:1839-50.

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

PROVE2: Severe (Grade 3) Adverse Events by Regimen



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

Source: Hézode C, et al. N Engl J Med. 2009;360:1839-50.

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

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."

Source: Hézode C, et al. N Engl J Med. 2009;360:1839-50.

Treatment Naïve

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

Jacobson IM, et. al. N Engl J Med. 2011;364:2405-16.

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

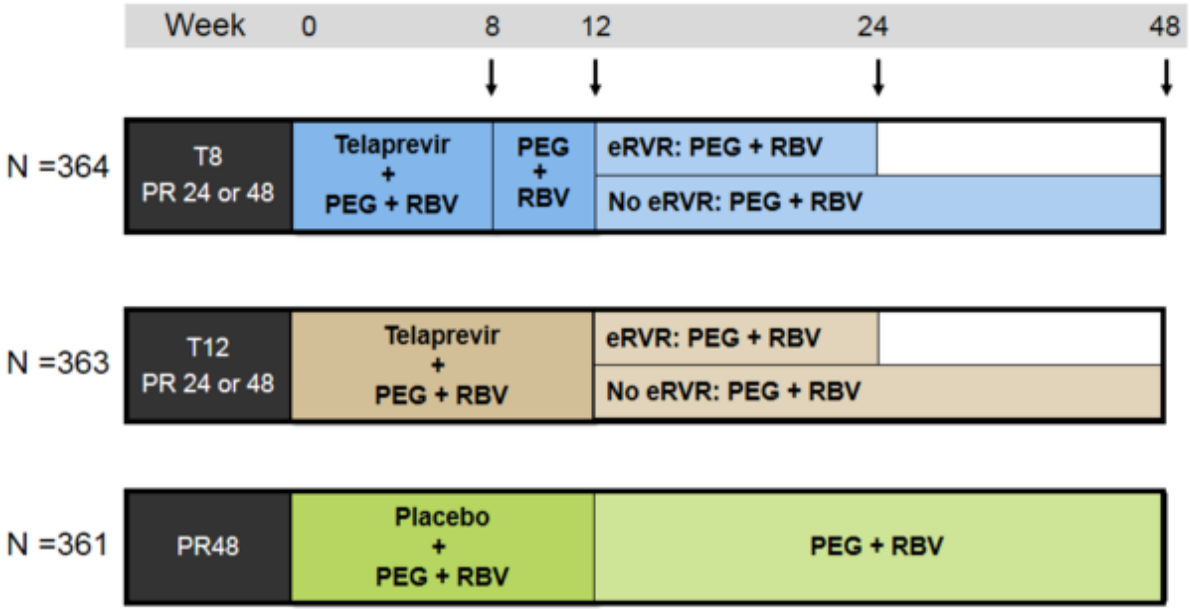
Telaprevir = 750 mg every 8 hours

Peginterferon alfa-2a = 180 µg weekly

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

Source: Jacobson IM, et. al. N Engl J Med. 2011;364:2405-16.

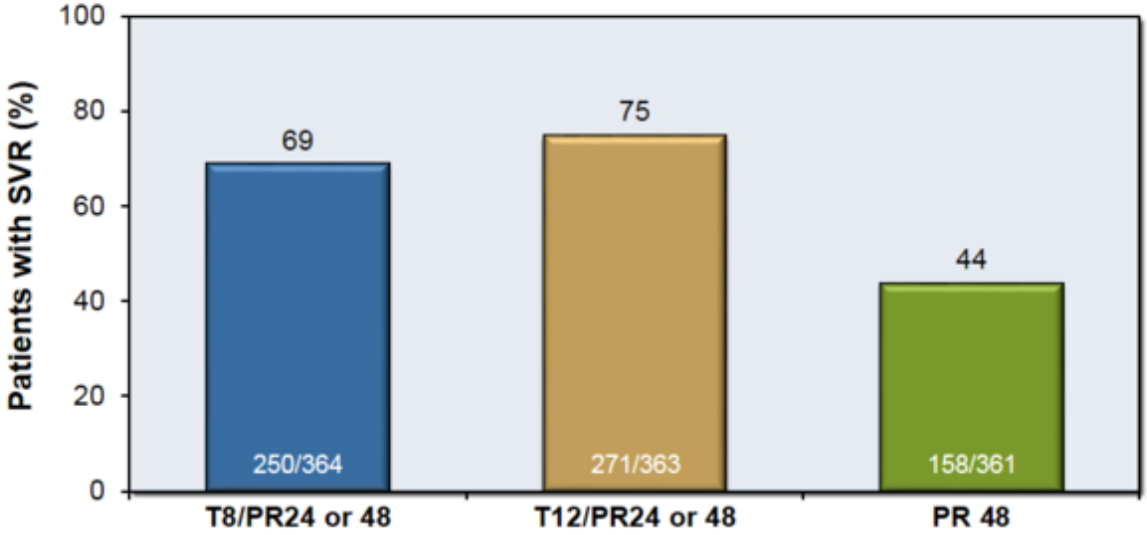
Telaprevir for Treatment-Naïve HCV Genotype 1
ADVANCE Study: Treatment Regimens



Source: Jacobson IM, et. al. N Engl J Med. 2011;364:2405-16.

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

ADVANCE: SVR24 by Regimen

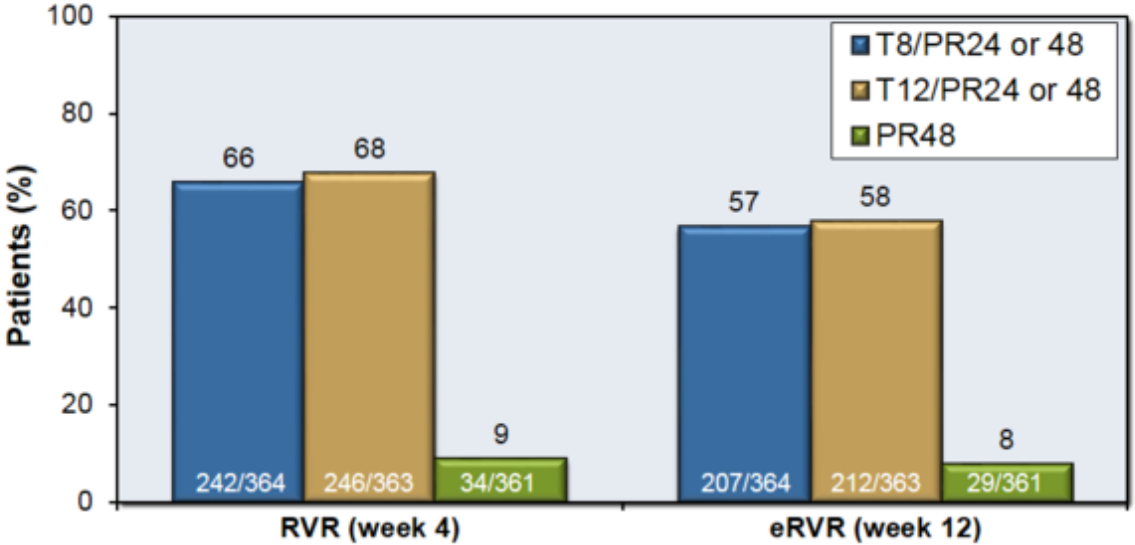


SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

Source: Jacobson IM, et. al. N Engl J Med. 2011;364:2405-16.

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

ADVANCE: Patients with RVR and eRVR

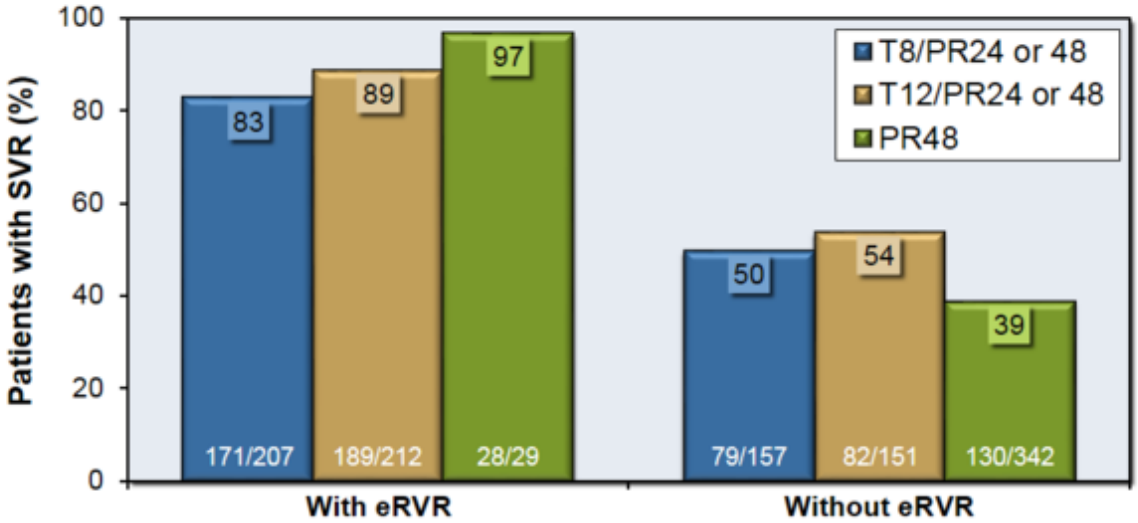


T = Telaprevir; PR = Peginterferon + Ribavirin; RVR = rapid virologic response; eRVR = extended rapid virologic response

Source: Jacobson IM, et. al. N Engl J Med. 2011;364:2405-16.

