PROVE2: Telaprevir and Peginterferon with or without Ribavirin for Chronic HCV Infection

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For the PROVE2 Study Team

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New England Journal of Medicine 2009;360(18):1839-1850

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PROVE = PROtease Inhibition for Viral Evaluation

PROVE2

PROVE2: PROtease Inhibition for Viral Evaluation 2

- Multicenter, randomized, partially double-blind, placebo-controlled, Phase 2b clinical trial
  - 323 treatment-naïve patients with chronic genotype 1 HCV infection
  - 28 centers in Europe
  - Compared telaprevir (TVR) -based therapy groups of 12- and 24-week durations with and without RBV (T12P12) against a 48-week Peg-IFN alfa-2a/RBV control group
- Objectives
  - Assess the efficacy and tolerability of various regimens combining telaprevir with Peg-IFN with or without RBV, as compared with Peg-IFN/RBV alone

Peg-IFN = Peginterferon alfa-2a (Pegasys®, Roche)
RBV = Ribavirin (Copegus®, Roche)
Hézode C et al, N Engl J Med 2009;360(18):1839-1850

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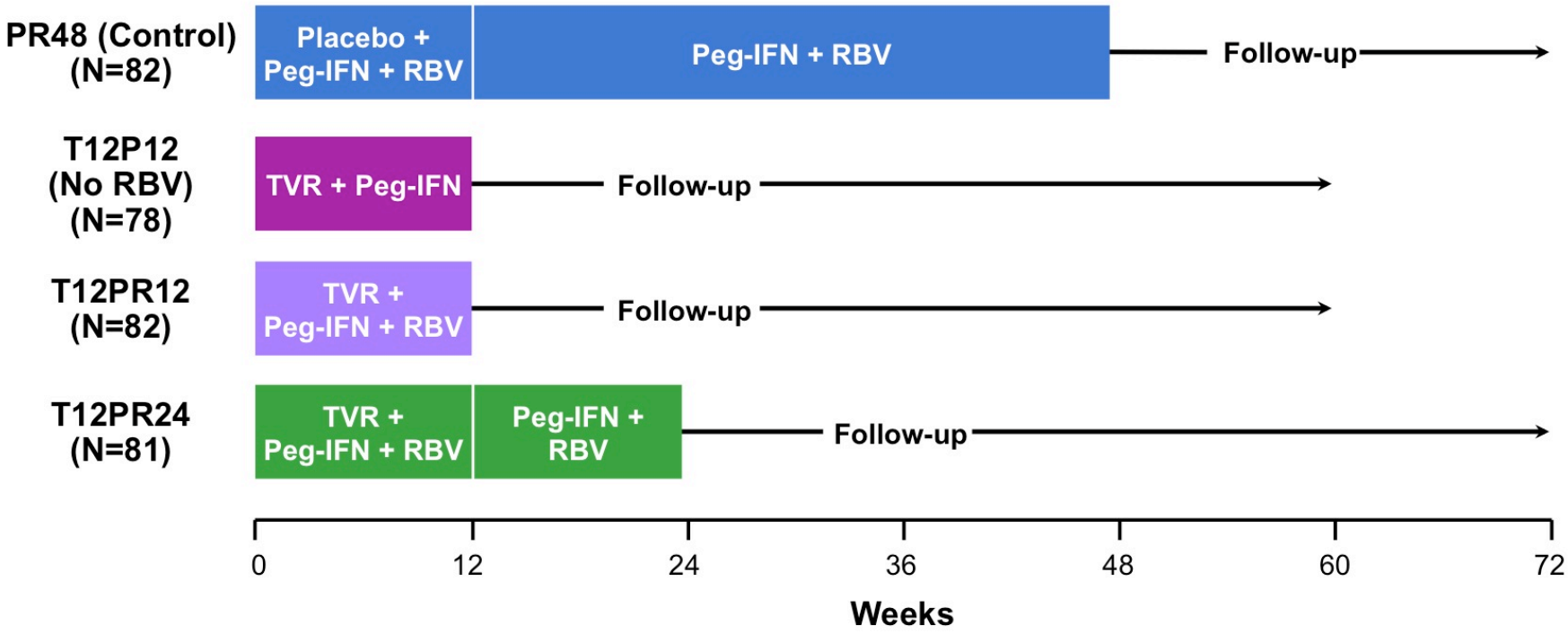
PROVE2: Study Design



