# PROVE1: Telaprevir with Peginterferon and Ribavirin for Chronic HCV Genotype 1 Infection

JG McHutchison, GT Everson, SC Gordon, IM Jacobson,
M Sulkowski, R Kauffman, L McNair, J Alam, AJ Muir,
*For the PROVE1 Study Team*

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New England Journal of Medicine 2009;360(18):1827-1838

# PROVE1: Telaprevir with Peginterferon and Ribavirin for Chronic HCV Genotype 1 Infection

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PROVE = PROtease Inhibition for Viral Evaluation



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# PROVE1: PROtease Inhibition for Viral Evaluation 1

- Phase 2b, randomized, parallel-group, double-blind, placebo-controlled trial
  - 250 treatment-naïve patients with chronic infection with hepatitis C virus (HCV) genotype 1
  - 37 US clinical centers
  - Compared telaprevir (TVR) -based therapy groups of 12-, 24- and 48-week durations against a 48-week Peg-IFN alfa-2a/RBV control group
- Objectives
  - Assess the SVR rates that could be achieved with TVR-based therapy
  - Evaluate if TVR could shorten the duration of current standard therapy
  - Assess the safety and efficacy of TVR-based therapy

Peg-IFN = Peginterferon alfa-2a (Pegasys®, Roche)
RBV = Ribavirin (Copegus®, Roche)
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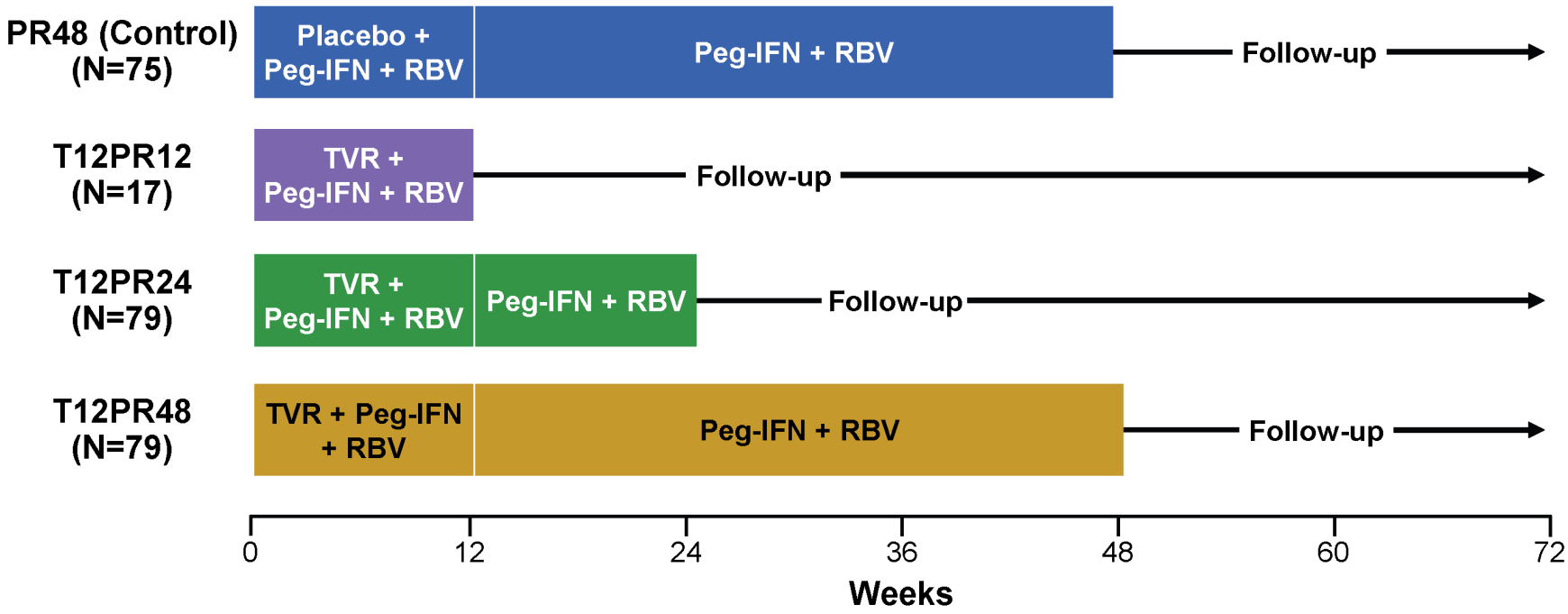
# PROVE1: Study Design