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

ADVANCE: SVR24 by eRVR Status

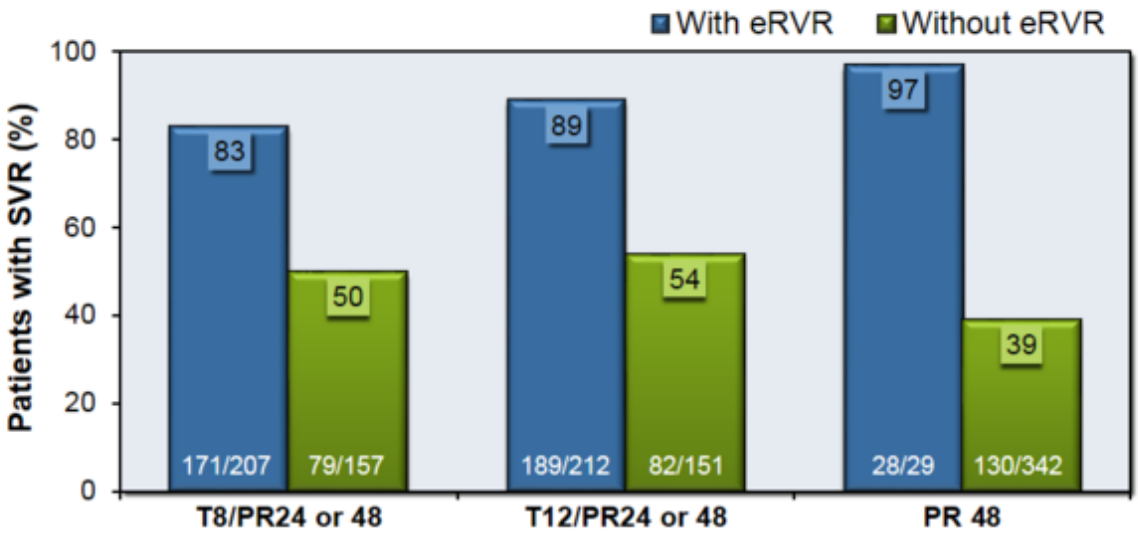


T = Telaprevir; PR= Peginterferon + Ribavirin; SVR = Sustained Virologic Response
eRVR = extended rapid virologic response (undetectable HCV RNA at weeks 4 and 12)

Source: Jacobson IM, et. al. N Engl J Med. 2011;364:2405-16.

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

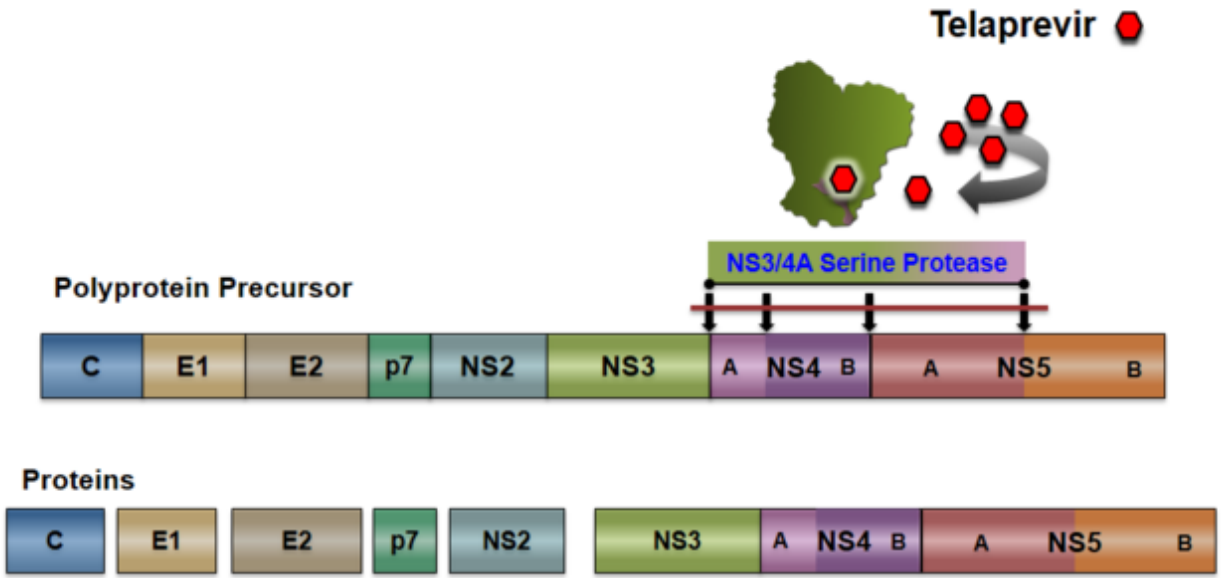
ADVANCE: SVR24 by eRVR Status



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

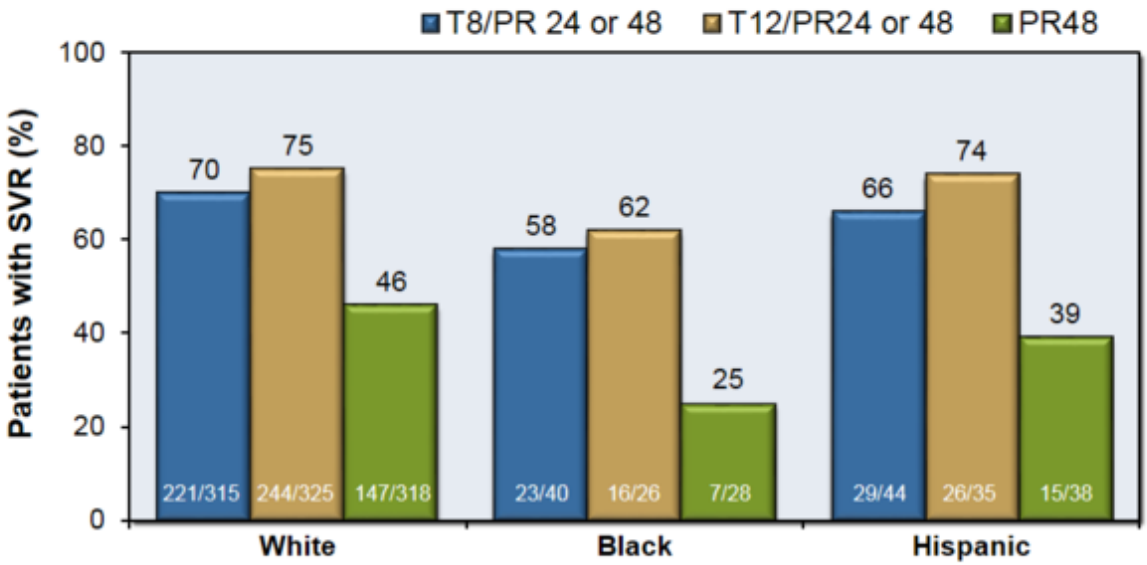
Source: Jacobson IM, et. al. N Engl J Med. 2011;364:2405-16.

