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CLINICAL—LIVER

Simeprevir With Peginterferon and Ribavirin Leads to High Rates of SVR in Patients With HCV Genotype 1 Who Relapsed After Previous Therapy: A Phase 3 Trial

Xavier Forns,[1] Eric Lawitz,[2] Stefan Zeuzem,[3] Ed Gane,[4] Jean Pierre Bronowicki,[5] Pietro Andreone,[6] Andrzej Horban,[7] Ashley Brown,[8] Monika Peeters,[9] Oliver Lenz,[9] Sivi Ouwerkerk–Mahadevan,[10] Jane Scott,[11] Guy De La Rosa,[12] Ronald Kalmeijer,[12] Rekha Sinha,[9] and Maria Beumont–Mauviel[9]

[1]*Liver Unit, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Barcelona, Spain;* [2]*Texas Liver Institute, University of Texas Health Science Center, San Antonio, Texas;* [3]*J.W. Goethe University Hospital, Frankfurt, Germany;* [4]*Auckland Hospital Clinical Studies Unit, Auckland, New Zealand;* [5]*INSERM U954, Université de Lorraine, Centre Hospitalier Universitaire de Nancy, Vandoeuvre Les Nancy, France;* [6]*Dipartimento di Scienze Mediche e Chirurgiche, Alma Mater Studiorum, University of Bologna, Bologna, Italy;* [7]*Medical University of Warsaw, Wolska, Warsaw, Poland;* [8]*Imperial College Healthcare National Health Service Trust, London, United Kingdom;* [9]*Janssen Infectious Diseases BVBA, Beerse, Belgium;* [10]*Janssen Research and Development, Beerse, Belgium;* [11]*Janssen Global Services, LLC, High Wycombe, United Kingdom;* [12]*Janssen Global Services, LLC, Titusville, New Jersey*

See related article, Rodriguez-Torres M et al, on page 1029 in *CGH*.

BACKGROUND & AIMS: Simeprevir is an oral, once-daily inhibitor of hepatitis c virus (HCV) protease NS3/4A. We investigated the safety and efficacy of simeprevir with peg-interferon α-2a and ribavirin (PR) in a randomized, double-blind, placebo-controlled, phase 3 trial of patients with HCV genotype 1 infection who relapsed after previous interferon-based therapy. **METHODS:** Patients were assigned randomly (2:1) to groups given simeprevir (150 mg, once daily) and PR (n = 260) or placebo and PR (n = 133) for 12 weeks. Patients then were given PR alone for 12 or 36 weeks (simeprevir group, based on response-guided therapy criteria) or 36 weeks (placebo group). **RESULTS:** Simeprevir and PR was significantly superior to placebo and PR; rates of sustained virologic response 12 weeks after planned end of treatment (SVR12) were 79.2% vs 36.1%, respectively (43.8% difference; 95% confidence interval, 34.6–53.0; $P < .001$). Among patients given simeprevir, 92.7% met the response-guided therapy criteria and were eligible to complete PR at week 24; of these, 83.0% achieved SVR12. HCV RNA was undetectable at week 4 in 77.2% of patients given simeprevir and 3.1% given placebo. On-treatment failure and relapse rates were lower among patients given simeprevir and PR than those given placebo and PR (3.1% vs 27.1%, and 18.5% vs 48.4%, respectively). Patients given simeprevir did not have adverse events beyond those that occurred in patients given PR alone. Most adverse events were grades 1/2; the prevalence of anemia and rash was similar in both groups. Patients in both groups reported similar severity of fatigue and functional impairments during the study, but duration was reduced among patients given simeprevir. **CONCLUSIONS:** In a phase 3 trial of patients who had relapsed after interferon-based therapy, the addition of simeprevir to PR was generally well tolerated, with an SVR12 rate of 79.2%. Most patients (92.7%) receiving simeprevir were able to shorten therapy to 24 weeks. ClinicalTrials.gov number: NCT01281839.

Keywords: PROMISE; Chronic Hepatitis C; Drug; DAA.

