



HEPATITIS WEB STUDY  HEPATITIS C ONLINE

# Telaprevir (*Incivek*)

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Last Updated: February 3, 2014

# Telaprevir Adverse Effects

Adverse Clinical Symptom with $\geq 5\%$ 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



2011/07/01

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\*

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\*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

# 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)

# 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\*

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\*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

# 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\*

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

# 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

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 ( <i>Hypericum perforatum</i> )
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

TELAPREVIR (*INCIVEK*)  
Resistance

# Viral Breakthrough & Telaprevir Resistance

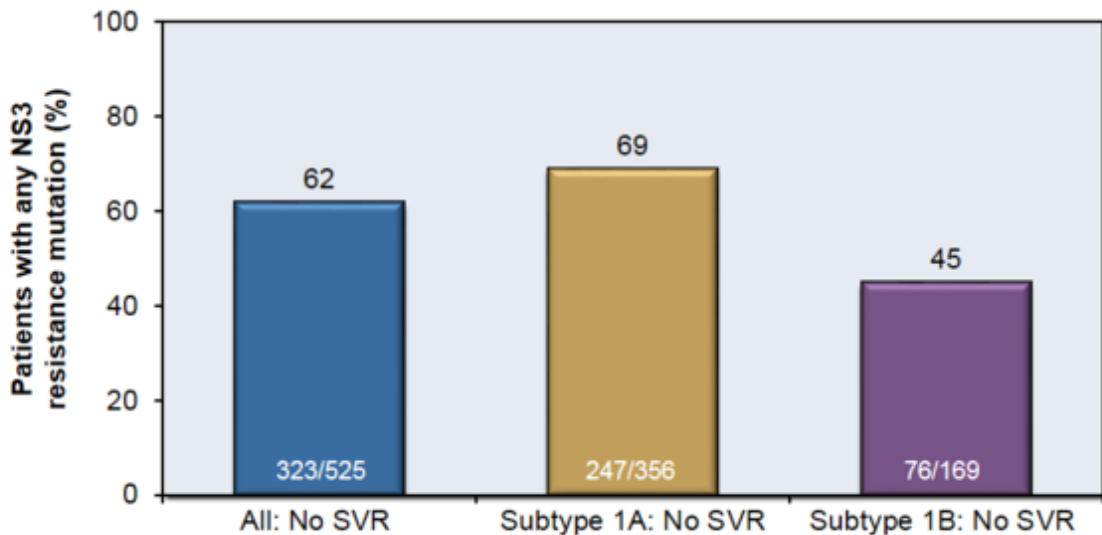
- 14 (8.7%) viral breakthroughs were observed
- Half of these occurred before or at week 4
- Viral breakthroughs were more frequent in patients with HCV genotype 1a (11/14) than 1b (3/14).
- 11 (79%) of 14 patients with viral breakthrough had variants harboring mutations (V36M, V36M/R155K, or A156S) 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

## 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.

# 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	+

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

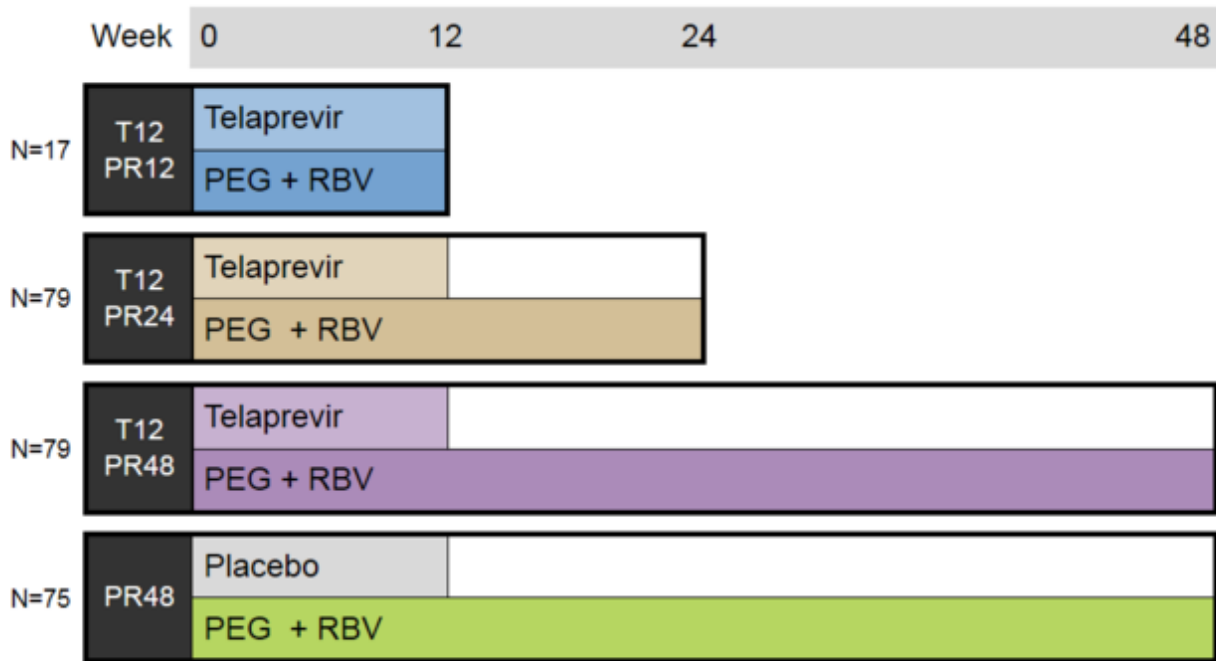
Ribavirin = 1000 mg/day for wt < 75 kg; 1200 mg/day for wt ≥ 75 kg

# 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

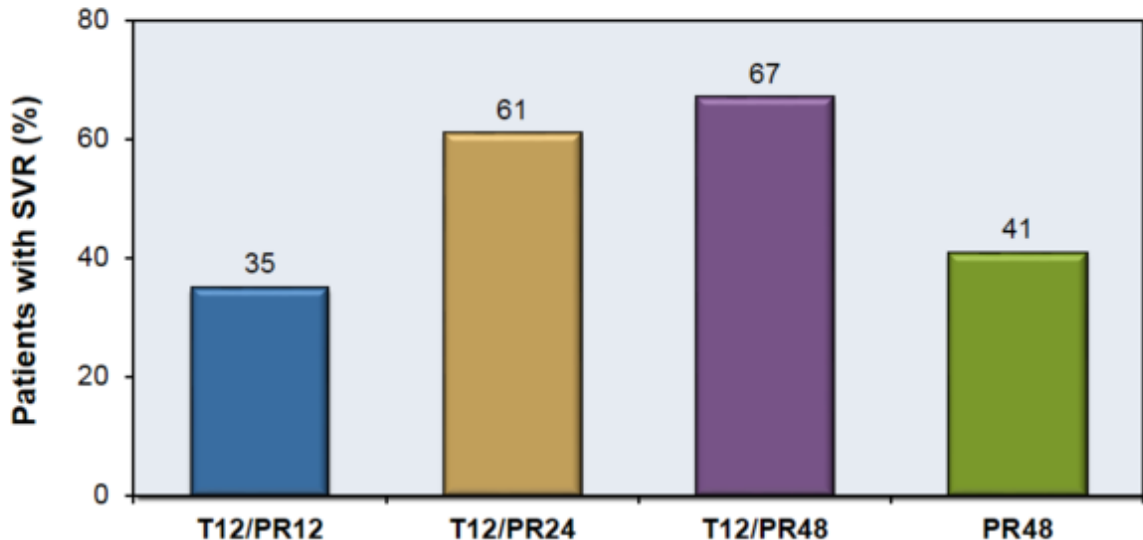
# Telaprevir for Treatment-Naïve HCV Genotype 1

## PROVE1 Study: Treatment Regimens



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

PROVE1: SVR24 by Regimen

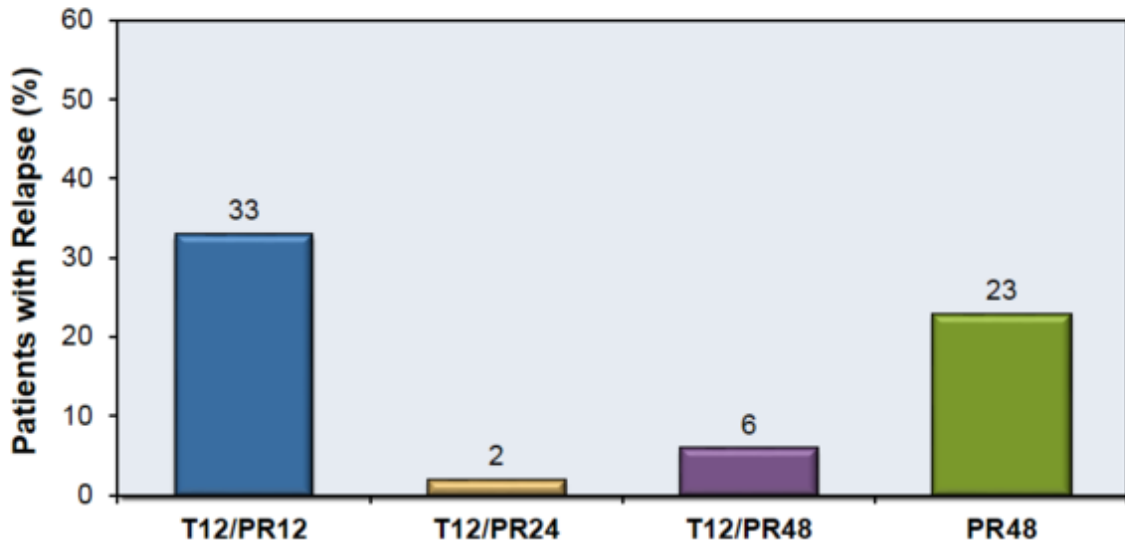


SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

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

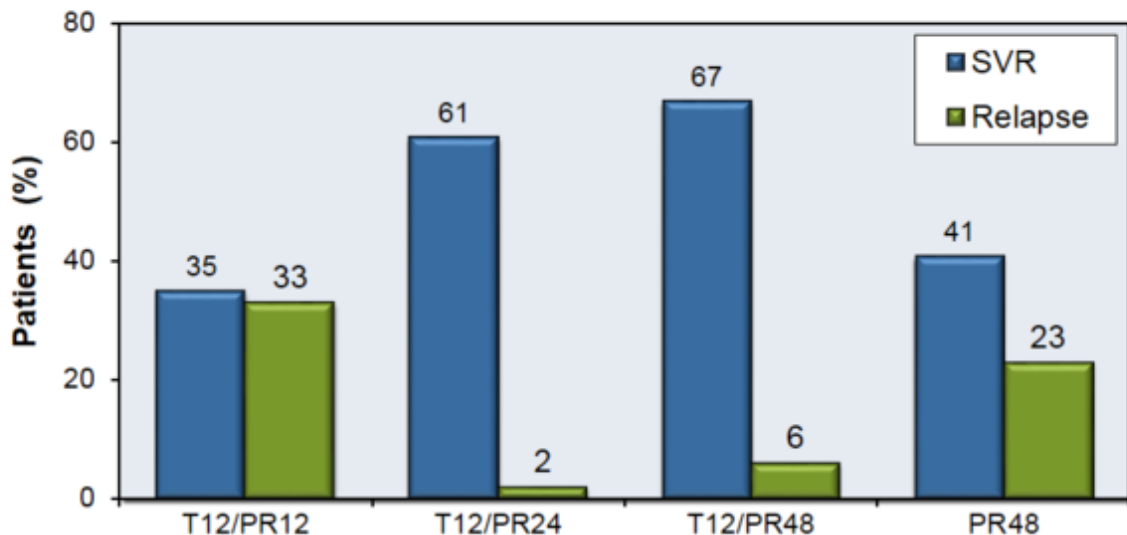


T = Telaprevir; PR = Peginterferon + Ribavirin

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

## 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.”

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  $\geq$  800,000 IU/ml
- Age = 18-65 and HIV-negative
- Setting: 28 sites in Europe
- Randomized to one of 4 arms