- Patients in the TVR-based treatment groups needed to have undetectable HCV RNA levels at the last study visit before the planned end of treatment (i.e., at week 10 for the T12PR12 and T12P12 groups and at week 20 for the T12PR24 group)

(P) Peg-IFN = pegylated interferon alfa-2a 180 µg/wk subcutaneous injection

(R) RBV = ribavirin 1000 mg/day (body weight <75 kg) or 1200 mg/day (body weight ≥75 kg)

(T) TVR = telaprevir 750 mg q8h (initial loading dose 1250 mg)

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PROVE2: Methods

- Primary endpoint
  - The proportion of patients in each group who achieved sustained virologic response (SVR), defined as undetectable plasma HCV RNA, 24 weeks after the end of therapy
- Patients
  - Treatment-naïve
  - Age 18 to 65 years
  - Chronically infected with HCV genotype 1
  - Patients with cirrhosis were excluded
- HCV RNA assessment by COBAS TaqMan HCV assay (Roche Molecular Systems) (lower limit of detection 10 IU/mL; lower limit of quantification 30 IU/mL)

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PROVE2: Methods

- Statistical analysis
  - Analyses of safety and efficacy included data from all patients who had undergone randomization and had received at least one dose of any study drug
  - The original primary efficacy analysis was a comparison of SVR rates between the control group (PR48) and the combined T12/P12 (which did not receive RBV) and T12/PR12 groups
  - After review of 3rd interim analysis data, a decision was made prospectively to change the primary analysis to the comparison with SVR rates between PR48 and each telaprevir-based regimen group (the original secondary analysis)
  - Fisher's exact test was used for statistical comparison, all tests were two-sided

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PROVE2: Baseline Characteristics

Characteristic	T12PR24 (N=81)	T12PR12 (N=82)	T12P12 (No RBV) (N=78)	PR48 (Control) (N=82)
Age, median (range)	46 (19–65)	44 (22–65)	45 (20–64)	45 (18–64)
BMI, median (range)	24 (17–35)	23 (17–32)	24 (18–41)	24 (17–35)
Male, no. (%)	54 (67)	49 (60)	43 (55)	46 (56)
White, no. (%)*	75 (93)	76 (93)	77 (99)	76 (93)
HCV RNA $\log_{10}$ IU/mL	6.5±0.6	6.4±0.6	6.3±0.6	6.4±0.6
HCV RNA ≥800,000 IU/mL, no. (%)	72 (89)	65 (79)	63 (81)	68 (83)
Bridging fibrosis, no. (%)	9 (11)	6 (7)	3 (4)	8 (10)
ALT IU/mL	56 (18–277)	50 (15–259)	58 (18–303)	55 (20–315)
HCV Genotype, no. (%) **1a** **1b** **Indeterminate**	 31 (38) 50 (62) 0	 37 (45) 45 (55) 0	 40 (51) 38 (49) 0	 35 (43) 45 (55) 2 (2)