- Patients in the T12PR24 and T12PR12 groups were required to have undetectable HCV RNA levels by Week 4 [known as a rapid virologic response (RVR)] to stop treatment at Week 24 or Week 12; if no RVR, treatment with Peg-IFN and RBV continued to Week 48

(P) Peg-IFN = pegylated interferon alfa-2a 180 µg/week, 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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# PROVE1: 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
- Statistical analysis
  - Analyses of efficacy and safety included data from all patients who had undergone randomization and had received at least one dose of any study drug
- HCV RNA assessment by COBAS TaqMan HCV assay (Roche Molecular Systems) (lower limit of detection of 10 IU/mL; lower limit of quantification of 30 IU/mL)

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# PROVE1: Baseline Characteristics

| Characteristic | T12PR24 (N=79) | T12PR48 (N=79) | T12PR12 (N=17) | PR48 (N=75) |
|---|---|---|---|---|
| **Age, median (range)** | 49 (21–61) | 50 (26–61) | 49 (34–63) | 49 (24–59) |
| **BMI, median (range)** | 26.9 (18–41) | 25.8 (19–44) | 28.6 (20–38) | 26.9 (19–38) |
| **Male, no. (%)** | 54 (68) | 48 (61) | 12 (71) | 43 (57) |
| **Race or ethnic group, no. (%)*** | | | | |
| **White** | 60 (76) | 60 (76) | 13 (76) | 59 (79) |
| **Black** | 7 (9) | 8 (10) | 13 (18) | 9 (12) |
| **Other** | 12 (15) | 11 (14) | 1 (6) | 7 (9) |
| **HCV Genotype, no. (%)** | | | | |
| **1a** | 53 (67) | 48 (61) | 9 (53) | 50 (67) |
| **1b** | 17 (22) | 27 (34) | 6 (35) | 20 (27) |
| **Indeterminate** | 9 (11) | 4 (5) | 2 (12) | 5 (7) |
| **HCV RNA $\log_{10}$ IU/mL** | 6.54±0.72 | 6.47±0.60 | 6.57±0.43 | 6.68±0.49 |
| **HCV RNA ≥800,000 IU/mL, no. (%)** | 66 (84) | 68 (86) | 15 (88) | 69 (92) |
| **Bridging fibrosis, no. (%)** | 14 (18) | 14 (18) | 4 (24) | 19 (25) |
| **ALT IU/mL** | 73±54 | 72±49 | 80±75 | 68±38 |