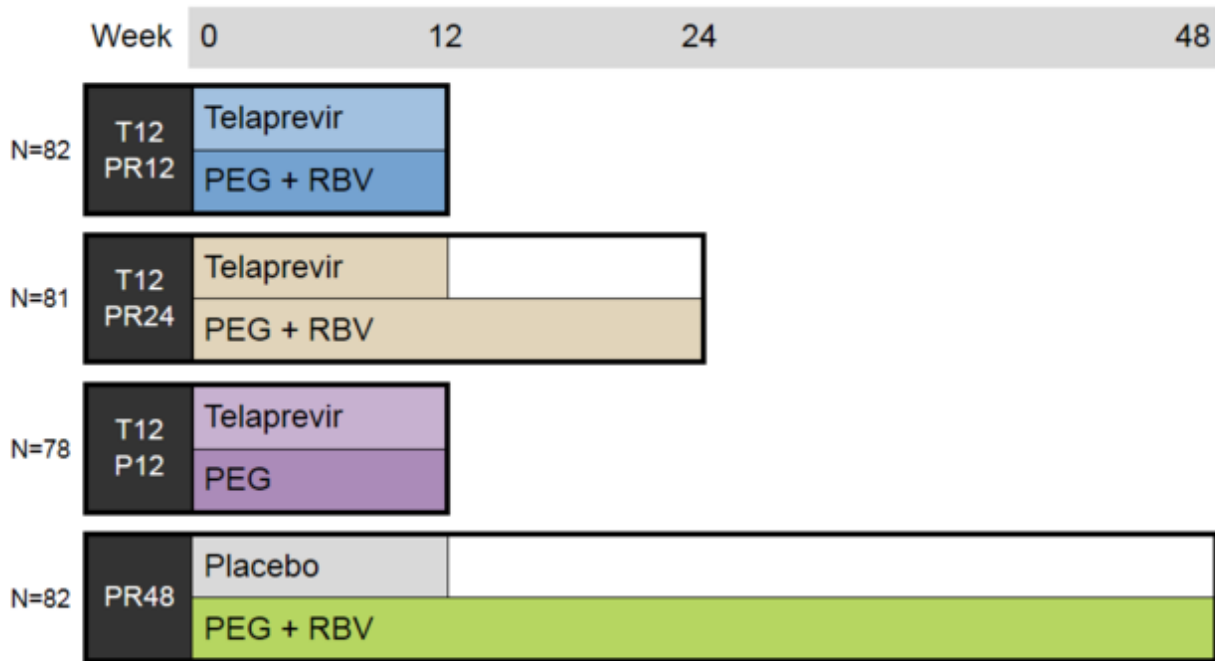
### Drug Dosing

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

Peginterferon alfa-2a = 180  $\mu$ g weekly

Ribavirin = 1000 mg/day for wt < 75 kg; 1200 mg/day for wt  $\geq$  75 kg

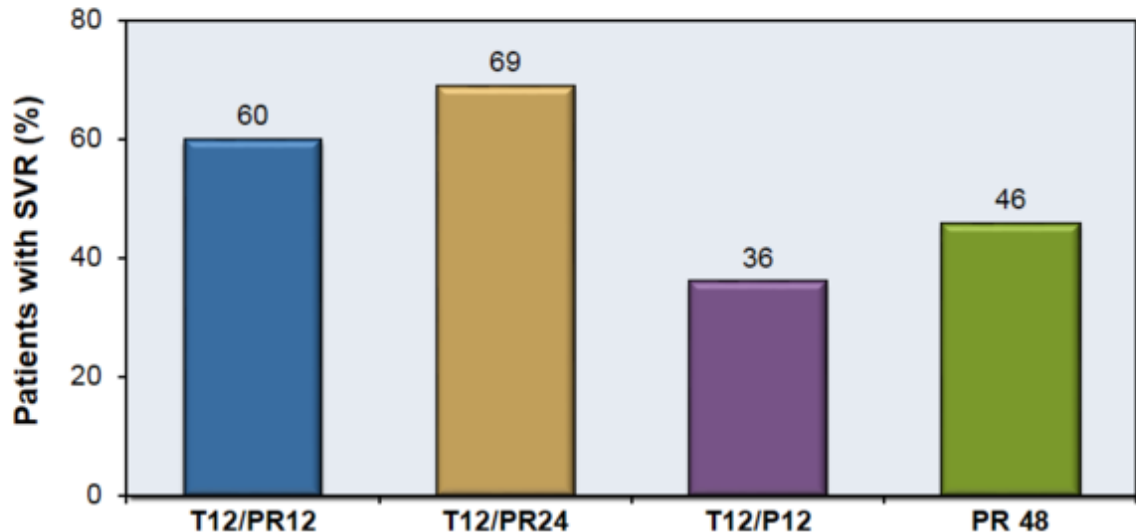
# Telaprevir for Treatment-Naïve HCV Genotype 1 PROVE2 Study: Treatment Regimens