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

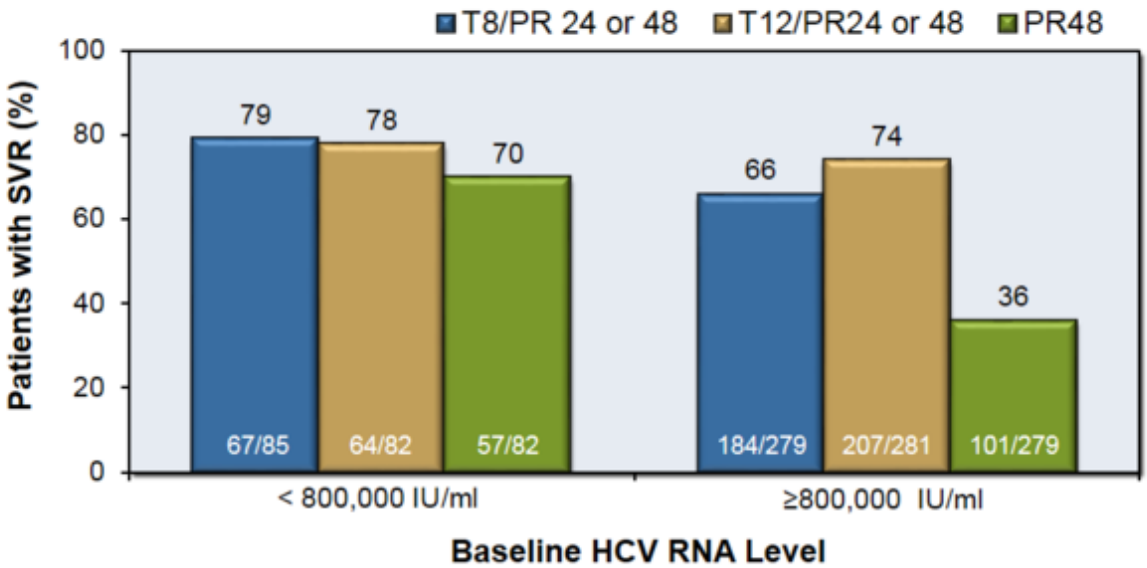


SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

Source: Jacobson IM, et. al. N Engl J Med. 2011;364:2405-16.

Telaprevir for Treatment-Naïve HCV Genotype 1
ADVANCE Study: Results by Baseline HCV RNA

ADVANCE: SVR24 by Baseline HCV RNA Level

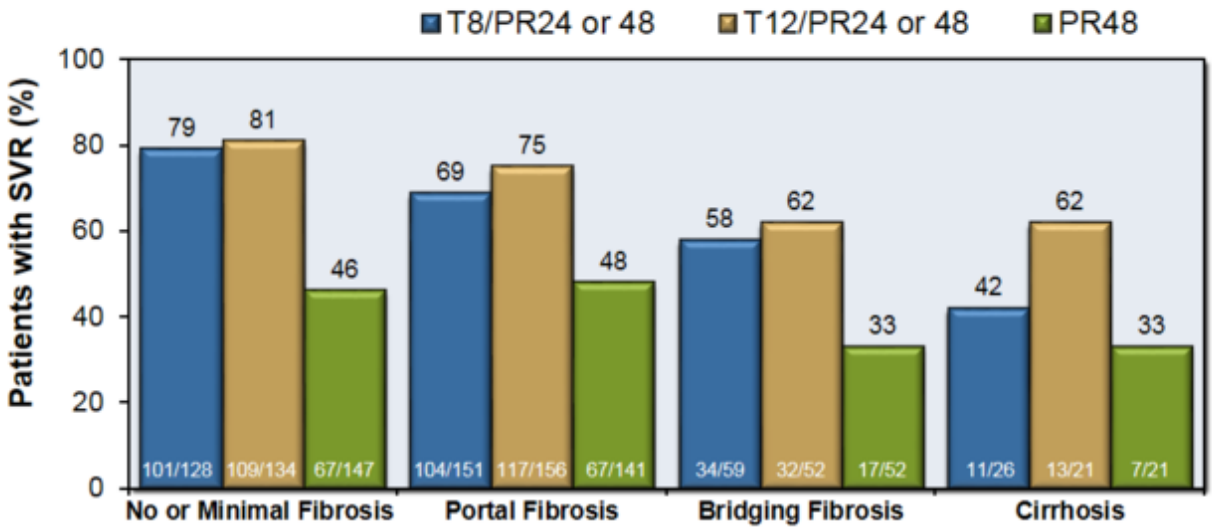


SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

Source: Jacobson IM, et. al. N Engl J Med. 2011;364:2405-16.

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

ADVANCE: SVR24 by Fibrosis Stage

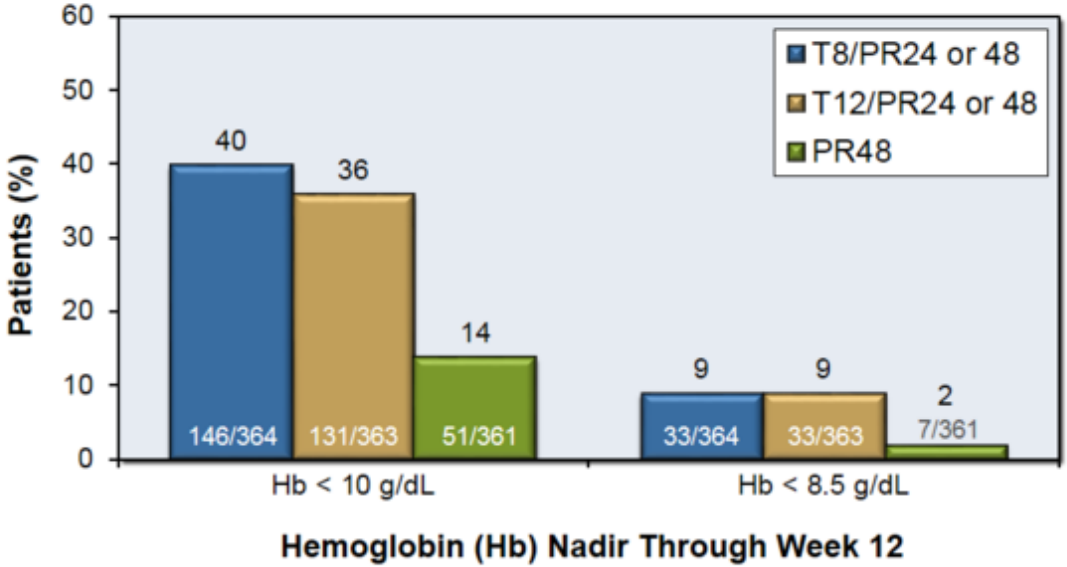


SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

Source: Jacobson IM, et. al. Hepatology. 2010;52 (Supplement 1):427A. Abstract 211.

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

ADVANCE: Percentage of Patients with Anemia

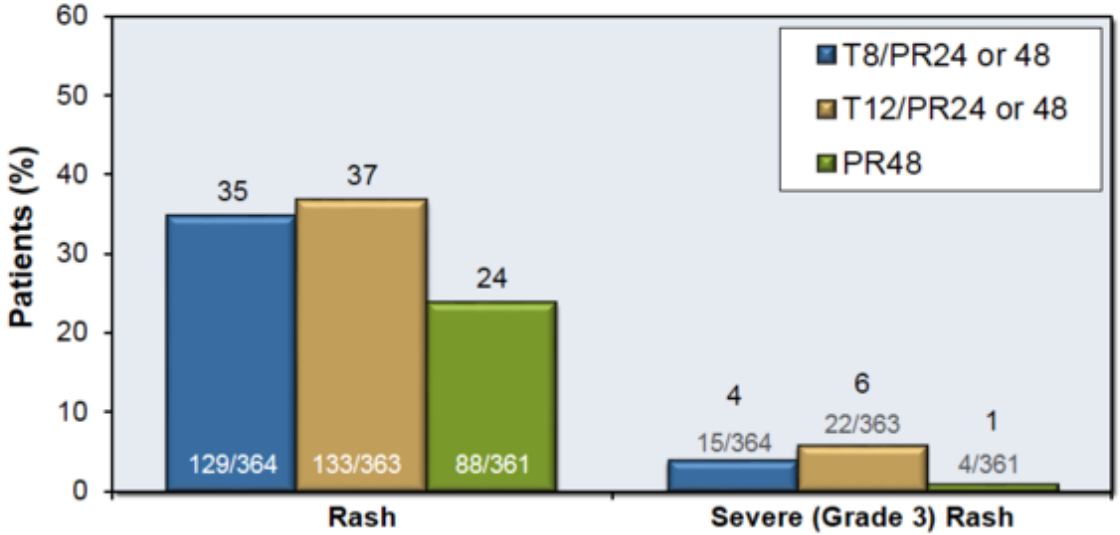


T = Telaprevir; PR = Peginterferon + Ribavirin

Source: Jacobson IM, et. al. N Engl J Med. 2011;364:2405-16.