Plus–minus values are means ±SD

*Race or ethnic group was self-reported

No notable differences between treatment groups

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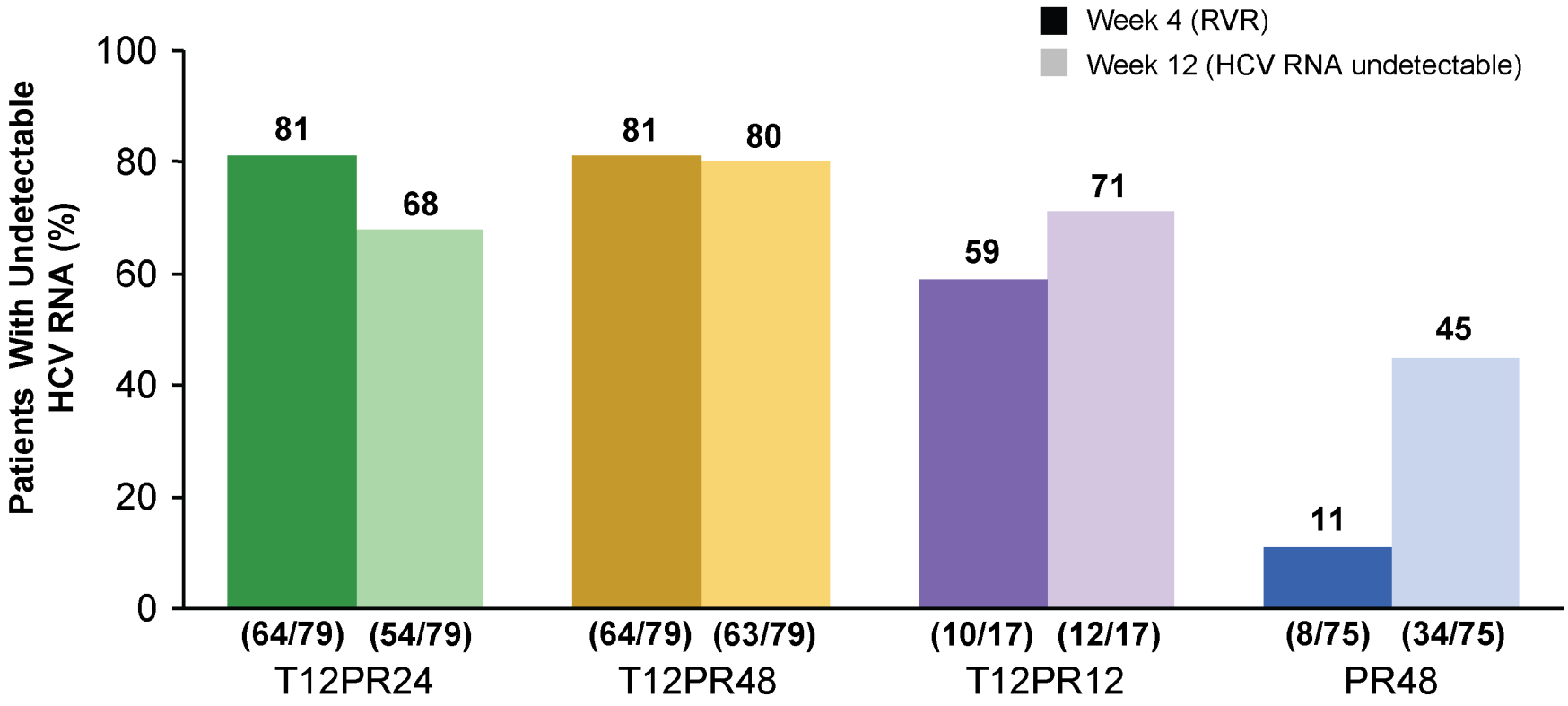
# PROVE1: Undetectable HCV RNA at Weeks 4 and 12