Plus–minus values are means ±SD

*Race or ethnic group was self-reported

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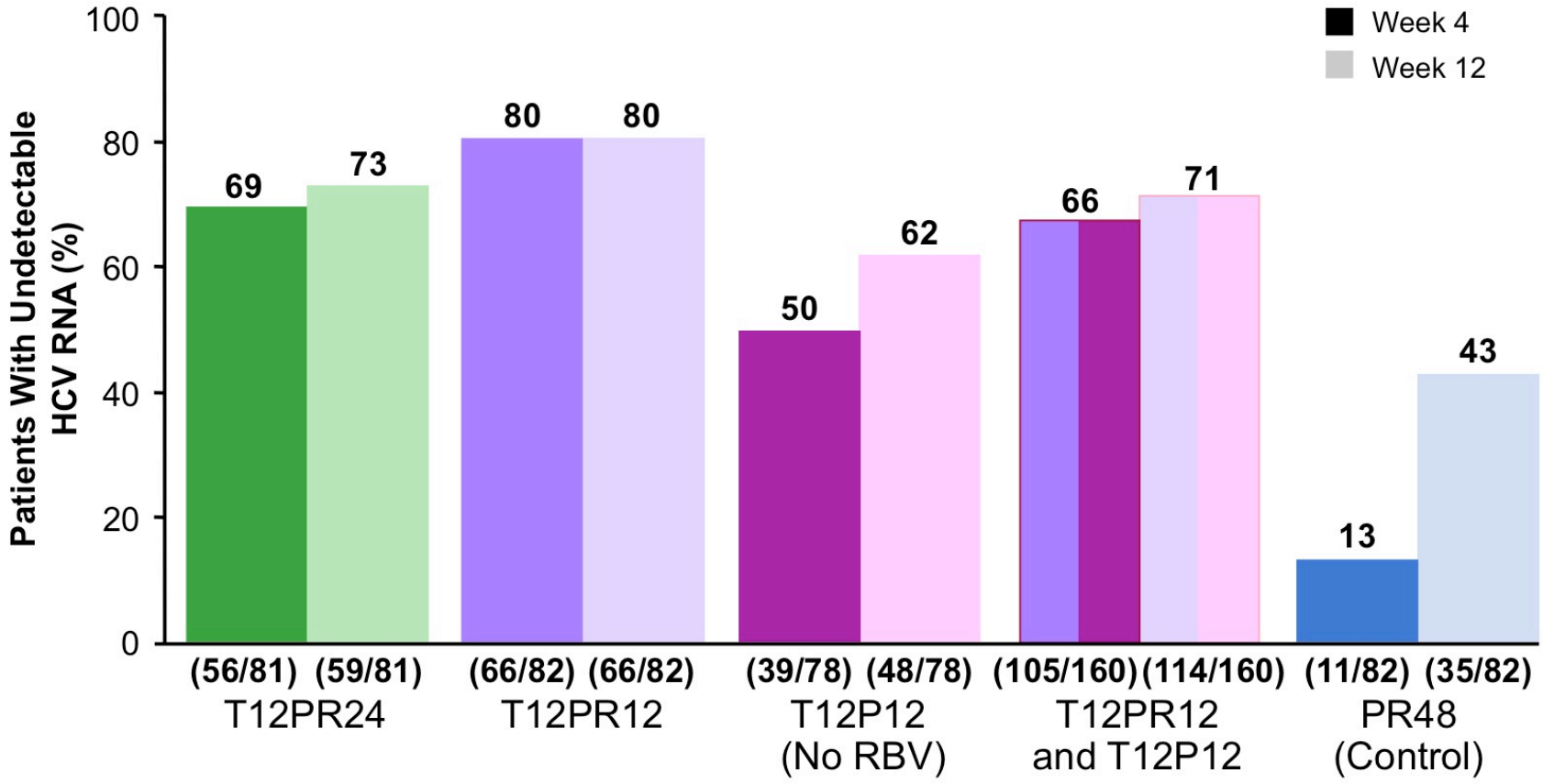
PROVE2: Undetectable HCV RNA at Week 4 and Week 12