# Telaprevir for Treatment-Naïve HCV Genotype 1

## PROVE2 Study: Results

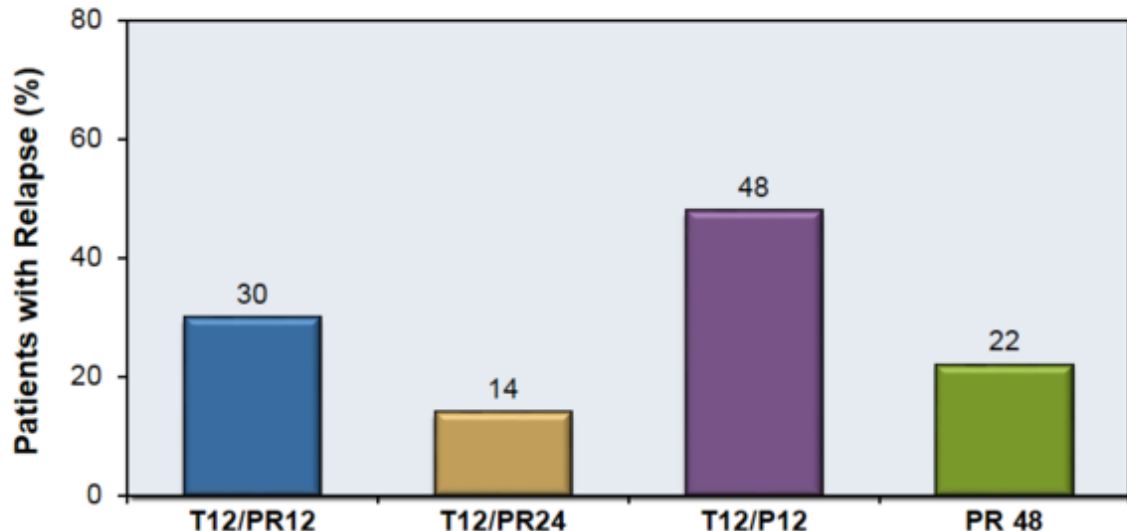
PROVE2: SVR24 by Regimen



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

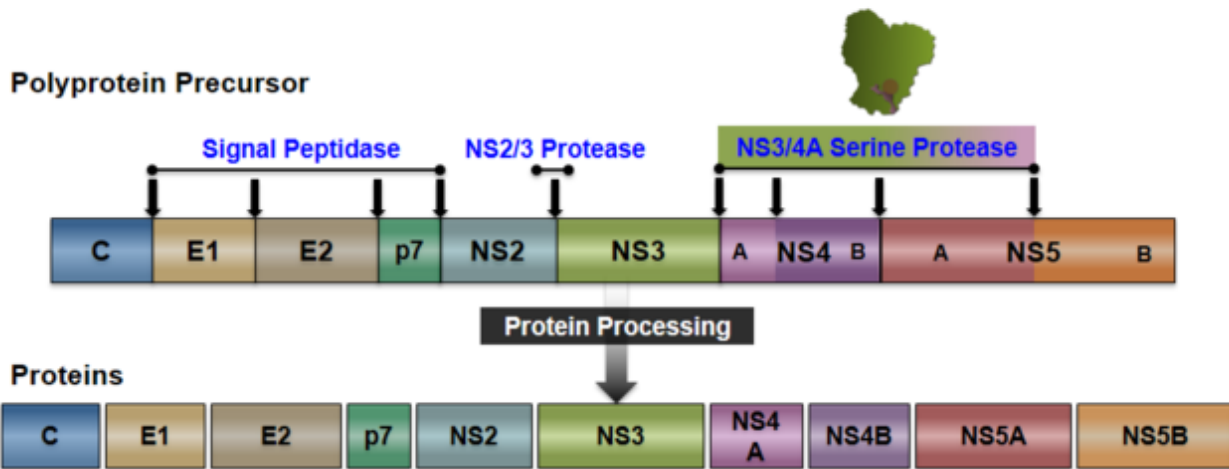


T = Telaprevir; P = Peginterferon; PR = Peginterferon + Ribavirin

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

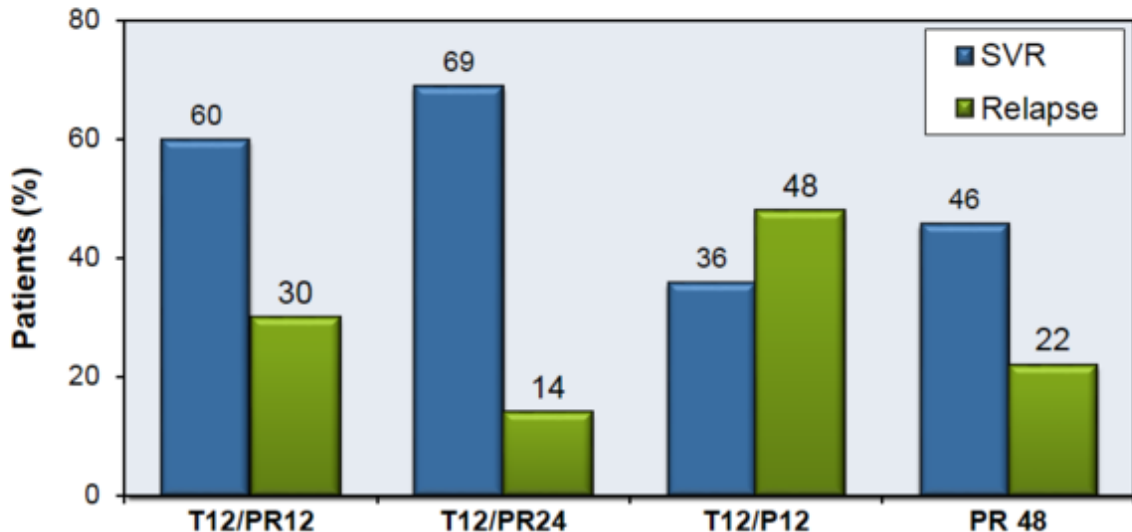
# HCV Protein Processing

## 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

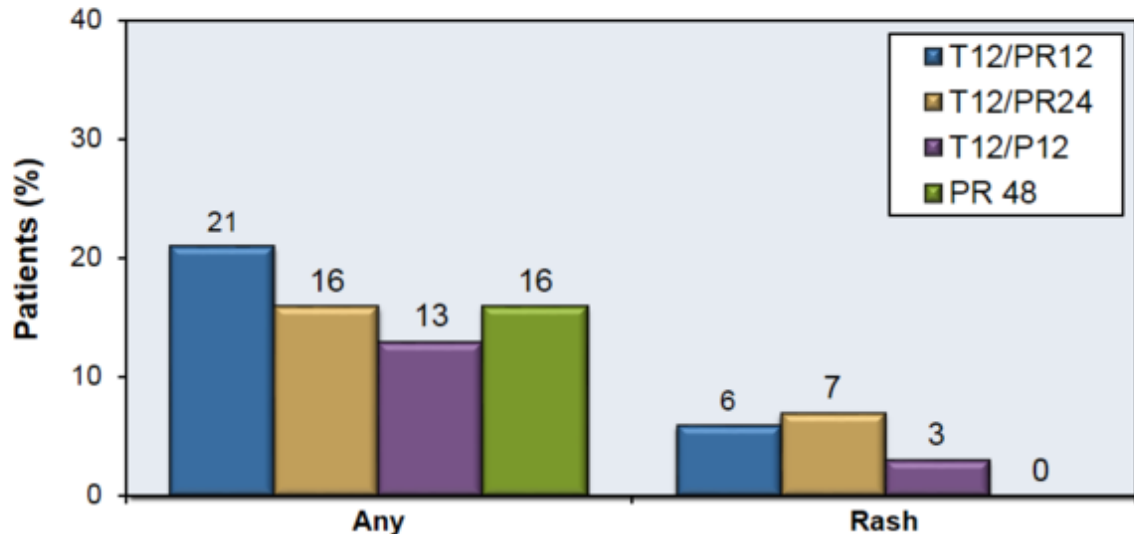


SVR = Sustained Virologic Response; T = Telaprevir; P = Peginterferon; PR = Peginterferon + Ribavirin

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

# 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.”

# 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  $\geq$  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

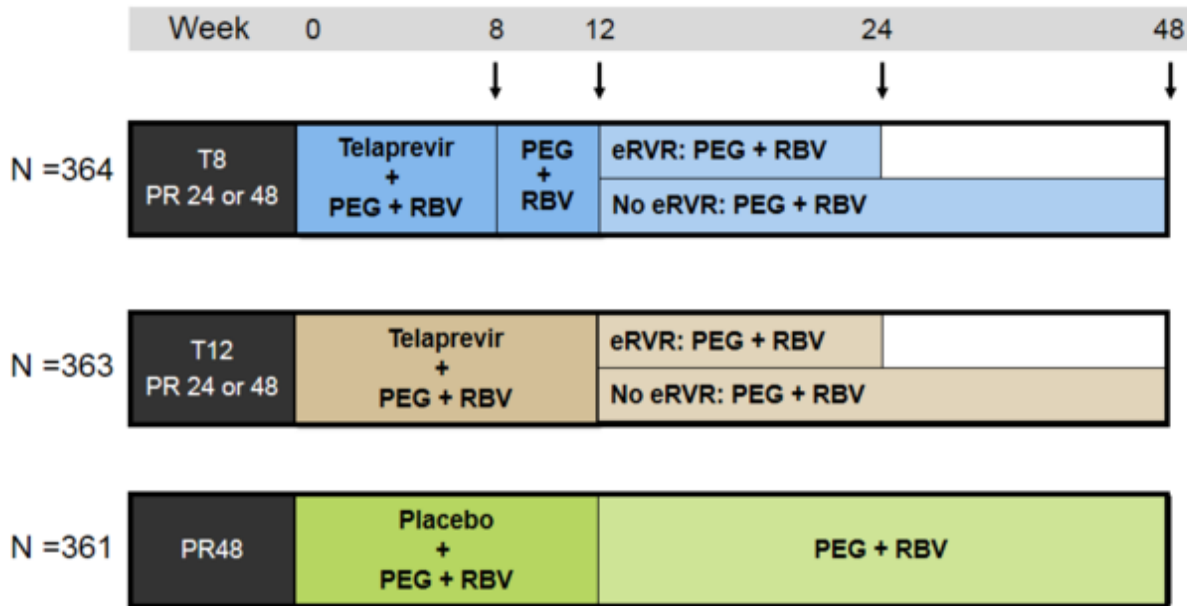
### Drug Dosing

Telaprevir = 750 mg every 8 hours

Peginterferon alfa-2a = 180  $\mu$ g weekly

Ribavirin = 1000 mg/day for wt < 75 kg; 1200 mg/day for wt  $\geq$  75 kg

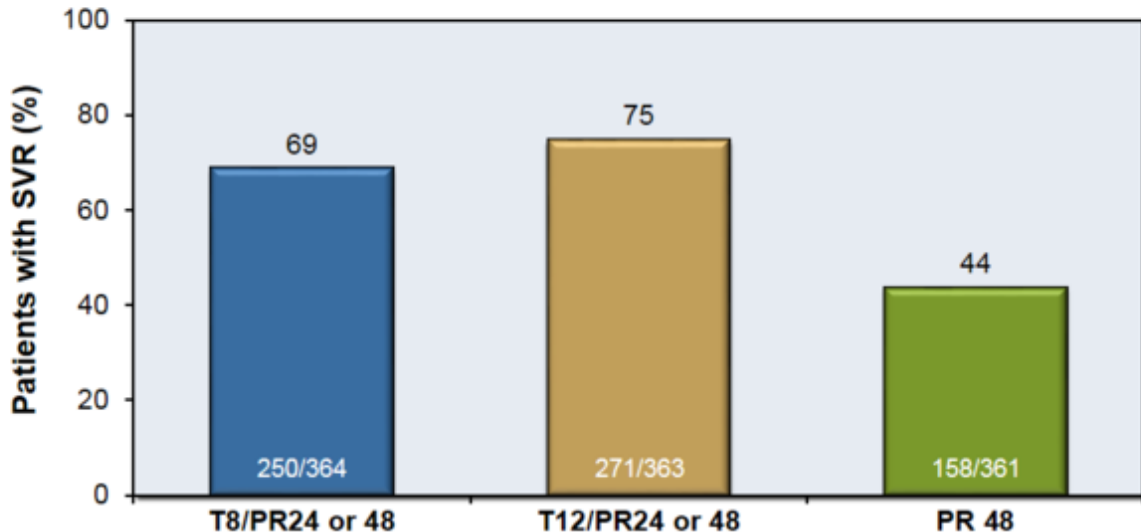
# Telaprevir for Treatment-Naïve HCV Genotype 1 ADVANCE Study: Treatment Regimens