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

ADVANCE: Percentage of Patients with Rash

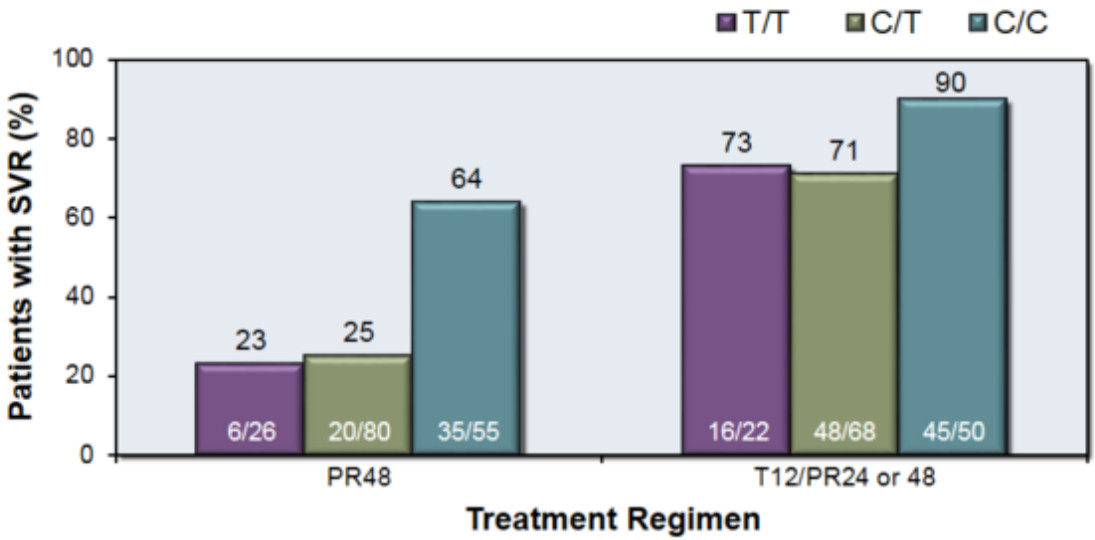


T = Telaprevir; PR = Peginterferon + Ribavirin

Source: Jacobson IM, et. al. N Engl J Med. 2011;364:2405-16.

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

ADVANCE: SVR24 by rs12979860 Genotype



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

Source: Telaprevir (*Incivek*) Prescribing Information. Vertex Pharmaceuticals.

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

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."

Source: Jacobson IM, et. al. N Engl J Med. 2011;364:2405-16.

Treatment Naïve

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

Sherman KE, et. al. N Engl J Med. 2011;365:1014-24.

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

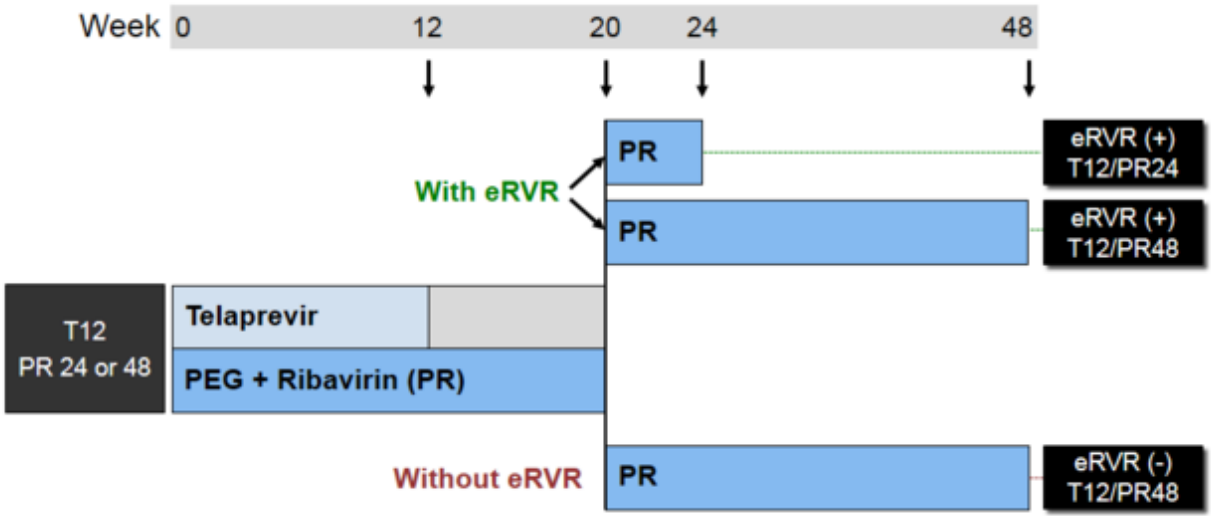
Telaprevir = 750 mg every 8 hours

Peginterferon alfa-2a = 180 µg per week

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

Source: Sherman KE, et. al. N Engl J Med. 2011;365:1014-24.

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



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

Source: Sherman KE, et. al. N Engl J Med. 2011;365:1014-24.

Telaprevir
Response Guided Therapy

Treatment-Naïve and Prior Relapse Patients^		
HCV RNA*	**Regimen**	**Total**
Weeks 4 & 12: Undetectable	Telaprevir 12 weeks Peginterferon + Ribavirin 24 weeks	24 Weeks
Weeks 4 and/or 12: Detectable at Low-level (≤ 1000 IU/ml)	Telaprevir 12 weeks Peginterferon + Ribavirin 48 weeks	48 Weeks
Prior Partial and Null Responders		
All Patients	Telaprevir 12 weeks Peginterferon + Ribavirin 48 weeks	48 Weeks

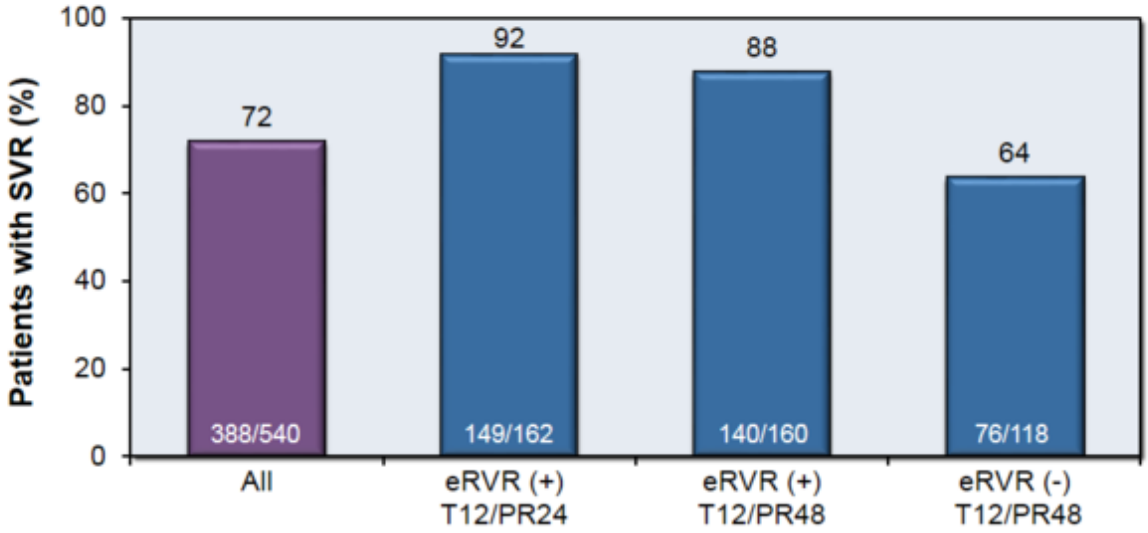
*In clinical trials, HCV-RNA in plasma was measured using a COBAS® TaqMan® assay with a lower limit of quantification of 25 IU/mL and a limit of detection of 10 IU/mL

^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



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

Source: Sherman KE, et. al. N Engl J Med. 2011;365:1014-24.

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

Source: Sherman KE, et. al. N Engl J Med. 2011;365:1014-24.

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

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."

Source: Sherman KE, et. al. N Engl J Med. 2011;365:1014-24.