Based on ITT (Intention to Treat) analysis

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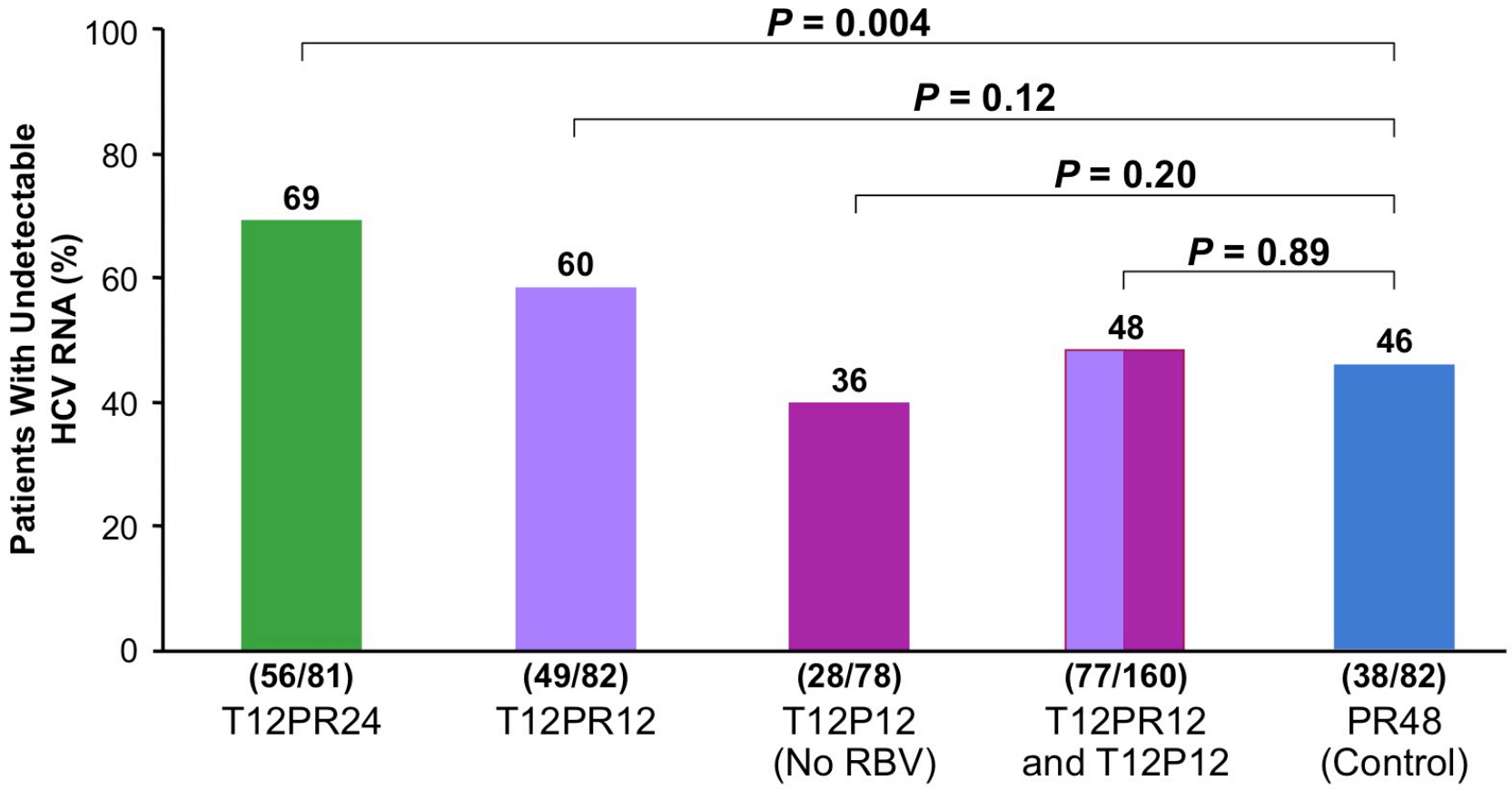
PROVE2: SVR Rates