# Telaprevir for Treatment-Naïve HCV Genotype 1

## ADVANCE Study: Results

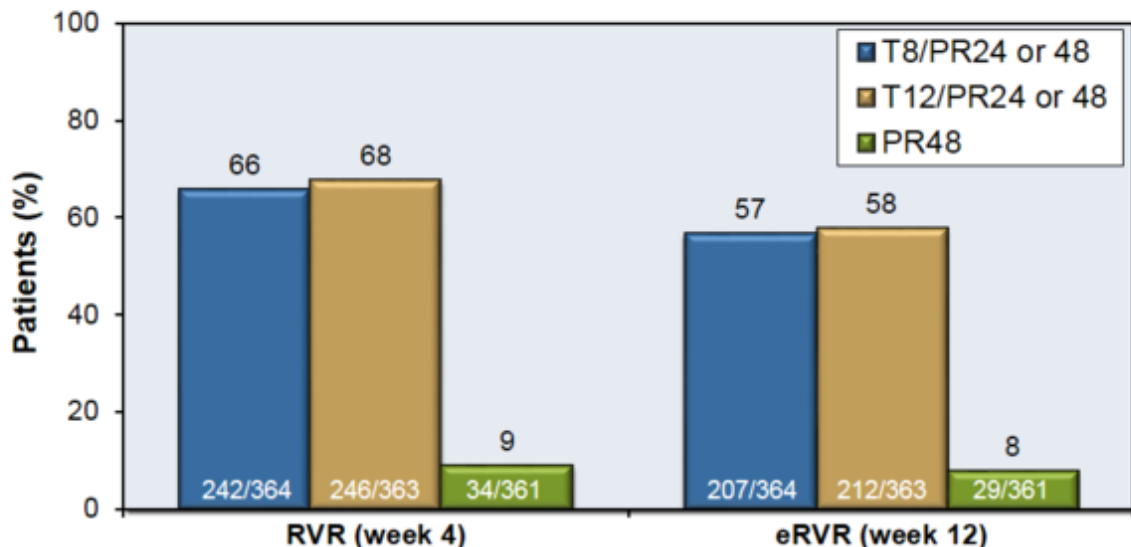
ADVANCE: SVR24 by Regimen



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

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

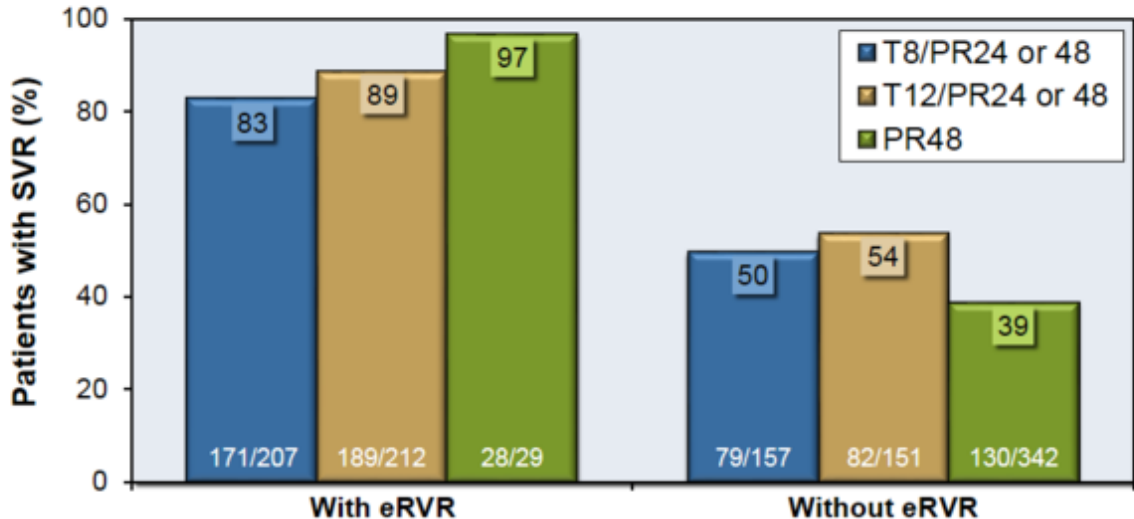
ADVANCE: Patients with RVR and eRVR



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

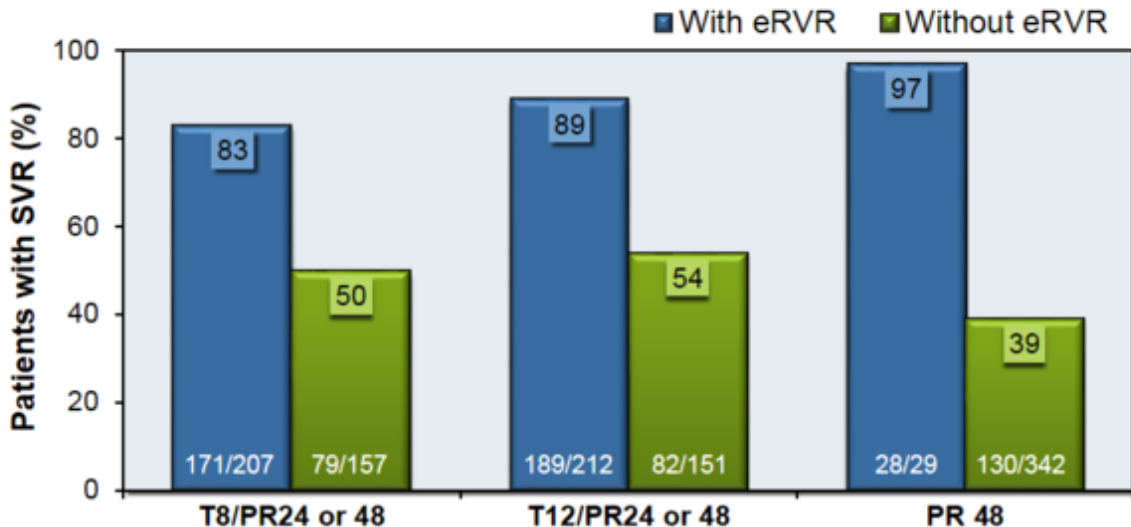
ADVANCE: SVR24 by eRVR Status



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

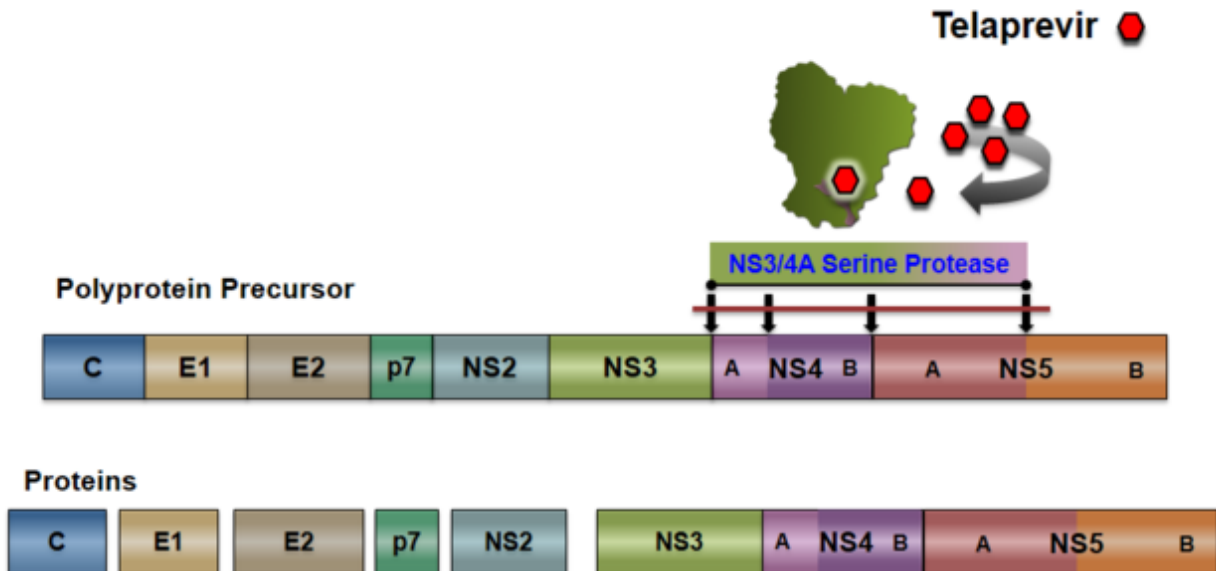
ADVANCE: SVR24 by eRVR Status



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

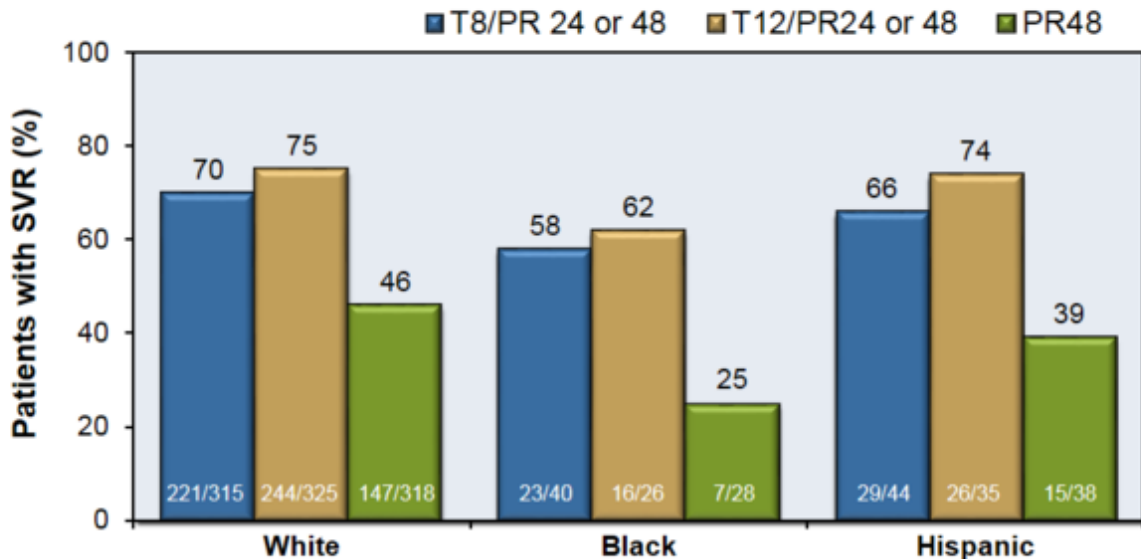
# Telaprevir: Mechanism of Action

## NS3/4A Serine Protease Inhibition



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