Phase 3

Treatment Naïve

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

Buti M, et al. Gastroenterology. 2013 Dec 4. [Epub ahead of print]

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

OPTIMIZE: Study Features

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

Drug Dosing

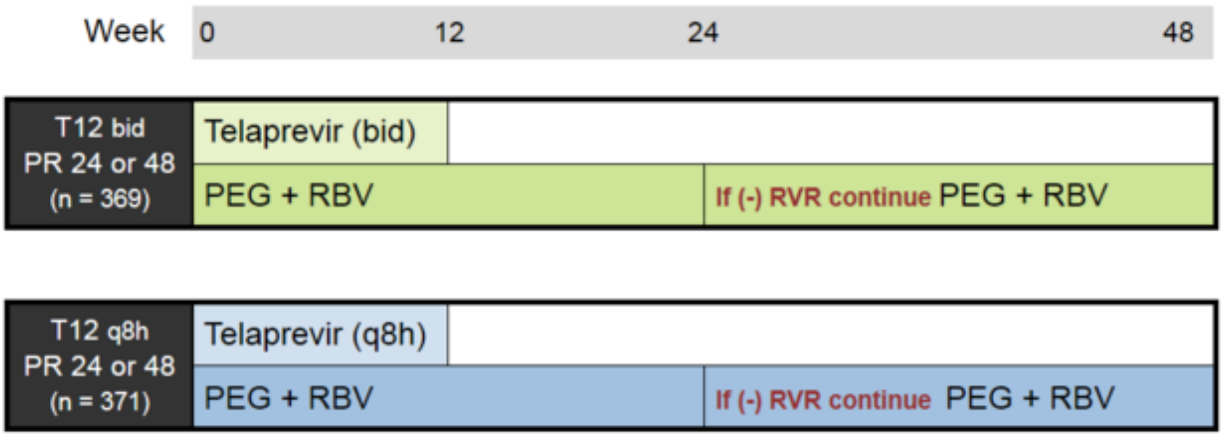
Telaprevir = 1125 mg bid or 750 mg q8h

Peginterferon alfa-2a = 180 µg weekly

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

Source: Buti M, et al. Gastroenterology. 2013 Dec 4. [Epub ahead of print]

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

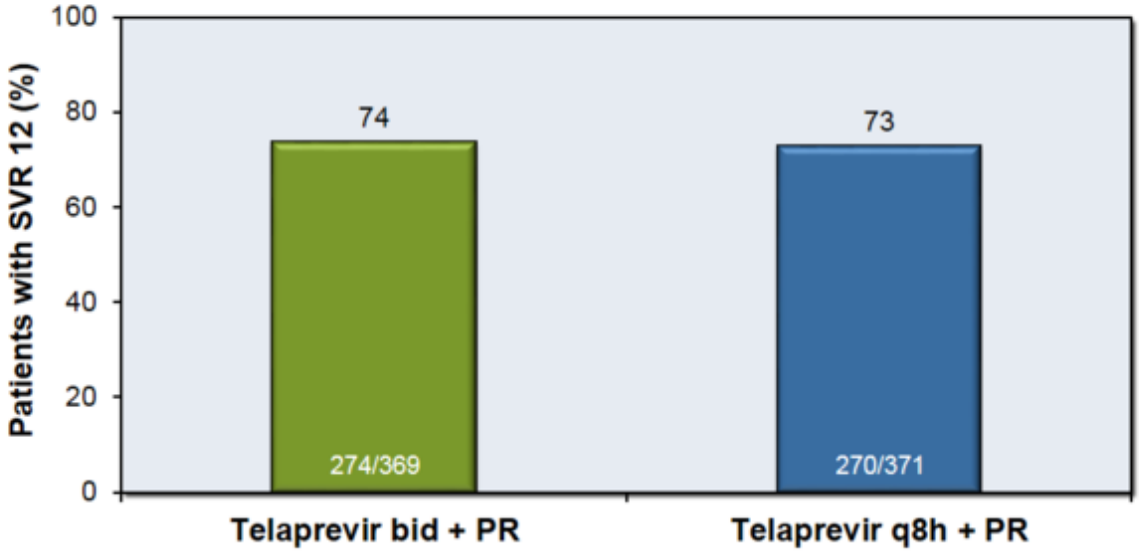


RVR = week 4 HCV RNA undetectable
PEG = peginterferon; RBV = ribavirin
Therapy stopped if HCV RNA > 1000 IU/mL at week 4 or HCV RNA > 25 IU/mL at weeks 12, 24, 32, or 40

Source: Buti M, et al. Gastroenterology. 2013 Dec 4. [Epub ahead of print]

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

OPTIMIZE: SVR12 by Regimen

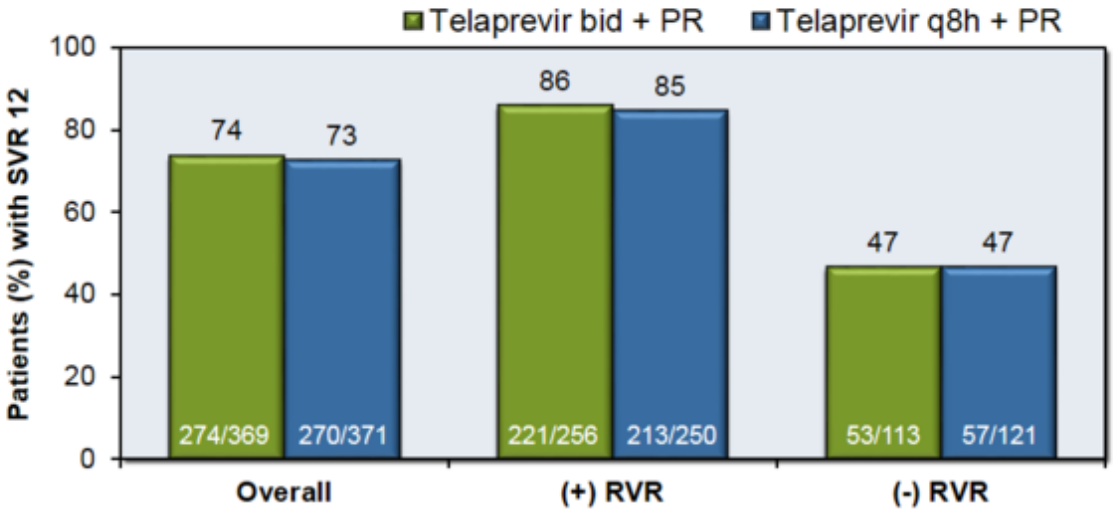


SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

Source: Buti M, et al. Gastroenterology. 2013 Dec 4. [Epub ahead of print]

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

OPTIMIZE: SVR12 by Week 4 Virologic Response

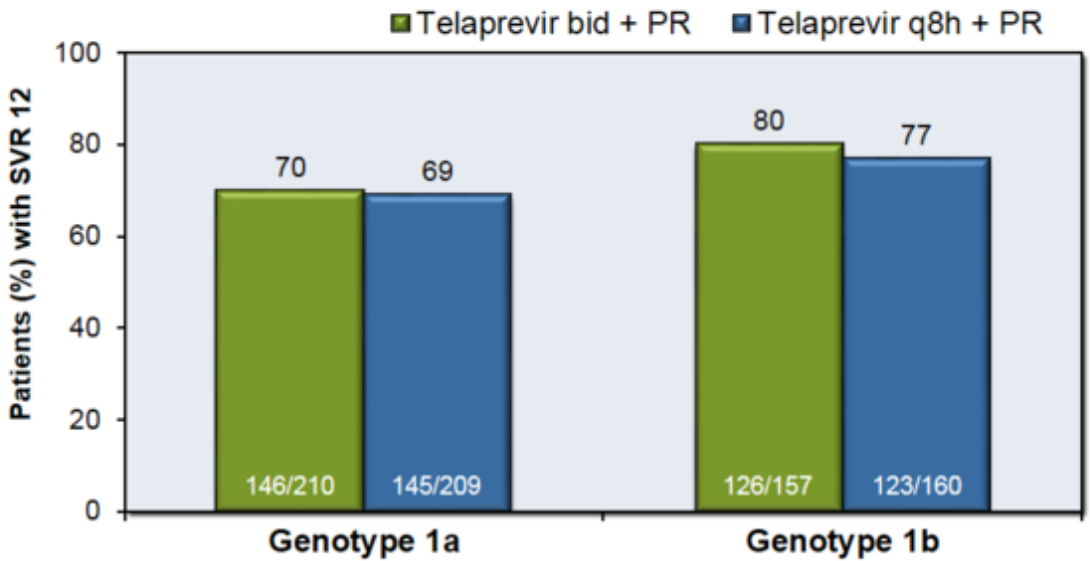


RVR = rapid virologic response (undetectable HCV RNA at week 4)
Abbreviations: SVR = sustained virologic response; PR = peginterferon + ribavirin

Source: Buti M, et al. Gastroenterology. 2013 Dec 4. [Epub ahead of print]