Undetectable was defined as <10 IU/mL, (COBAS TaqMan assay, Roche Molecular Systems)
Based on ITT (Intention to Treat) analysis
RVR = Rapid Virologic Response
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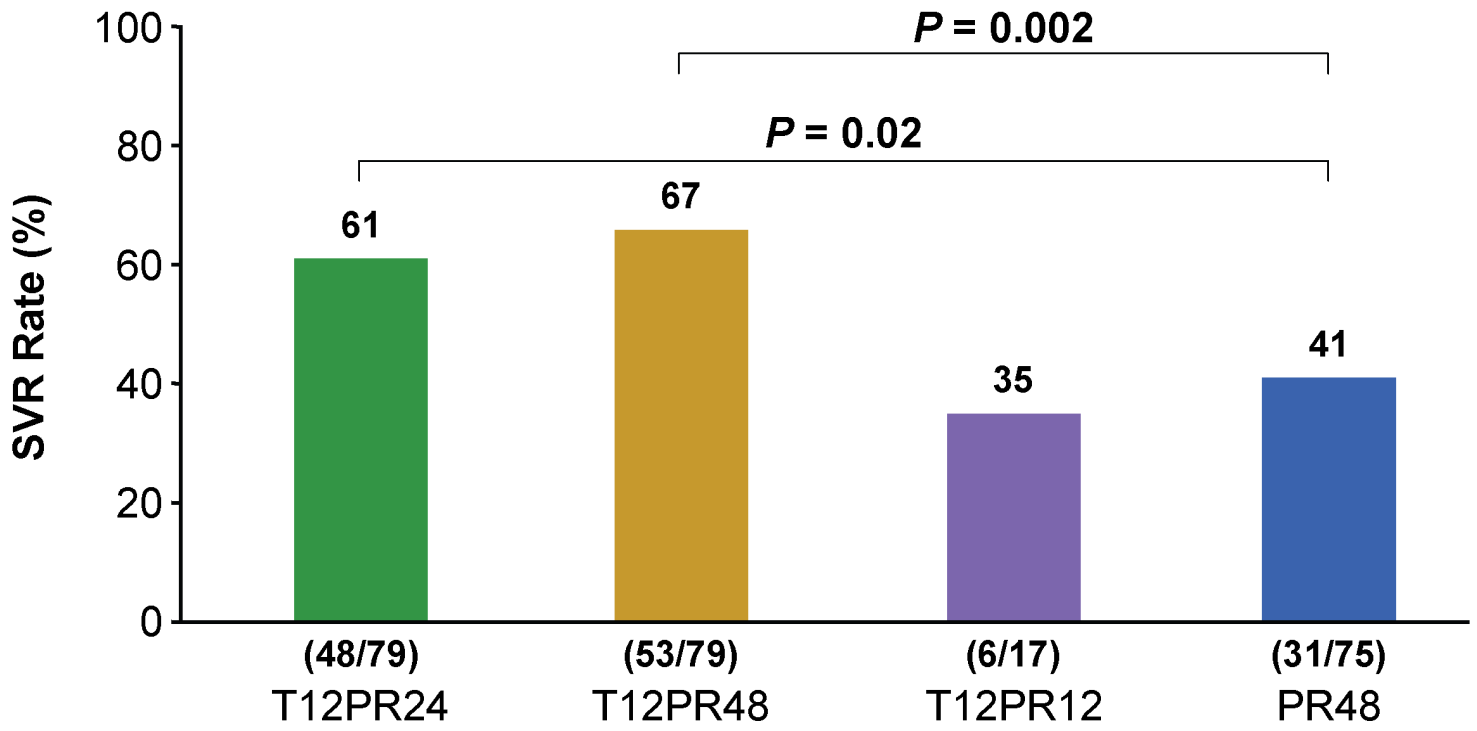
# PROVE1: SVR Rates