ADVANCE: SVR24 by Race

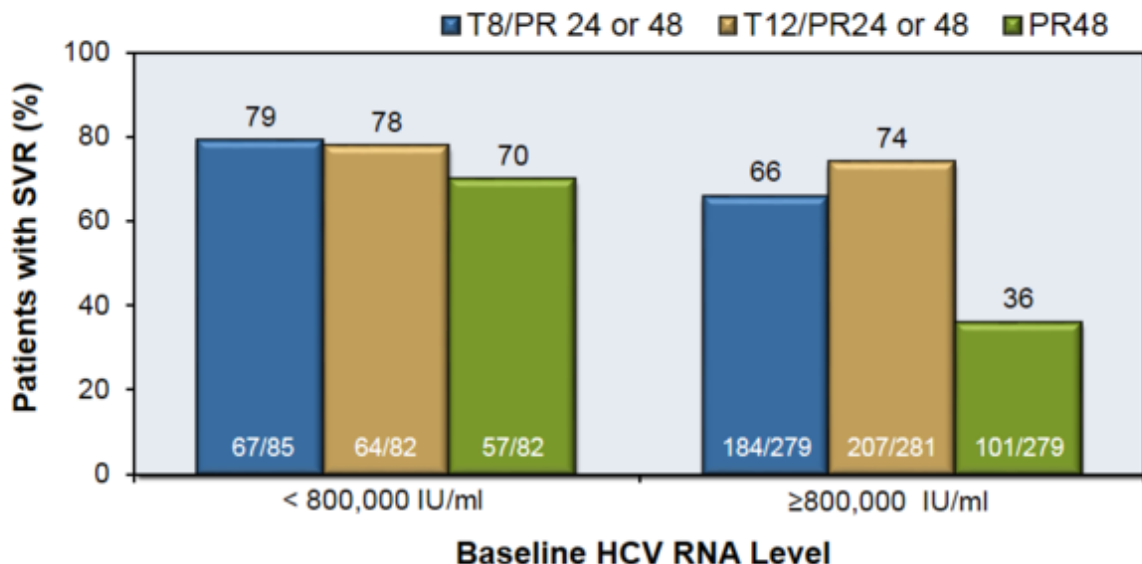


SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

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

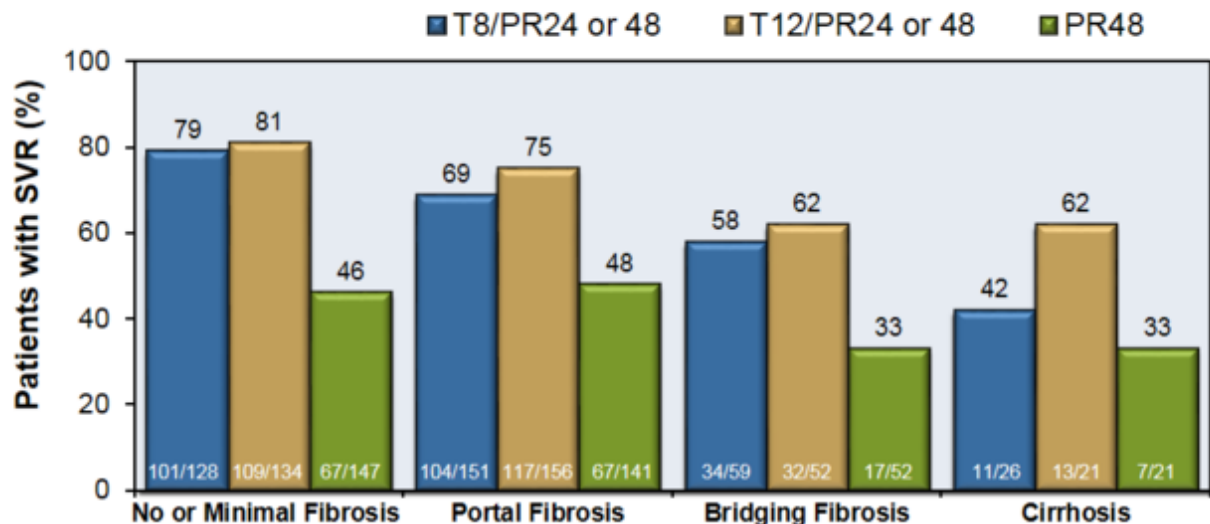


SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

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

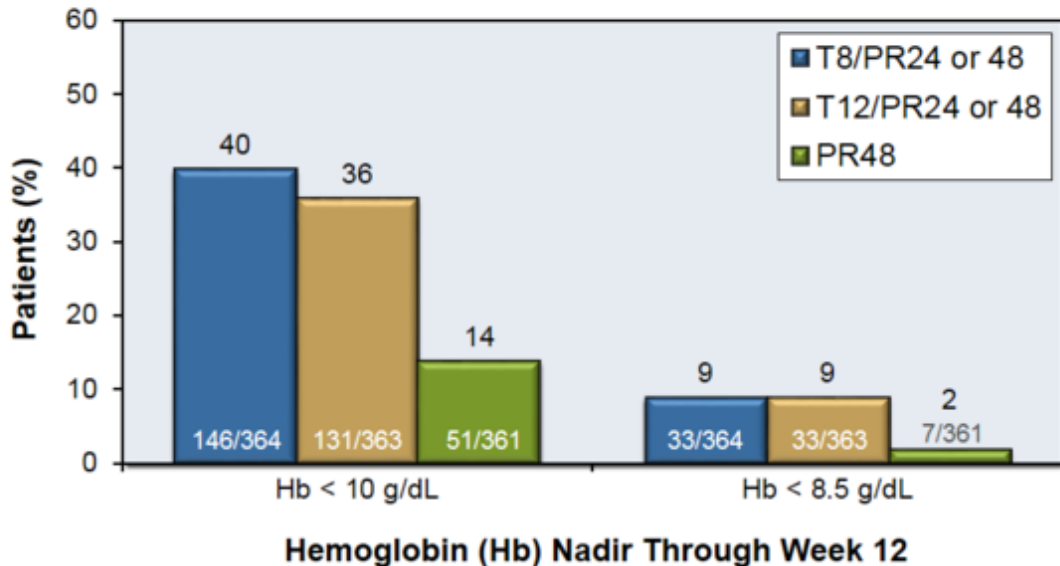


SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

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

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

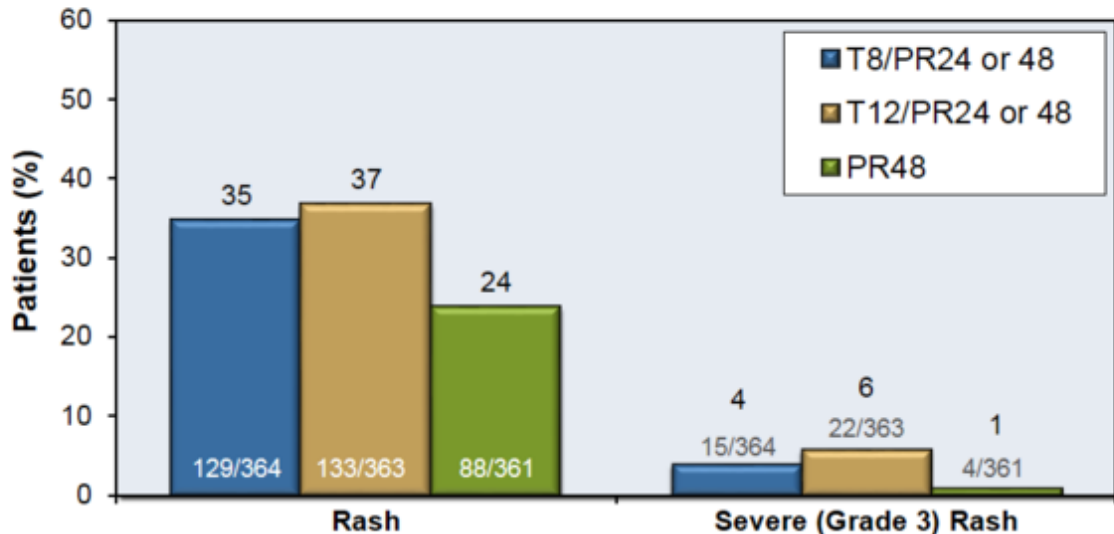
## ADVANCE: Percentage of Patients with Anemia



T = Telaprevir; PR = Peginterferon + Ribavirin

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

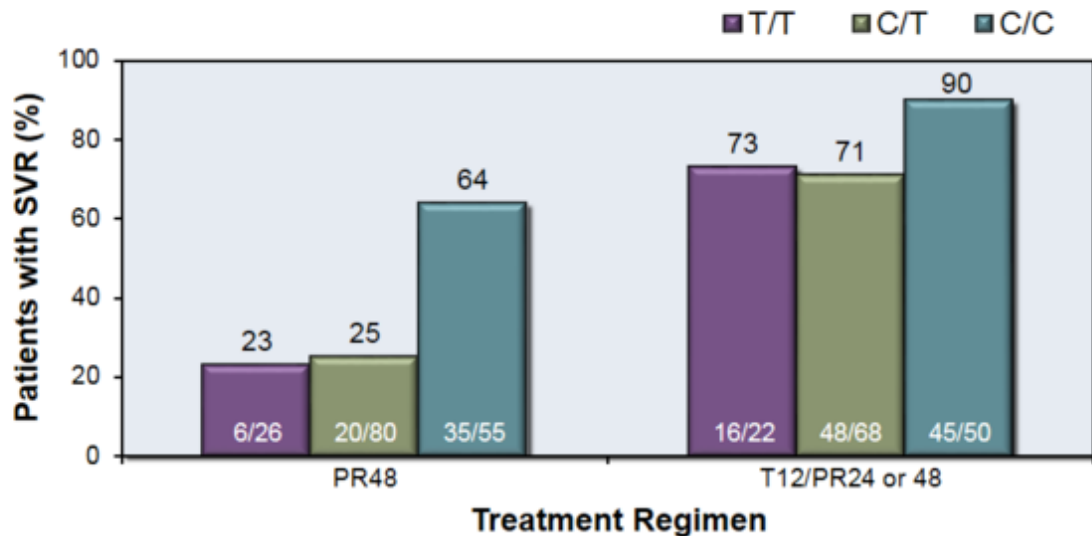
## ADVANCE: Percentage of Patients with Rash