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

OPTIMIZE: SVR12 by Genotype 1 Subtype

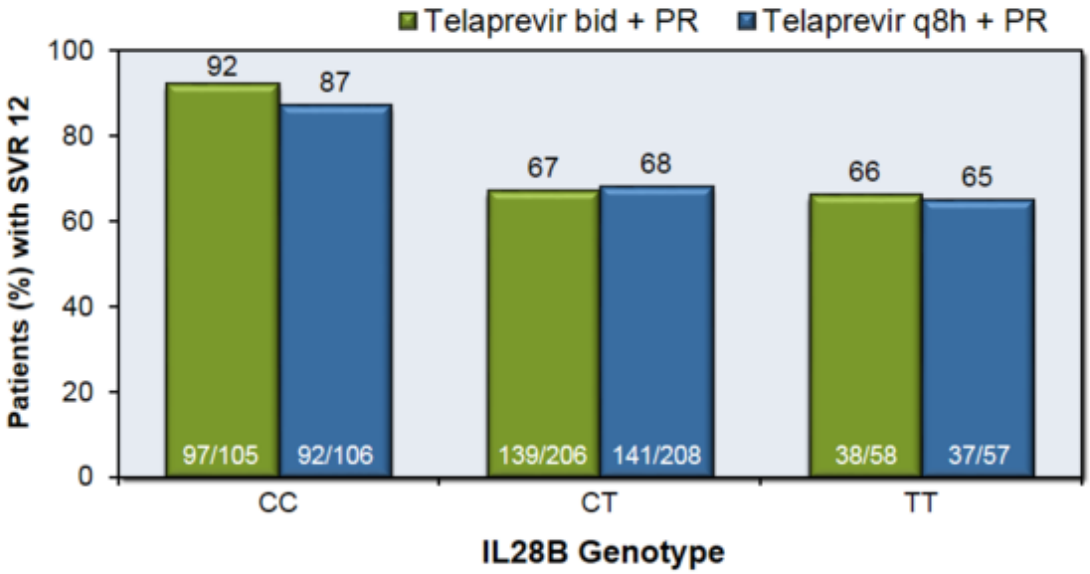


Abbreviations: Abbreviations: SVR = sustained virologic response; PR = peginterferon + ribavirin

Source: Buti M, et al. Gastroenterology. 2013 Dec 4. [Epub ahead of print]

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

OPTIMIZE: SVR12 by Host *IL28B* Genotype

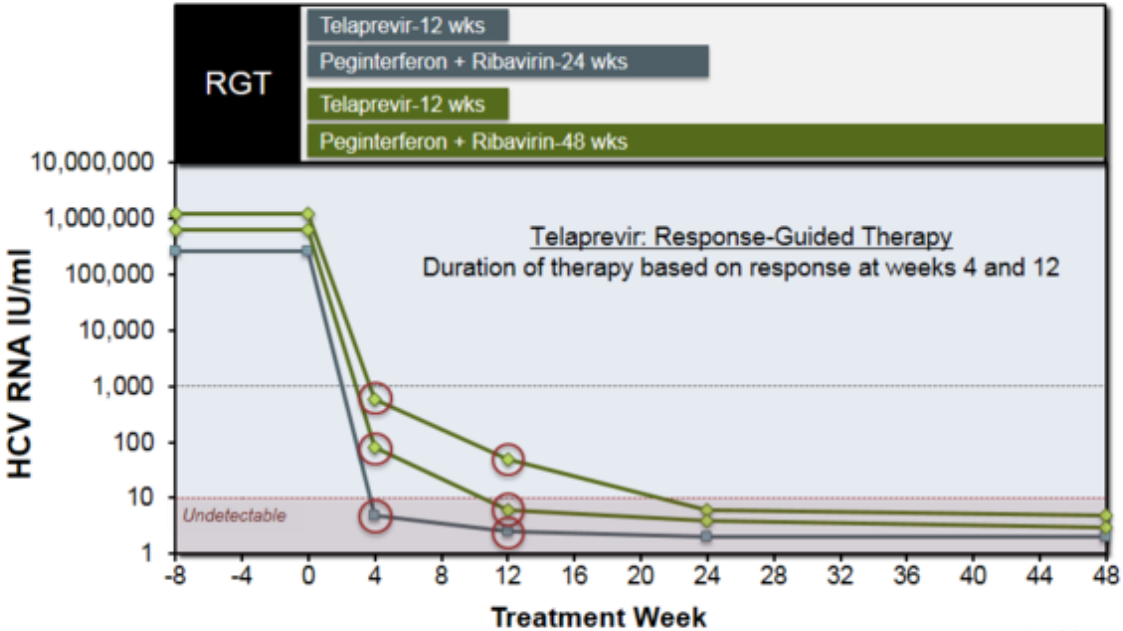


Abbreviations: SVR = sustained virologic response; PR = peginterferon + ribavirin

Source: Buti M, et al. Gastroenterology. 2013 Dec 4. [Epub ahead of print]

Telaprevir Response-Guided Therapy
Treatment Naïve and Prior Relapse Patients

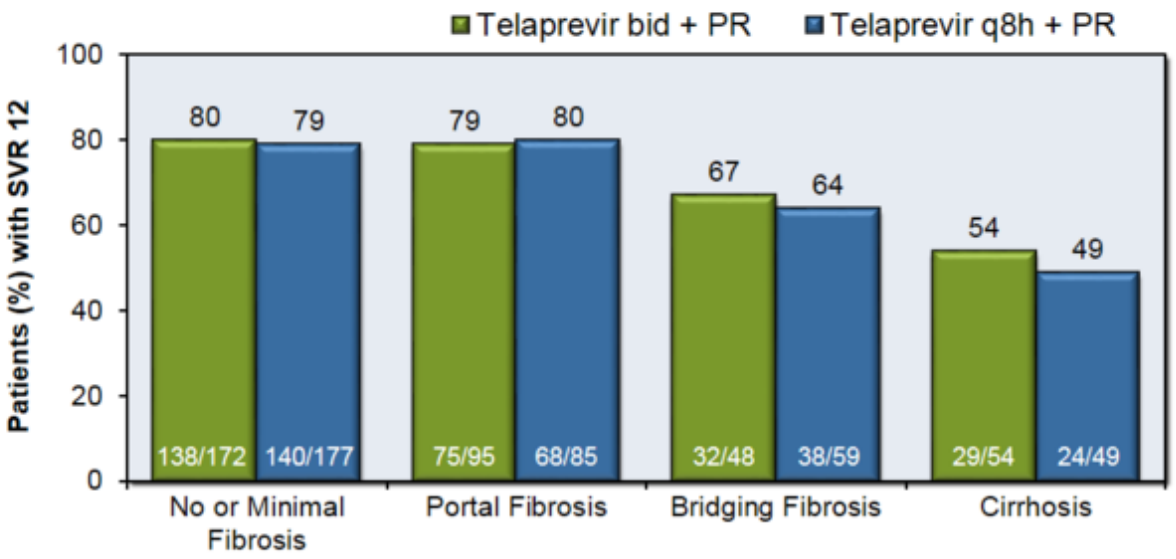
Telaprevir: Response Guided Therapy (RGT) for Treatment Naïve and Prior Relapse Patients



Hepatitis web study

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

OPTIMIZE: SVR12 by Fibrosis Stage



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

Source: Buti M, et al. Gastroenterology. 2013 Dec 4. [Epub ahead of print]

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

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."

Source: Buti M, et al. Gastroenterology. 2013 Dec 4. [Epub ahead of print]

Treatment Experienced

Telaprevir in Treatment Experienced GT-1
PROVE3

McHutchison JG, et al. N Engl J Med. 2010;362:1292-303.

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

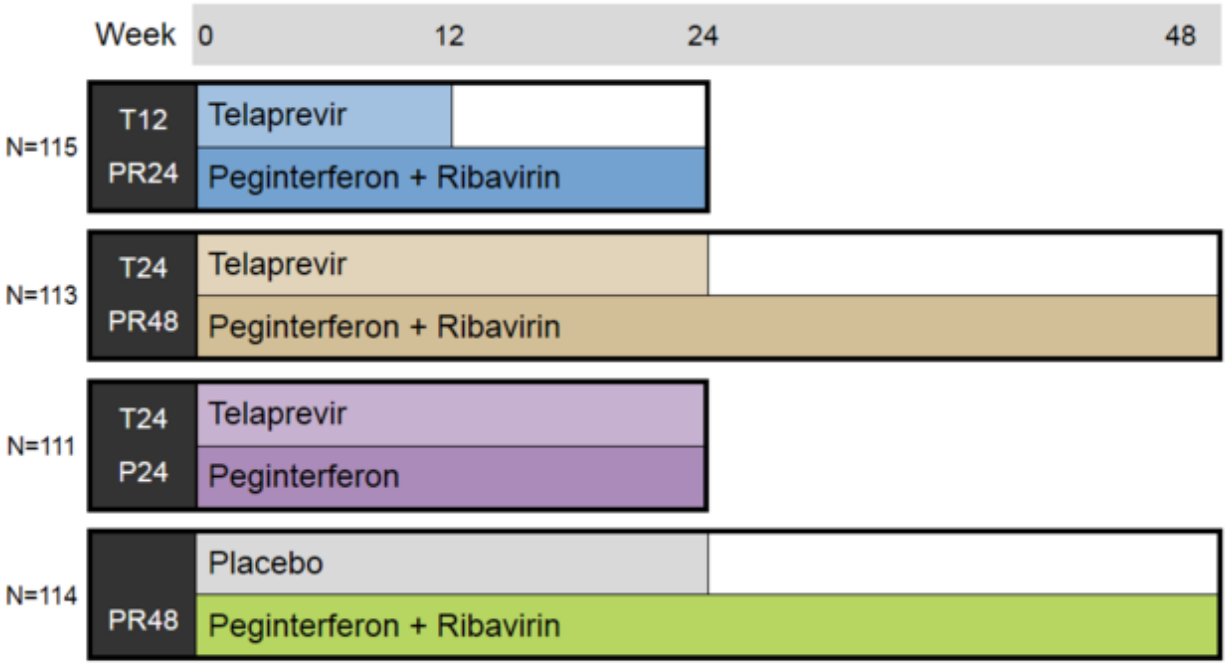
PROVE3: Study Features

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

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

Source: McHutchison JG, et al. N Engl J Med. 2010;362:1292-303.