2-sided Fisher's exact test.
Based on ITT (Intention to Treat) analysis
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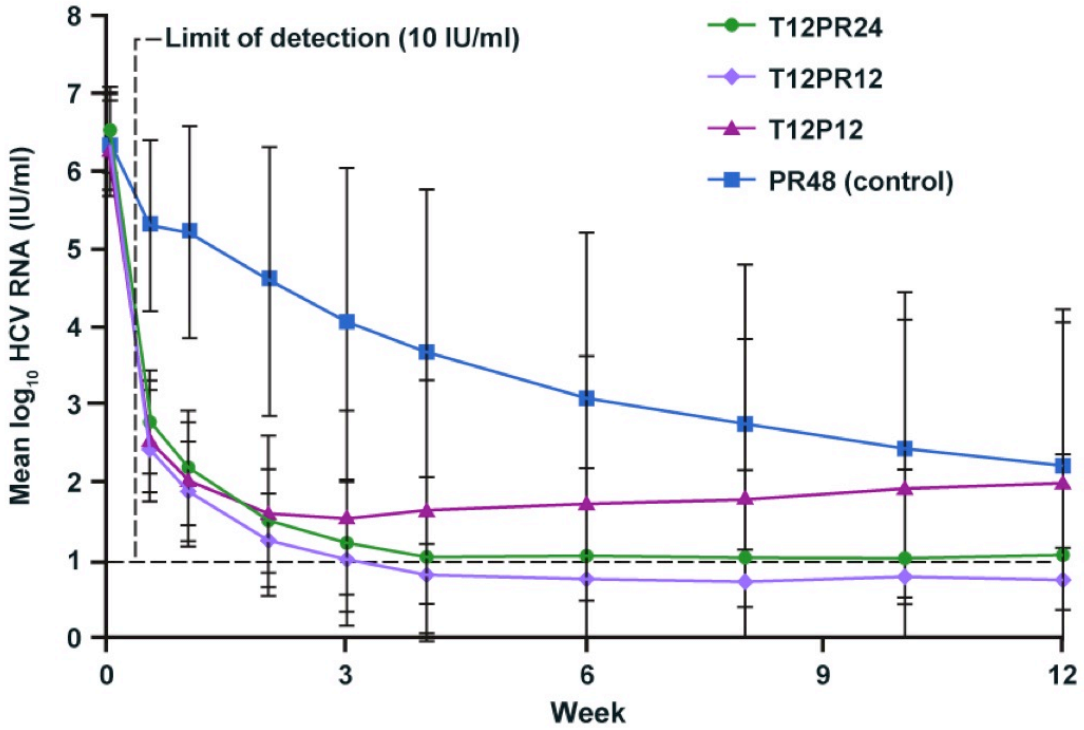
PROVE2: Mean Log_{10} HCV RNA Levels During the First 12 Weeks of Treatment



No. of Patients										
T12PR24	81	74	80	77	76	74	73	70	68	67
T12PR12	82	79	81	80	80	80	79	78	75	72
T12P12	78	72	78	74	74	73	73	72	70	70
PR48 (control)	82	78	80	80	79	79	78	77	77	77

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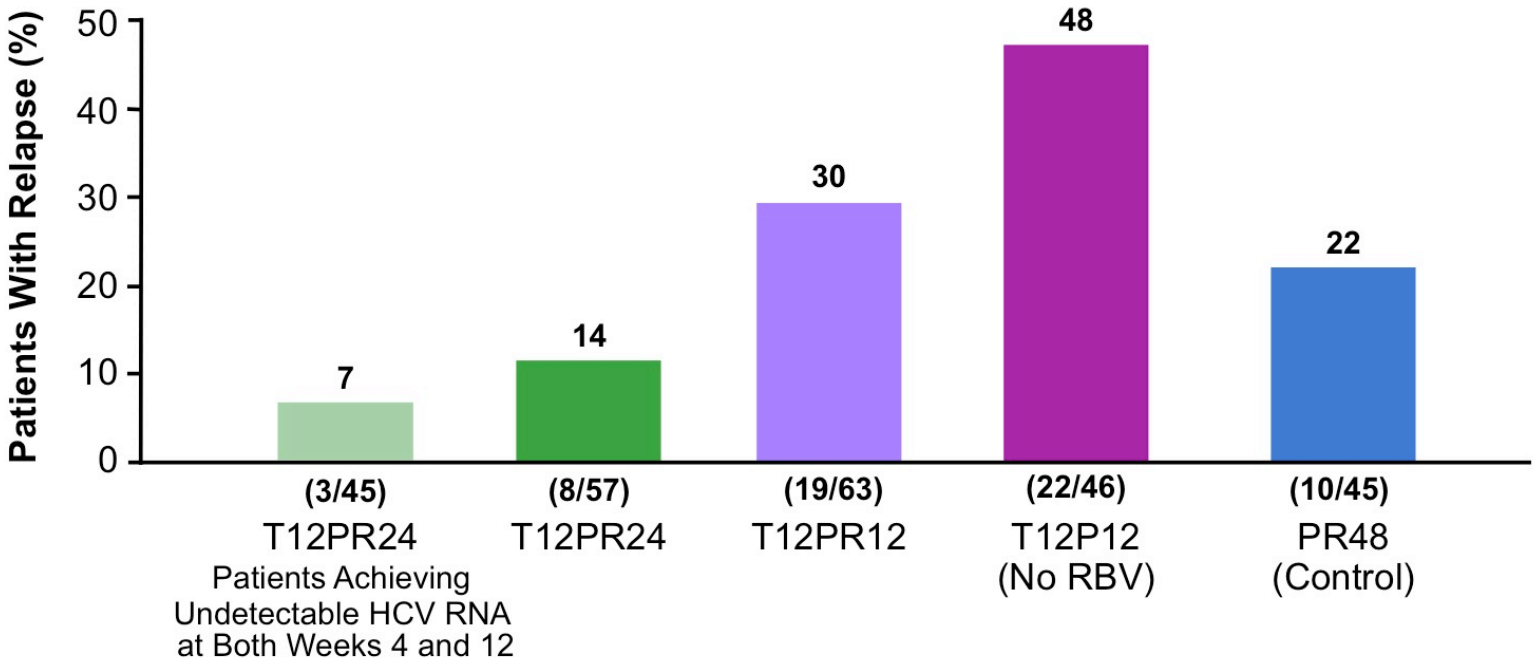
PROVE2: Relapse Rates – 24 Weeks After Completion of Assigned Treatment