T = Telaprevir; PR = Peginterferon + Ribavirin

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

ADVANCE: SVR24 by rs12979860 Genotype



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

# 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.”

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

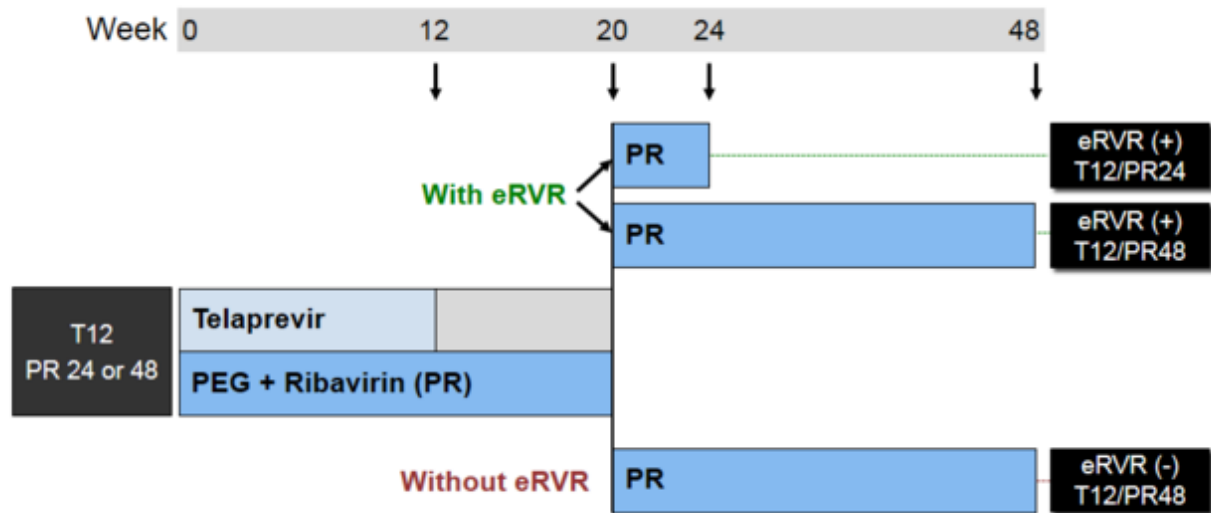
### Drug Dosing

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

# 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)

# Telaprevir Response Guided Therapy

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

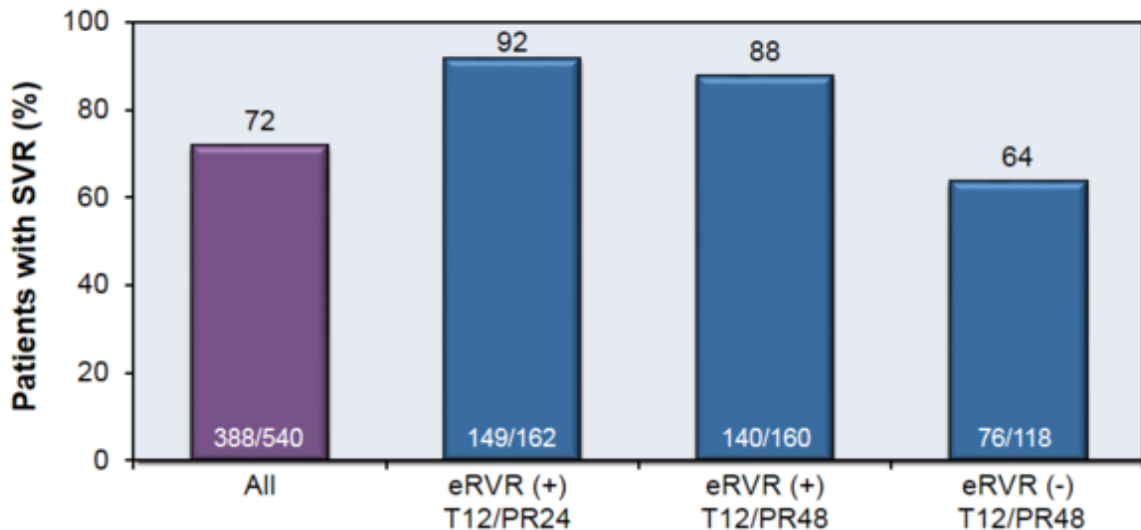
\*In clinical trials, HCV-RNA in plasma was measured using a COBAS® TaqMan® assay with a lower limit of quantification of 25 IU/mL and a limit of detection of 10 IU/mL

<sup>^</sup>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

# 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)

# 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

# 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.”

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  $\geq$  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  $\mu$ g weekly

Ribavirin = 1000 mg/day for wt  $<$  75 kg; 1200 mg/day for wt  $\geq$  75 kg

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

Week 0                      12                      24                      48

T12 bid  
PR 24 or 48  
(n = 369)

Telaprevir (bid)

PEG + RBV

If (-) RVR continue PEG + RBV

T12 q8h  
PR 24 or 48  
(n = 371)

Telaprevir (q8h)

PEG + RBV

If (-) RVR continue PEG + RBV

RVR = week 4 HCV RNA undetectable

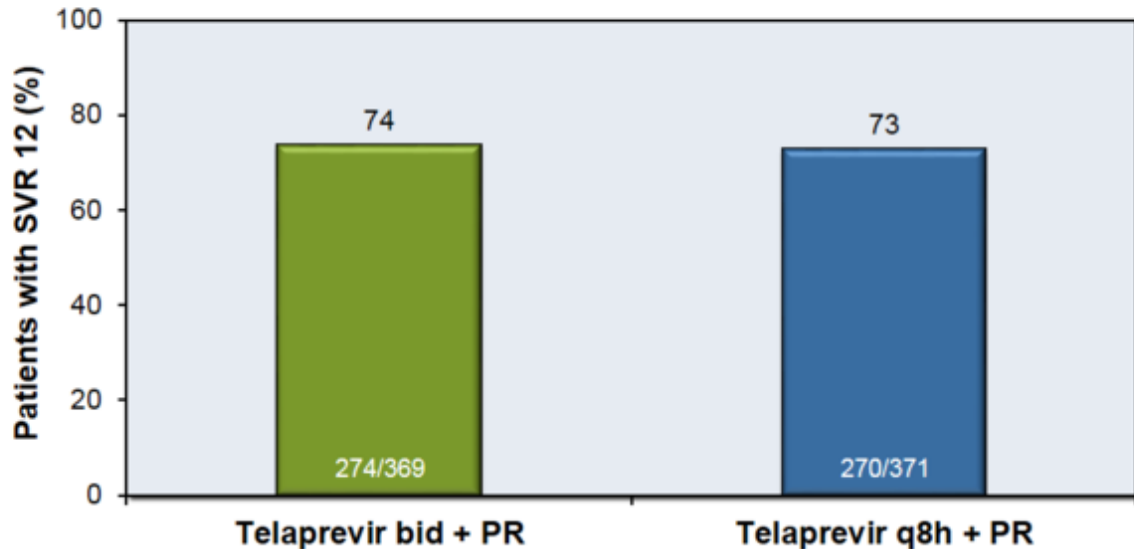
PEG = peginterferon; RBV = ribavirin

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

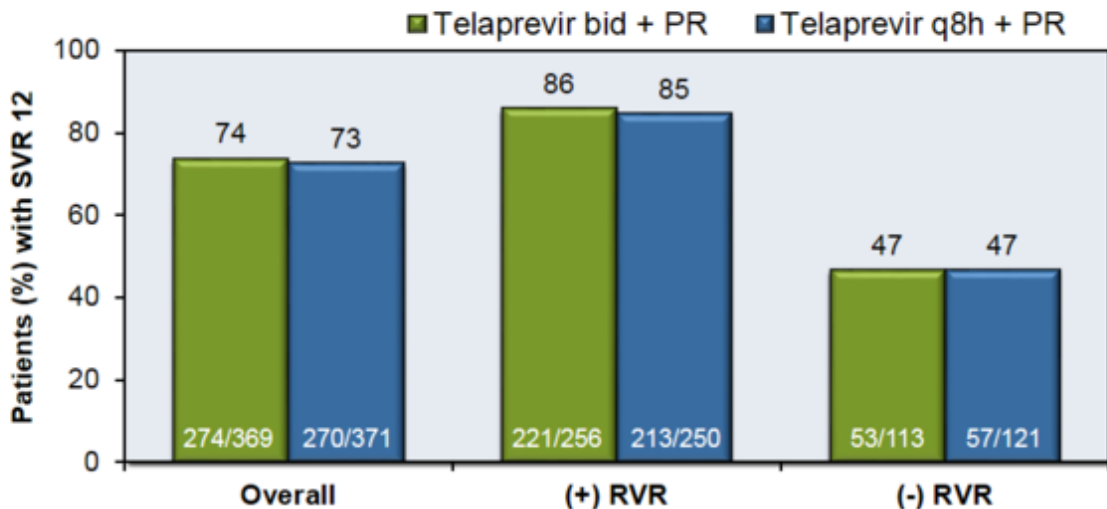
### OPTIMIZE: SVR12 by Regimen



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

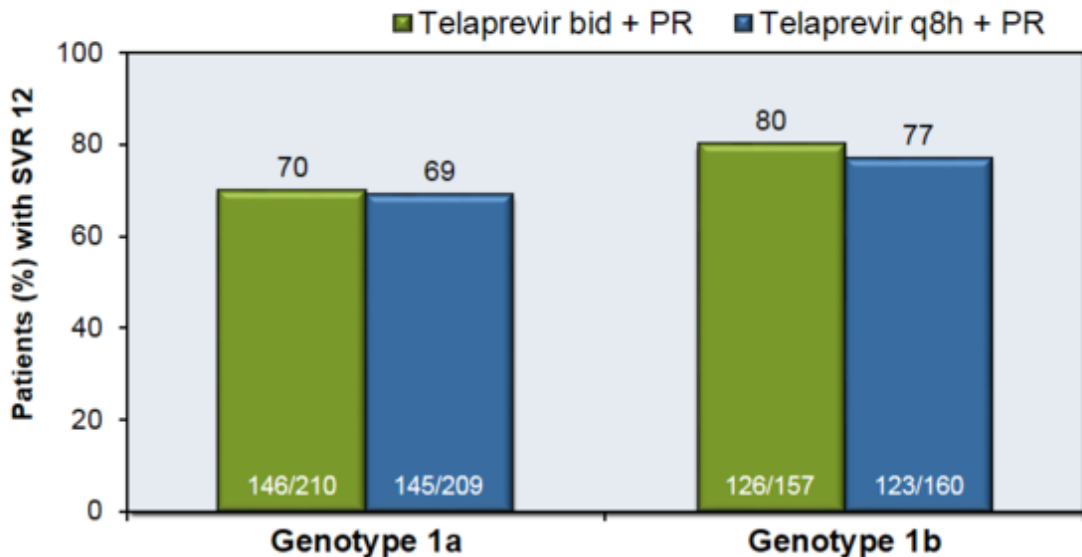


RVR = rapid virologic response (undetectable HCV RNA at week 4)

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

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

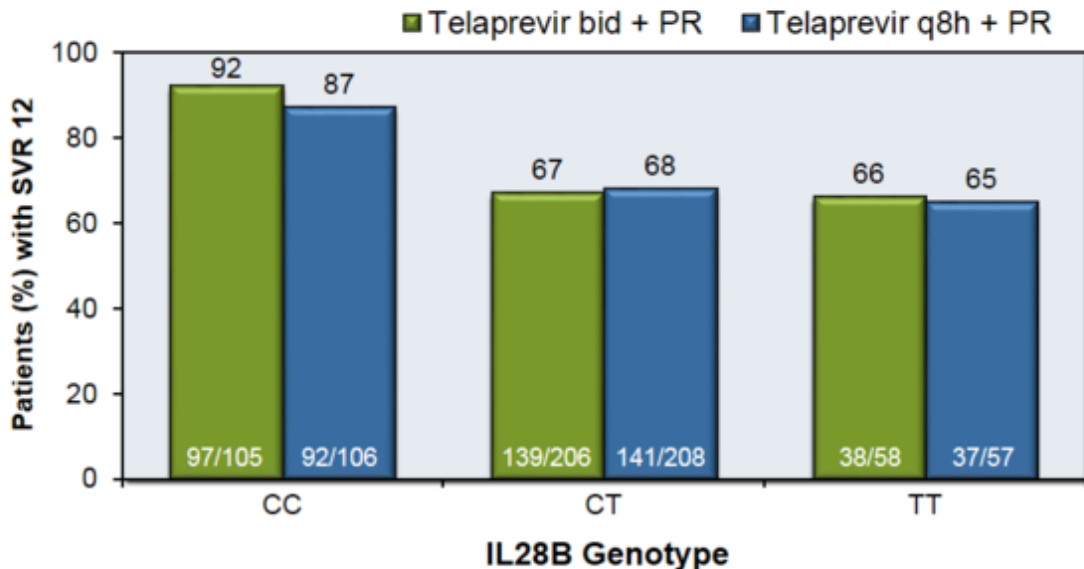
## OPTIMIZE: SVR12 by Genotype 1 Subtype