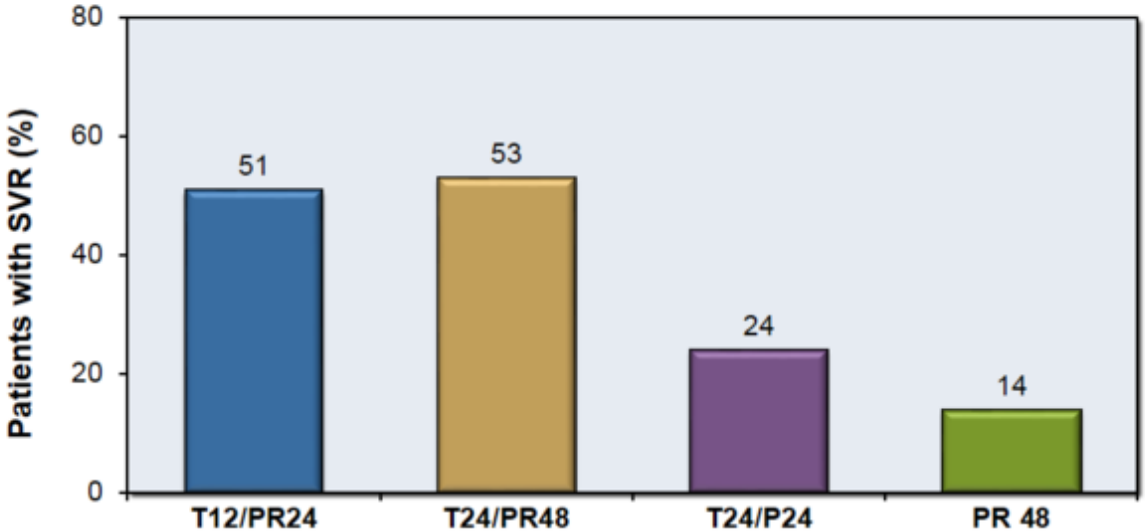
Telaprevir for Treatment-Experienced HCV Genotype 1 PROVE3 Study: Treatment Regimens



Source: McHutchison JG, et al. N Engl J Med. 2010;362:1292-303.

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

PROVE3: SVR24 by Regimen

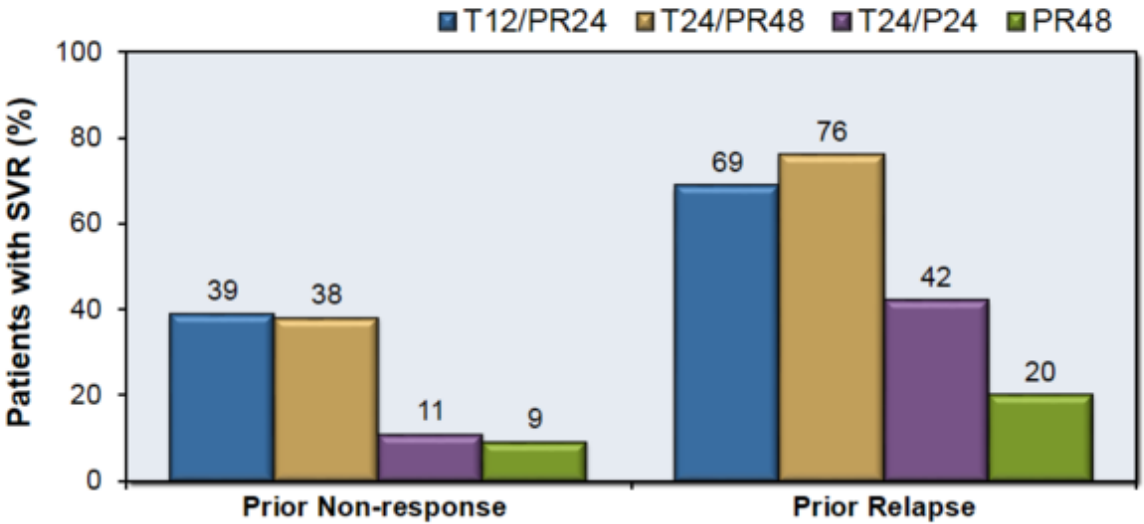


SVR = sustained virologic response; T = Telaprevir; P = Peginterferon; PR = Peginterferon + Ribavirin

Source: McHutchison JG, et al. N Engl J Med. 2010;362:1292-303.

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

PROVE3: SVR24 by Prior Response Status

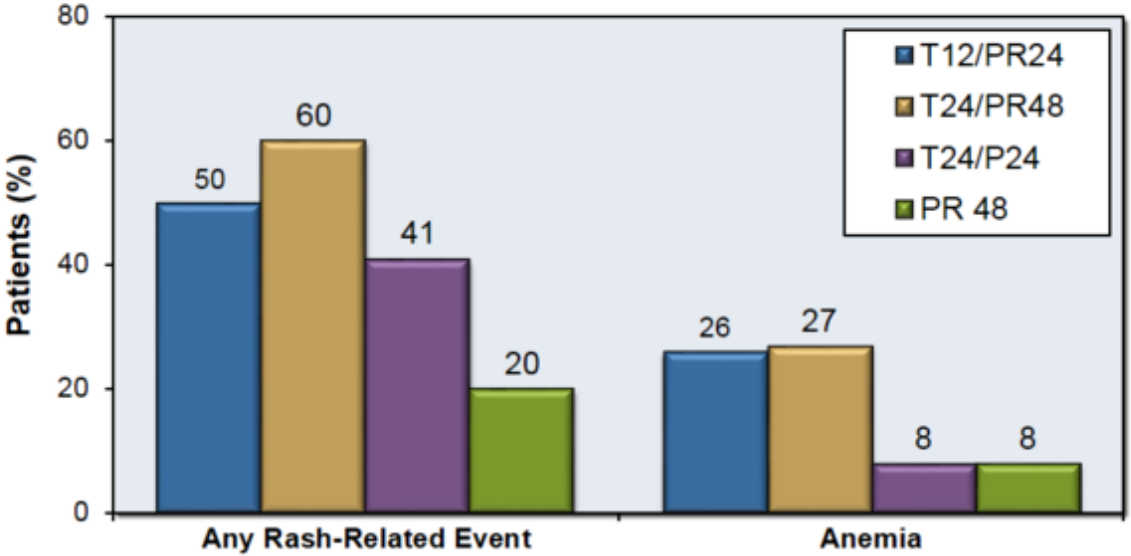


SVR = sustained virologic response; T = Telaprevir; P = Peginterferon; PR = Peginterferon + Ribavirin

Source: McHutchison JG, et al. N Engl J Med. 2010;362:1292-303.

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

PROVE3: Adverse Events



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

Source: McHutchison JG, et al. N Engl J Med. 2010;362:1292-303.

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

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."

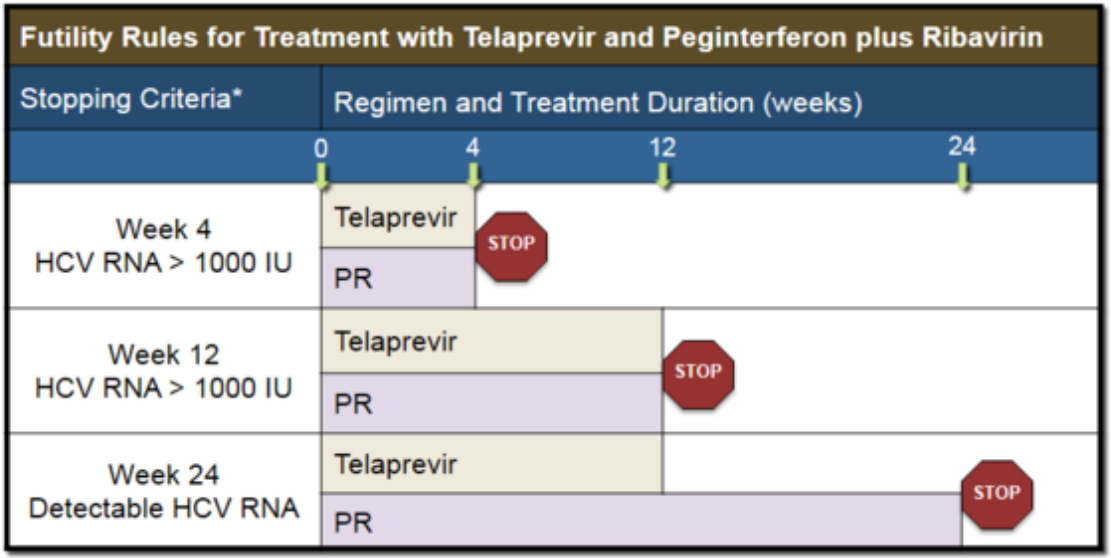
Source: McHutchison JG, et al. N Engl J Med. 2010;362:1292-303.