- Relapse is defined as undetectable HCV RNA (<10 IU/mL) at the time of completion of treatment but detectable levels during the follow-up period
- Denominator is the number of patients with undetectable HCV RNA at completion of assigned treatment duration
- Out of 118 patients followed-up through Week 48 (post end-of-treatment), 2 patients who discontinued early (one each from T12PR24 and T12P12 group) experienced late relapse (Week 48 and 36, respectively). In both, viral sequence analysis confirmed recurrence of original infection

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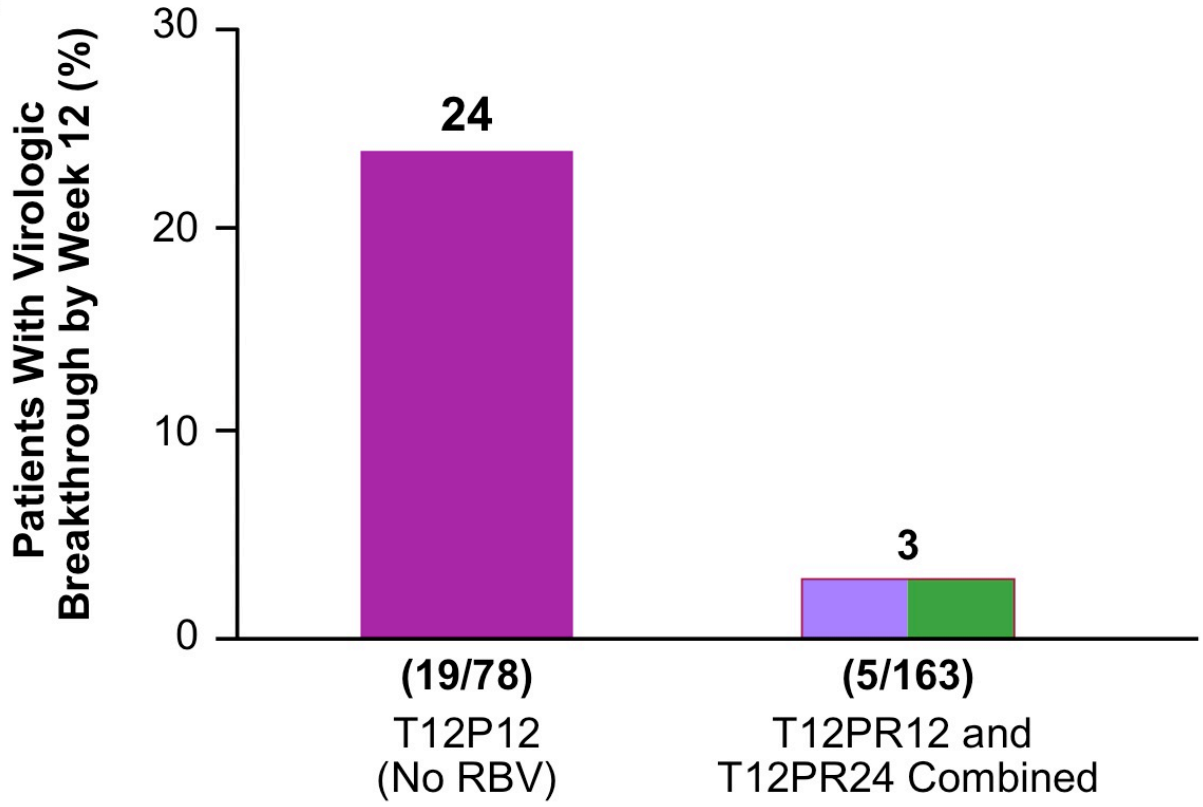
PROVE2: On-Treatment Virologic Breakthrough (During First 12 Weeks)