(P) Peg-IFN = pegylated interferon alfa-2a 180 µg/week 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)
Based on ITT (Intention to Treat) analysis
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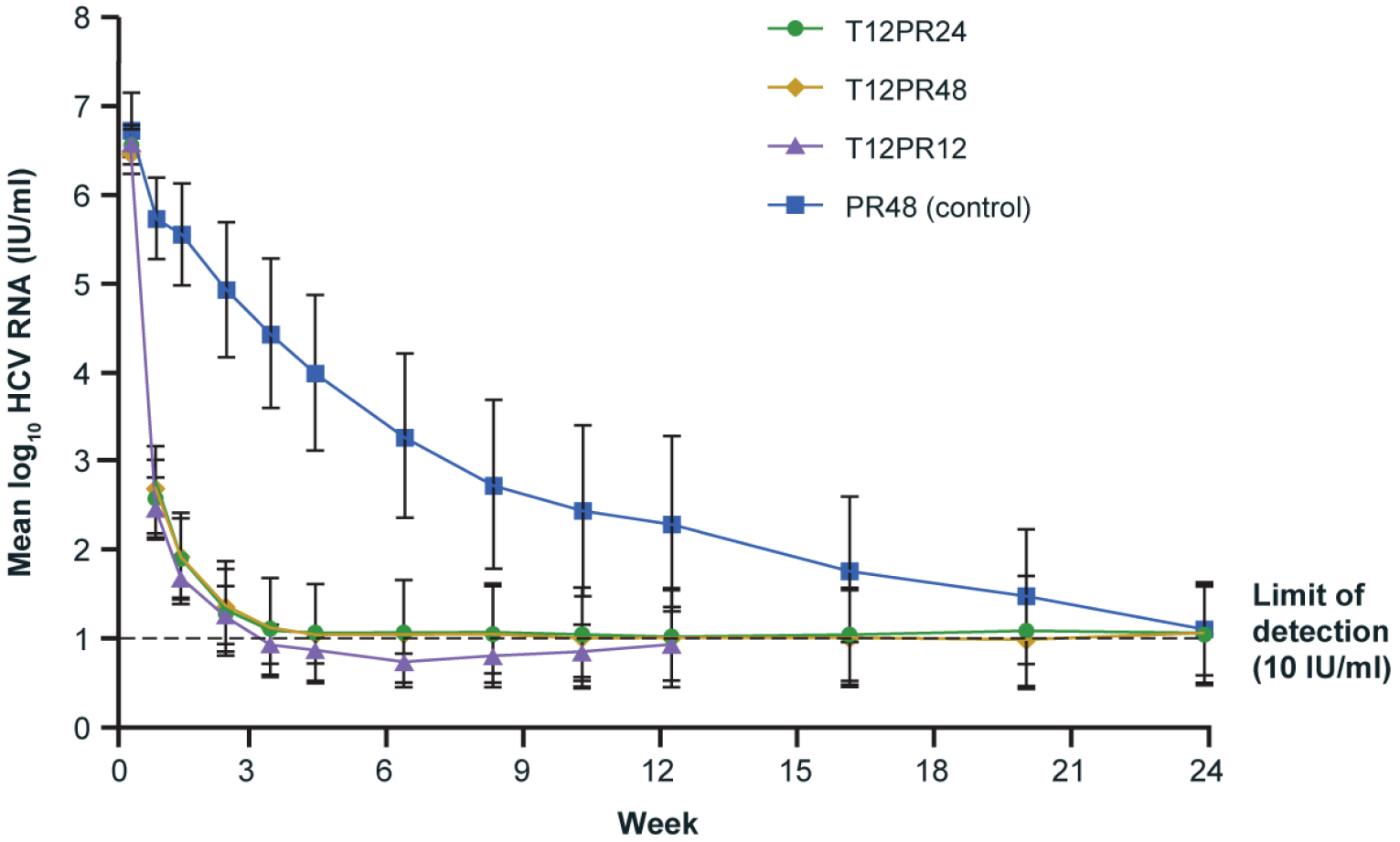
# PROVE1: Mean $Log_{10}$ HCV RNA Levels From Baseline Through Week 24