Treatment Experienced

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

Zeuzem S, et al. N Engl J Med. 2011;364:2417-28.

Telaprevir
Treatment Futility Rules for All Patients



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

Source: Zeuzem S, et al. N Engl J Med. 2011;364:2417-28.

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

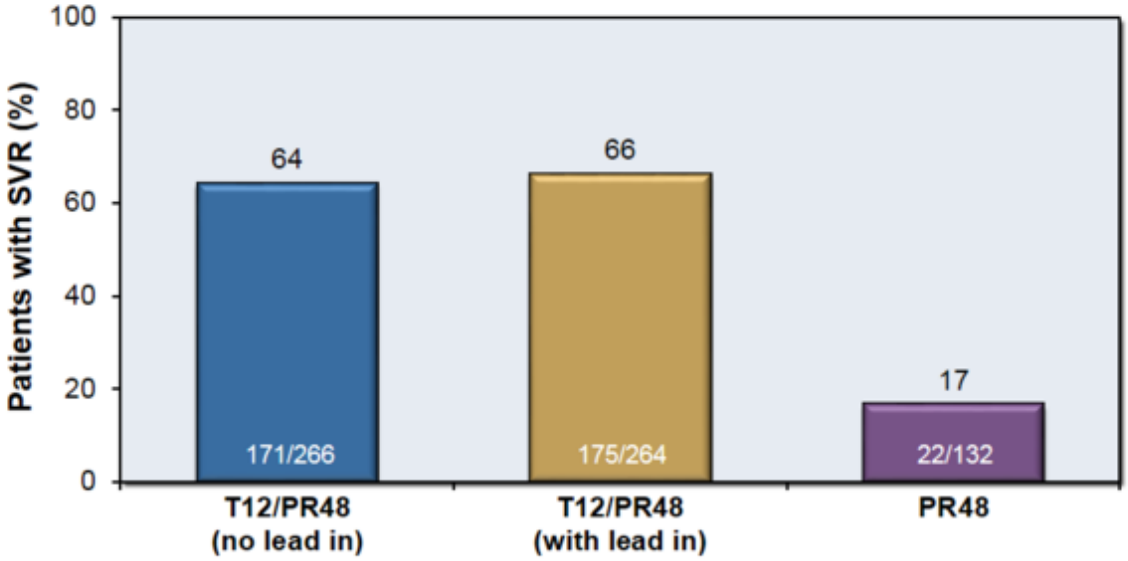
Source: Zeuzem S, et al. N Engl J Med. 2011;364:2417-28.

Telaprevir for Treatment-Experienced HCV Genotype 1
REALIZE: Treatment Regimens

Source: Zeuzem S, et al. N Engl J Med. 2011;364:2417-28.

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

REALIZE: SVR24 by Regimen

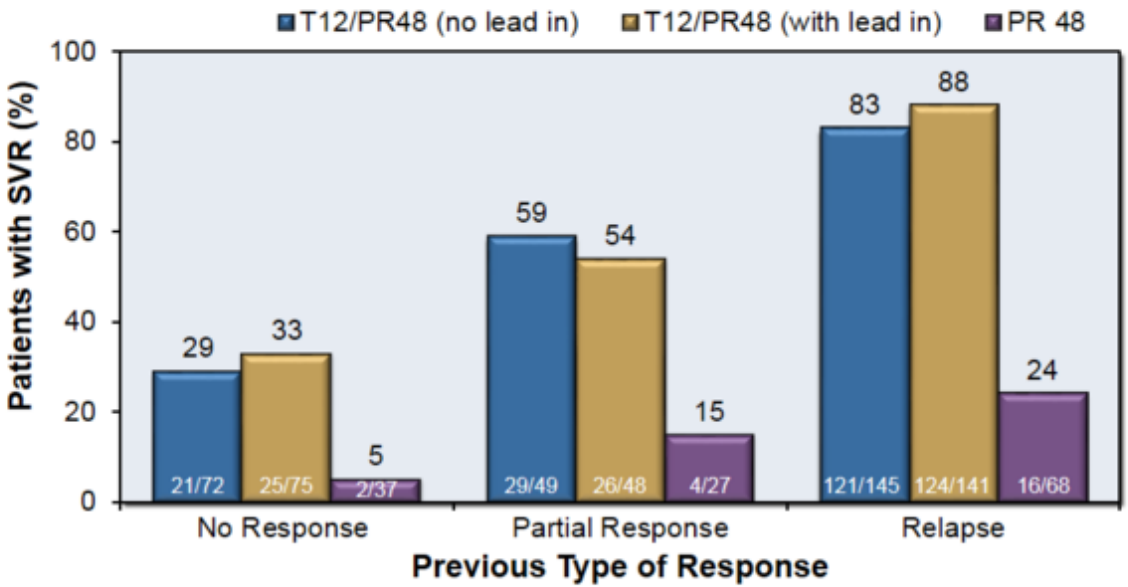


SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

Source: Zeuzem S, et al. N Engl J Med. 2011;364:2417-28.

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

REALIZE: SVR24 by Prior Response

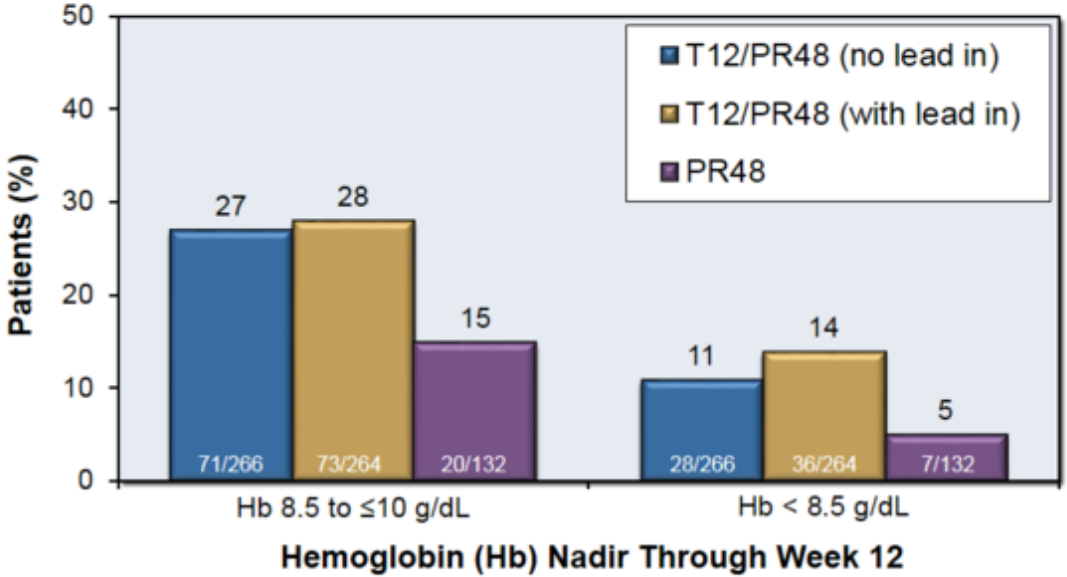


SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

Source: Zeuzem S, et al. N Engl J Med. 2011;364:2417-28.

Telaprevir for Treatment-Experienced HCV Genotype 1
REALIZE: Adverse Effects

REALIZE: Anemia



T = Telaprevir; P = Peginterferon + Ribavirin

Source: Zeuzem S, et al. N Engl J Med. 2011;364:2417-28.

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

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."

Source: Zeuzem S, et al. N Engl J Med. 2011;364:2417-28.

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

Hepatitis Web Study
http://depts.washington.edu/hepstudy/

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

Hepatitis web study

TELAPREVIR (*INCIVEK*)

Adverse Effects