- Virologic breakthrough during treatment was defined as an increase of more than 1 log10 IU/mL from the lowest HCV RNA level or as an HCV RNA level above 100 IU/mL in patients with previously undetectable (<10 IU/mL) HCV RNA



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PROVE2: Most Common Adverse Events* (%)

Adverse Event	T12PR24 (N=81)	T12PR12 (N=82)	T12P12 (No RBV) (N=78)	PR48 (Control) (N=82)
	percent of patients			
Asthenia	**46**	**52**	**38**	**32**
Influenza-like illness	40	39	36	52
Fatigue	26	28	33	37
Pruritus	**51**	**63**	**59**	**35**
Dry Skin	26	26	28	35
Any rash	**49**	**44**	**47**	**35**
Nausea	48	48	31	40
Diarrhea	25	32	26	28
Headache	44	39	47	45
Insomnia	28	34	14	39
Dyspnea	22	26	14	16
Cough	19	17	10	26
Arthralgia	10	10	26	17
Anemia	27	18	9	17

*Reported in >25% of patients regardless of severity in any treatment group

Bold text indicates an adverse event for which the incidence in any telaprevir-based group was at least 10% higher than the incidence in the control group

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PROVE2: Adverse Events and Discontinuations

n (%)	T12PR24 (N=81)	T12PR12 (N=82)	T12P12 (No RBV) (N=78)	PR48 (Control) (N=82)
Discontinuations	**20 (25)**	**10 (12)**	**8 (10)**	**16 (19)**
Adverse events	11 (14)	9 (11)	7 (9)	6 (7)
Lost to follow-up	0	0	0	2 (2)
Others*	9 (6)	1 (1)	1 (1)	8 (10)

*Others includes the following reasons: discontinuation at investigator discretion, withdrawal of consent, noncompliance, refusal of treatment, non-responder, inclusion criteria not met

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PROVE2: Summary of Results

- In the 24-week telaprevir-based regimen there was a significantly higher SVR rate (69%) with a shortened treatment duration compared with the control group (46%, *P*=0.004) in treatment-naïve, chronic HCV genotype 1-infected patients
- Virologic breakthrough was 3% in patients receiving telaprevir-based therapy with peginterferon and ribavirin
- The most common adverse events reported more frequently in patients receiving telaprevir-based therapy with peginterferon and ribavirin than in the control group were pruritus, rash and anemia
  - Rash led to discontinuation of all study drugs in 7% of patients
  - Anemia led to discontinuation of all study drugs in 1% of patients

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PROVE2: Conclusions

- Twelve weeks of telaprevir with 24 weeks of peginterferon and ribavirin resulted in significantly higher rates of sustained virologic response than 48 weeks of peginterferon and ribavirin alone
  - A statistically significant improvement was not seen with T12PR12 or T12P12
- Ribavirin is a necessary part of the treatment regimen
- Larger studies in patients with hepatitis C virus infection are required to assess the safety and efficacy of telaprevir