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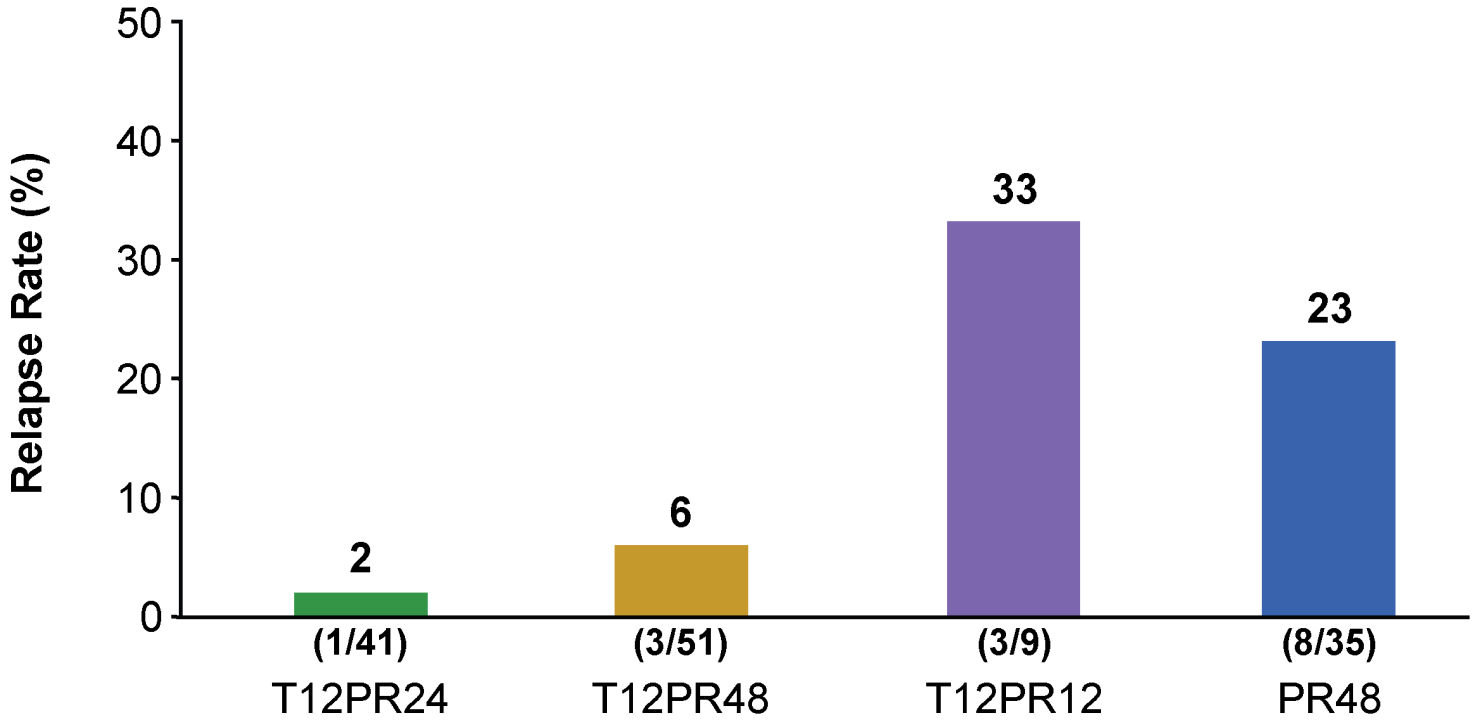
# PROVE1: Relapse Rates




- 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

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# PROVE1: On-Treatment Virologic Breakthrough (During First 12 Weeks)

- Infrequent virologic breakthrough in telaprevir-based treatment groups
  - Breakthrough was defined as an increase in HCV RNA level of 1-$\log_{10}$ unit, as compared with the lowest value, or as an increase to an HCV RNA value of more than 100 IU/mL, if the HCV RNA had become undetectable (<10 IU/mL)
  - Most virologic breakthroughs occurred in the first 4 weeks of treatment
    - Week 1 – Week 4 was 5% (9/175)
    - Week 1 – Week 12 was 7% (12/175, total)
  - Most breakthroughs (10/12) occurred in patients before the HCV RNA level became undetectable

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# PROVE1: Most Common* Adverse Events – All Grades

| Adverse Event | T12PR24 (N=79) | T12PR48 (N=79) | T12PR12 (N=17) | PR48 (N=75) |
|---|---|---|---|---|
| | *percent of patients* | | | |
| Fatigue | 70 | 73 | 82 | 76 |
| **Nausea** | **56** | **48** | **65** | **29** |
| Influenza-like illness | 49 | 38 | 35 | 43 |
| **Pruritus** | **48** | **40** | **24** | **23** |
| Headache | 47 | 43 | 53 | 60 |
| Insomnia | 44 | 34 | 35 | 39 |
| **Diarrhea** | **42** | **34** | **24** | **28** |
| **Anemia** | **37** | **29** | **35** | **27** |
| **Rash (any)** | **60** | **61** | **53** | **41** |
| **Severe** | **9** | **5** | **6** | **1** |
| **Moderate** | **18** | **17** | **0** | **8** |
| **Mild** | **33** | **39** | **47** | **32** |
| **Erythema at injection site** | **28** | **32** | **35** | **24** |
| Dizziness | 28 | 19 | 24 | 19 |
| Pyrexia | 20 | 19 | 12 | 29 |
| Dry Skin | 18 | 17 | 6 | 25 |
| Irritability | 17 | 10 | 12 | 29 |

*Reported in at least 25% of patients in any treatment group

Events in bold are those in which one or more of the three groups receiving telaprevir had an event incidence that was 10% higher than that in the PR48 (control) group.