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

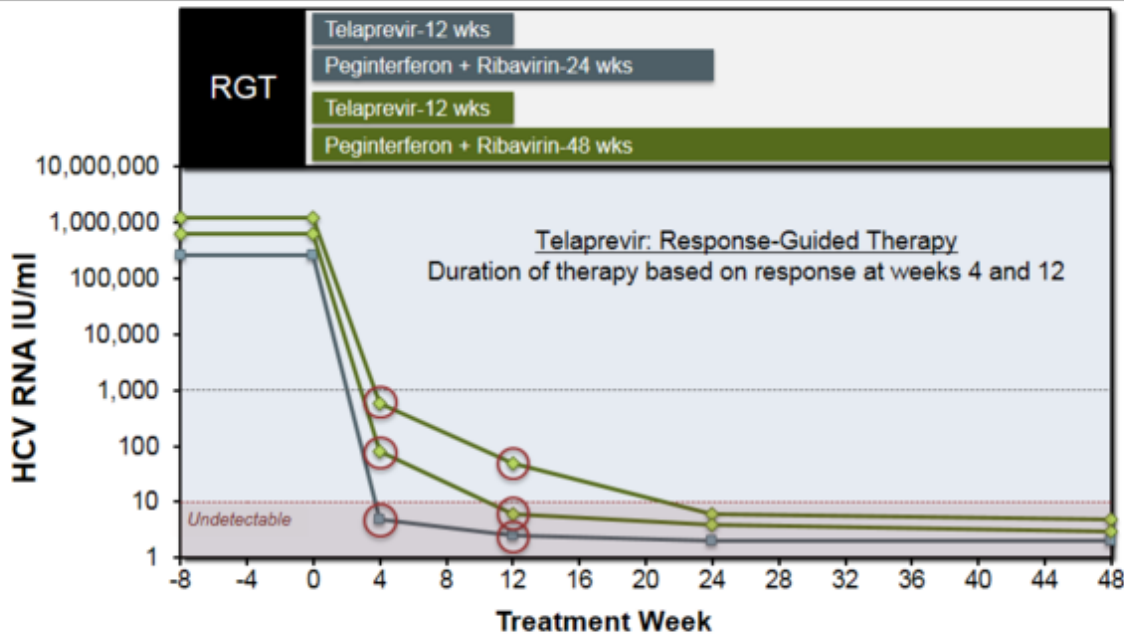


Abbreviations: SVR = sustained virologic response; PR = peginterferon + ribavirin

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

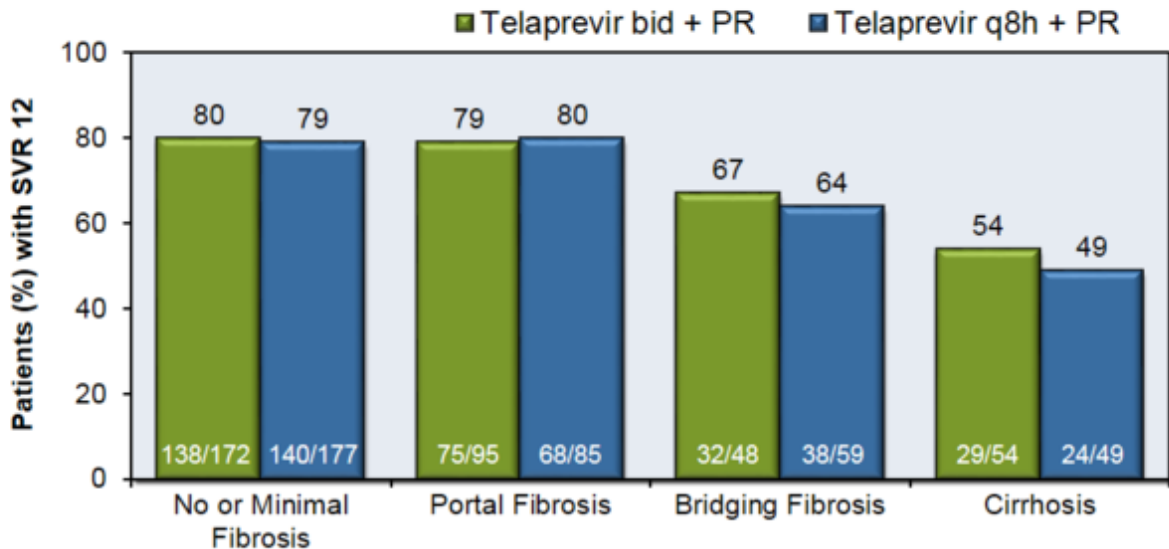
# Telaprevir Response-Guided Therapy Treatment Naïve and Prior Relapse Patients

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



# 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 hrs 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

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  $\geq$  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

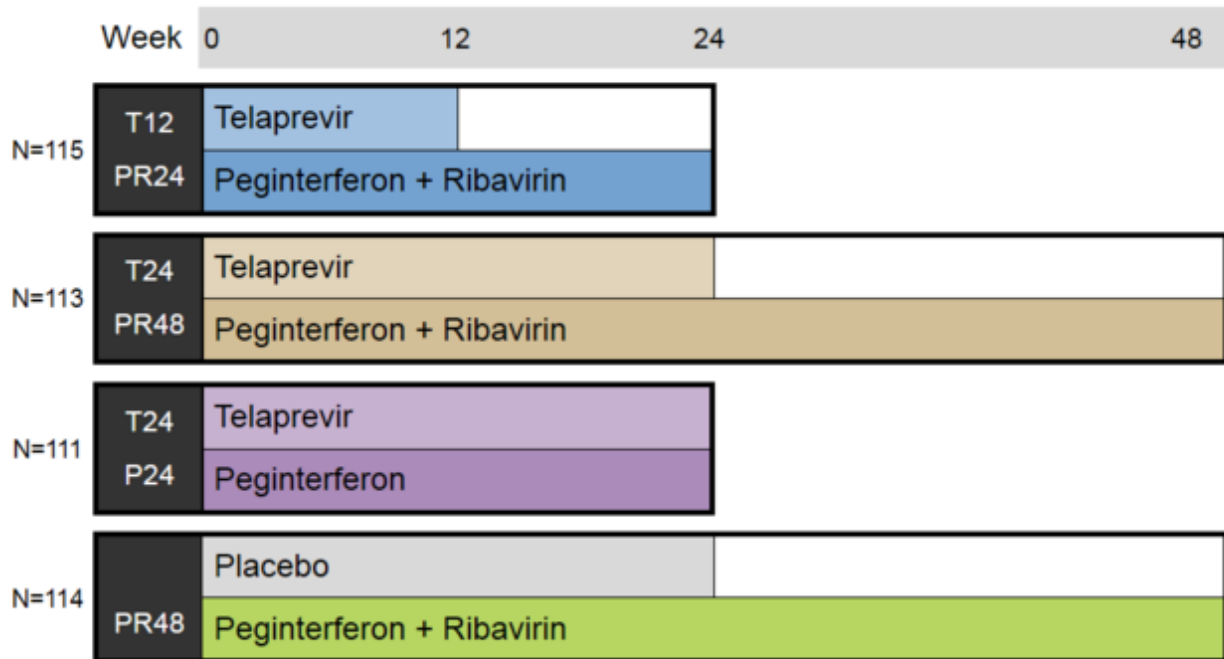
### Drug Dosing

Telaprevir = 1125 mg loading dose, then 750 mg every 8 hours

Peginterferon alfa-2a = 180  $\mu$ g weekly

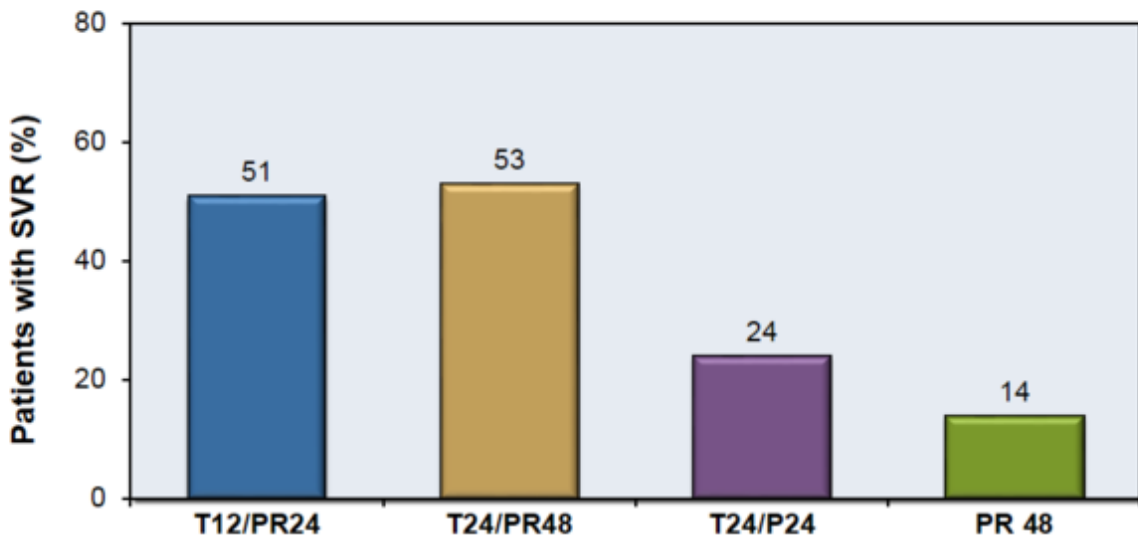
Ribavirin = 1000 mg/d for wt < 75 kg; 1200 mg/d for wt  $\geq$  75 kg