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PROVE2: Study Investigators

Y. Benhamou
GH, Pitié-Salpêtrière
Paris, France

T. Berg
Universitätsklinikum Charité,
Berlin, Germany

M. Bourlière
Hôpital Saint-Joseph,
Marseille, France

J.-P. Bronowicki
Hôpital de Brabois
Nancy, France

P. Buggisch
Universitätsklinikum Hamburg-Eppendorf,
Hamburg, Germany

P. Couzigou
Hôpital du Haut-Lévèque,
Bordeaux, France

H. Diepolder
Klinikum Grosshadern,
Munich, Germany

G. Dusheiko
Royal Free Hospital, and University
College London Institute of Hepatology
London, UK

A. Erhardt
Universitätsklinikum Düsseldorf,
Dusseldorf, Germany

P. Ferenci
Medizinische Universität Wien,
Vienna, Austria

G. Gerken
Universitätsklinikum Essen,
Essen, Germany

T. Goeser
Universitätsklinik Köln,
Cologne, Germany

J.-D. Grangé
Hôpital Tenon,
Paris, France

R. Günther
Universitätsklinikum Kiel, Kiel

P. Marcellin
Hôpital Beaujon,
Clichy, France

P. Mathurin
Hôpital Claude Hurriez,
Lille, France

D. Mutimer
Queen Elizabeth Hospital,
Birmingham, UK

J.-M. Pawlotsky (C. Hézode)
Hôpital Henri Mondor,
Université Paris 12
Créteil, France

S. Pol
Hôpital Cochin,
Paris, France

J. Rasenack
Universitätsklinikum Freiburg,
Freiburg, Germany

W. Schmidt
Ruhr-Universität Bochum,
Bochum, Germany

L. Serfaty
Hôpital Saint Antoine,
Paris, France

U. Spengler
Universitätsklinikum Bonn,
Bonn, Germany

A. Tran
Hôpital de l´Archet 2,
Nice, France

C. Trépo
Hotel Dieu,
Lyon, France

H. Wedemeyer
Medizinische Hochschule Hannover,
Hannover, Germany

J.-P. Zarski
Hôpital de la Tronche,
Grenoble, France

S. Zeuzem (N. Forestier)
Universitätsklinikum des Saarlandes,
Homburg, Germany

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PROVE2: Disclosures

Dr. Hézode reports receiving consulting fees from Roche and Novartis and lecture fees from Gilead Sciences, Roche and Schering-Plough.

Dr. Forestier reports receiving consulting fees from Tibotec Pharmaceuticals and lecture fees from Roche.

Dr. Dusheiko reports receiving consulting fees from Hoffmann-La Roche, Schering-Plough, Tibotec Pharmaceuticals, and Vertex Pharmaceuticals.

Dr. Ferenci reports receiving consulting fees from Novartis, Roche, Salix Pharmaceuticals, and Vertex Pharmaceuticals, lecture fees from Merz Pharmaceuticals, Roche, and Salix Pharmaceuticals, grant support from Roche, and investigator fees from Human Genome Sciences, Roche, Tibotec Pharmaceuticals, and Vertex Pharmaceuticals.

Dr. Pol reports receiving consulting fees from Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead Sciences, Idenix, Novartis, Roche, Schering-Plough, Tibotec Pharmaceuticals and Wyeth, lecture fees from Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead Sciences, Roche, Schering-Plough, Tibotec, and Wyeth, and grant support from Roche.

Dr. Goeser, grant support from Roche.

Dr. Bronowicki reports receiving consulting and lecture fees from Roche and Schering-Plough.

Dr. Bourlière reports receiving consulting fees from Gilead Sciences, Roche, and Schering-Plough and lecture fees from Roche and Schering-Plough.

Dr. Gharakhanian, Mr. Bengtsson, and Drs. McNair, George, Kieffer, Kwong, Kauffman, and Alam report being current or former employees of Vertex Pharmaceuticals and holding stock options in this entity.

Dr. Pawlotsky reports receiving consulting fees from Abbott, AstraZeneca, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Roche, Schering-Plough, Tibotec Pharmaceuticals, Valeant Pharmaceuticals, and Vertex Pharmaceuticals and grant support from Gilead Sciences.

Dr. Zeuzem reports receiving consulting fees from Vertex and Roche and lecture fees from Roche.

No other potential conflict of interest relevant to this article was reported.

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