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# PROVE1: Adverse Events Leading to Discontinuation

| | All Telaprevir-based Treatment Groups Combined (N=175) | | PR48 (N=75) | |
|---|---|---|---|---|
| | Week 1–12 | After Week 12* | Week 1–12 | After Week 12* |
| **Adverse Event** | *number of patients (percent)* | | | |
| **Any** | 31 (18) | 6 (3) | 3 (4) | 5 (7) |
| **Rash or pruritus** | 12 (7) | - | - | 1 (1) |
| **Anemia** | 3 (2) | - | - | - |
| **Gastrointestinal event** | 2 (1) | 2 (1) | 1 (1) | - |
| **Psychiatric event (depression, anxiety)** | 4 (2) | 1 (1) | 1 (1) | - |
| **Other event, or multiple events** | 10 (6) | 3 (2) | 1 (1) | 4 (5) |

*Telaprevir dosing completed

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# PROVE1: Summary of Results

- Patients with chronic HCV genotype 1 infection achieved
  - 61% and 67% SVR in the 24- and 48-week telaprevir-based treatment groups, respectively
  - 41% SVR with 48 weeks of Peg-IFN/RBV
- Relapse rate of 2% in patients in the T12PR24 group
- Virologic breakthrough occurred in 7% of the telaprevir-based treatment groups
- The most common adverse events reported more frequently in telaprevir-based treatment groups than in the control group were gastrointestinal events, skin events (rash, pruritus) and anemia
  - Other adverse events reported were similar in type and frequency to those seen with Peg-IFN/RBV treatment
  - Treatment discontinuation due to adverse events through Week 12 were 18% in the telaprevir-based treatment groups and 4% in the control group

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# PROVE1: Conclusions

- The addition of telaprevir to peginterferon alfa-2a and ribavirin significantly increased sustained virologic response in treatment-naïve genotype 1 chronic hepatitis C virus patients
- Further studies are needed to evaluate the safety, efficacy, and duration of telaprevir-based regimens and to confirm these results

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# PROVE1: Study Investigators

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# PROVE1: Disclosures

**Dr. McHutchison** reports receiving consulting fees from Vertex and Schering-Plough and grant support from Schering-Plough, Roche, and Vertex.

**Dr. Everson** reports receiving consulting fees from Vertex and Roche, lecture fees from Roche, and grant support from Vertex and Roche.

**Dr. Gordon** reports receiving consulting fees from Vertex, lecture fees from Schering-Plough and Roche, and grant support from Glaxo-SmithKline, Valeant, Schering-Plough Research Institute, Gilead, GlobeImmune, Conatus, Merck, Roche, Vertex, Human Genome Sciences, Coley, Phynova, Exalenz, Echosens, Biolex, Bristol-Myers Squibb, Idera, Intercept, and SciClone.

**Dr. Jacobson** reports receiving consulting fees and grant support from Vertex.

**Dr. Sulkowski** reports receiving consulting fees from Vertex, Schering-Plough, Roche, Merck, Human Genome Sciences, and Boehringer Ingelheim, lecture fees from Schering-Plough and Roche, and grant support from Vertex.

**Dr. Kauffman** reports owning equity in and being an employee of Vertex Pharmaceuticals.

**Drs. McNair and Alam** report being employees of Vertex Pharmaceuticals and holding stock options in this entity.

**Dr. Muir** reports receiving consulting fees from Vertex and Schering-Plough, lecture fees from Schering-Plough, and grant support from Vertex and Schering-Plough.

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

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