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



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

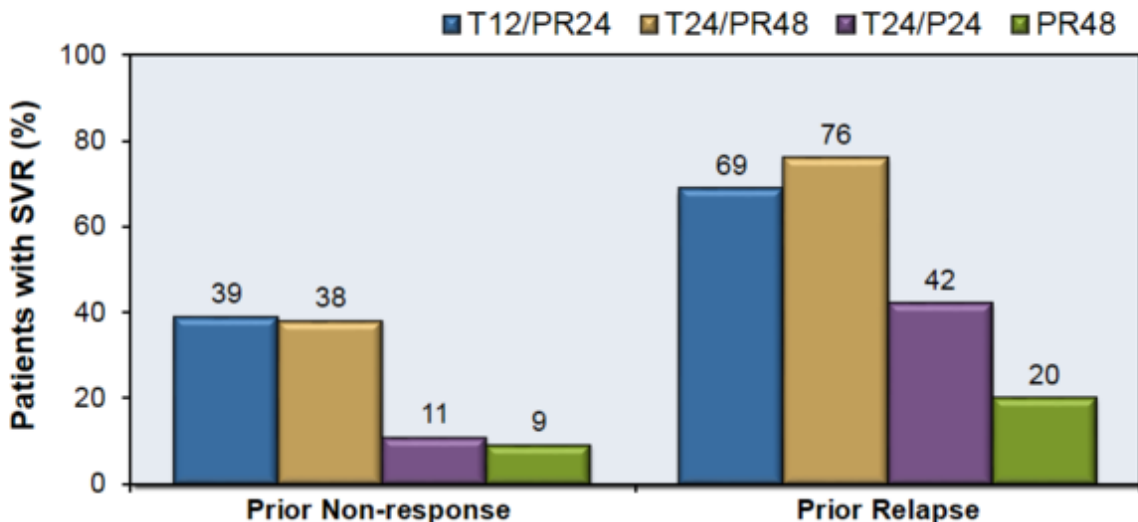
## PROVE3: SVR24 by Regimen



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

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

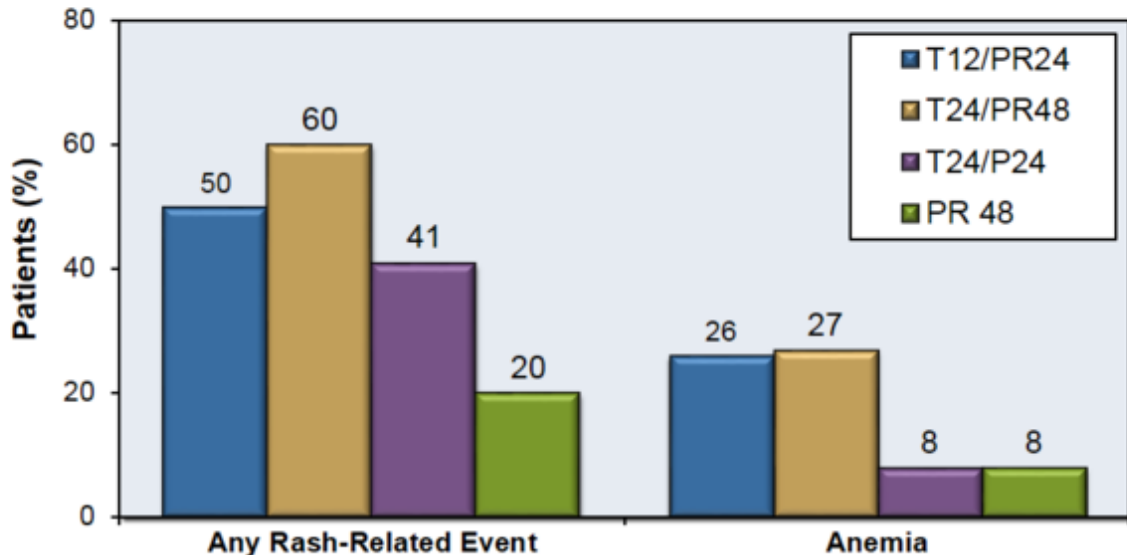
## PROVE3: SVR24 by Prior Response Status



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

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

## PROVE3: Adverse Events



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.”

## 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

Futility Rules for Treatment with Telaprevir and Peginterferon plus Ribavirin				
Stopping Criteria*	Regimen and Treatment Duration (weeks)			
	0                      4                      12                      24			
Week 4 HCV RNA > 1000 IU	<table border="1"> <tr> <td>Telaprevir</td> <td rowspan="2"></td> </tr> <tr> <td>PR</td> </tr> </table>	Telaprevir		PR
Telaprevir				
PR				
Week 12 HCV RNA > 1000 IU	<table border="1"> <tr> <td>Telaprevir</td> <td rowspan="2"></td> </tr> <tr> <td>PR</td> </tr> </table>	Telaprevir		PR
Telaprevir				
PR				
Week 24 Detectable HCV RNA	<table border="1"> <tr> <td>Telaprevir</td> <td rowspan="2"></td> </tr> <tr> <td>PR</td> </tr> </table>	Telaprevir		PR
Telaprevir				
PR				

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.

# 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

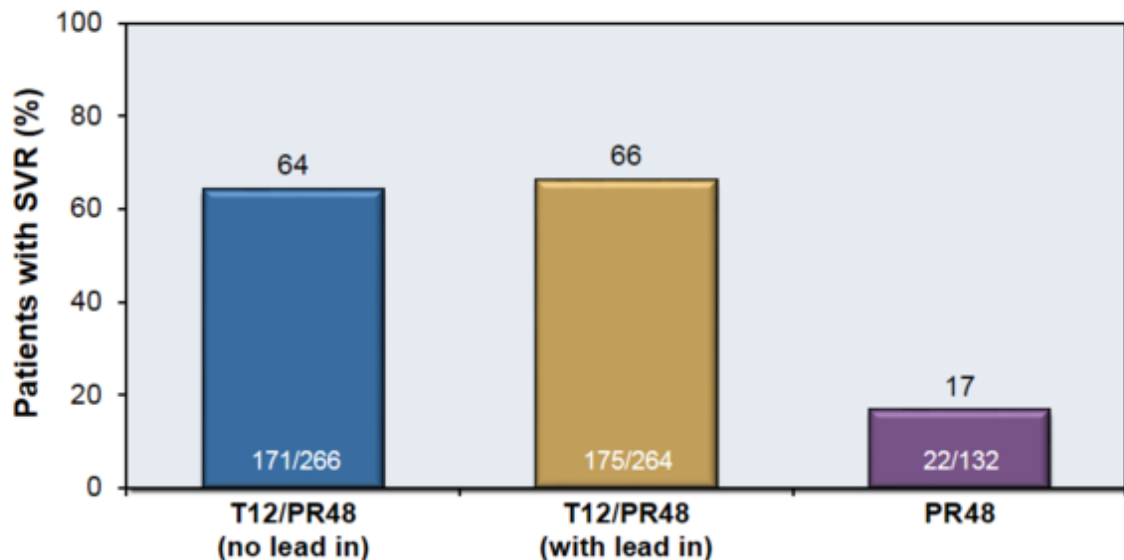
# Telaprevir for Treatment-Experienced HCV Genotype 1

## REALIZE: Treatment Regimens



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

## REALIZE: SVR24 by Regimen



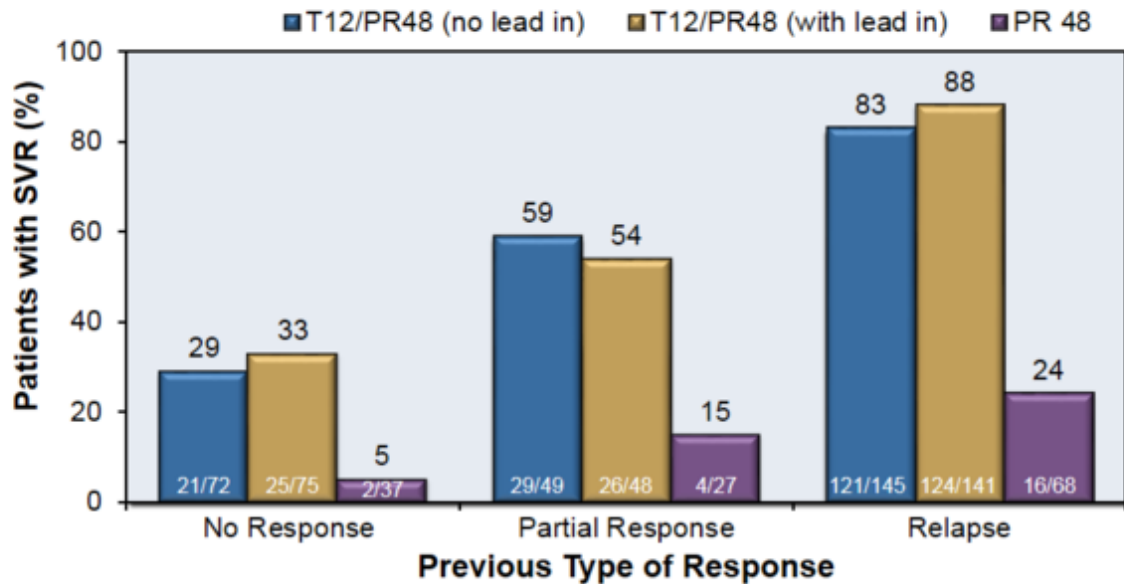
SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

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



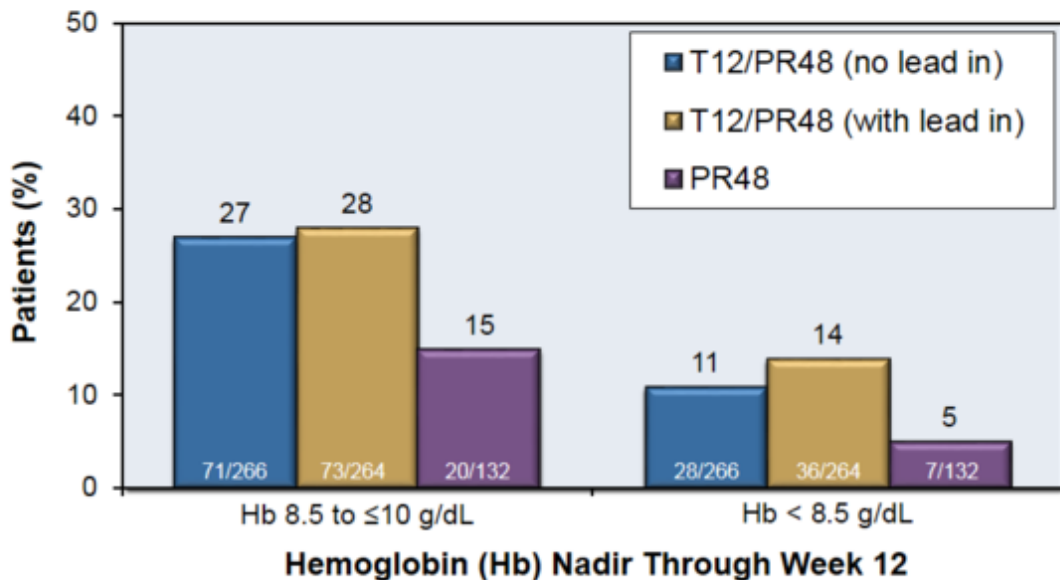
SVR = Sustained Virologic Response; T = Telaprevir; PR = Peginterferon + Ribavirin

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.”

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

<http://depts.washington.edu/hepstudy/>

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

TELAPREVIR (*INCIVEK*)  
Adverse Effects