Approximately 150 million individuals worldwide are chronically infected with hepatitis C virus (HCV), with 350,000 people dying annually of HCV-related conditions.[1] Historically, the standard of care for chronic HCV infection was peginterferon (PegIFN)α and ribavirin (RBV).[2–4] However, 50%–60% of HCV genotype 1–infected patients do not achieve sustained virologic response (SVR) with PegIFNα/RBV,[5,6] and up to 32% of responders relapse after cessation of therapy.[7] Re-treatment of relapsed patients with PegIFNα/RBV has SVR rates of approximately 20%–50%.[8–10]

The direct-acting antiviral agents (DAAs), boceprevir and telaprevir, can improve SVR rates when dosed with PegIFNα/RBV,[11–14] with the potential for a shorter treatment duration in some patients.[11,13,15] The telaprevir 50% inhibitory concentration (IC_{50}) values in a genotype 1b HCV replicon and in genotype 1a HCV-infected human fetal hepatocytes were 354 nmol/L and 280 nmol/L, respectively,[16] whereas the boceprevir median effective concentration (EC_{50}) in a genotype 1b HCV replicon was approximately 200 nmol/L, with an approximately 2-fold lower value in a genotype 1a HCV replicon.[17] Data concerning the efficacy of response-guided treatment (RGT) with telaprevir in patients who have relapsed after prior IFN-based therapy are

Abbreviations used in this paper: **AE, adverse event; CI, confidence interval; DAA, direct-acting antiviral agent; EC_{50}, median effective concentration; EOT, end of treatment; FDA, Food and Drug Administration; HCV, hepatitis C virus; IQR, interquartile range; PegIFN, peginterferon; PR, peginterferon α-2a/ribavirin; RBV, ribavirin; RGT, response-guided treatment; RVR, rapid virologic response; SAE, serious adverse event; SVR, sustained virologic response; SVR12, sustained virologic response at 12 weeks; SVR24, sustained virologic response at 24 weeks.**

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lacking. Boceprevir must be administered as 4 pills, 3 times daily, whereas telaprevir must be administered 2 or 3 times daily (6 pills in total).[18] Boceprevir and telaprevir also are associated with a high incidence of adverse events (AEs), including anemia, rash, and renal dysfunction.[19–22] Recently, the nucleotide analog NS5B polymerase inhibitor sofosbuvir also was approved for the treatment of chronic HCV infection in the United States and Europe, representing an improvement on first-generation DAAs.[23,24]

Simeprevir (TMC435) is administered orally, once daily, as a single pill[25]; has been approved in Japan, Canada, the United States and Russia; and is under regulatory review in Europe for the treatment of chronic HCV infection. The median simeprevir EC_{50} and EC_{90} values against a HCV genotype 1b replicon were 9.4 and 19 nmol/L, respectively.[26] Activity of simeprevir against a selection of genotype 1a (N = 78) and 1b (N = 59) chimeric replicons carrying NS3 sequences from HCV NS3/4A protease inhibitor-naive subjects resulted in median fold change in EC_{50} of 1.4 (interquartile range [IQR], 0.8–11) and 0.4 (IQR, 0.3–0.7), compared with reference genotype 1b replicon. Genotype 1a (N = 33) and 1b (N = 2) isolates with a baseline Q80K polymorphism, a naturally occurring NS3 polymorphism that confers low-level resistance to simeprevir, resulted in a median fold change in simeprevir EC_{50} of 11 (IQR, 7.4–13) and 8.4, respectively.

Simeprevir has antiviral activity in patients infected with HCV genotypes 1, 2, 4, 5, and 6,[27–30] and is being evaluated in both PegIFNα/RBV and IFN-free combinations.[27,28,31–34] Simeprevir in combination with PegIFNα/RBV showed SVR rates of approximately 80% in phase 3 trials in treatment-naive patients with HCV genotype 1 infection, with most patients (>84%) able to reduce their treatment duration to 24 weeks.[33,34] In these studies, no additional AEs were observed with simeprevir compared with those seen with PegIFNα/RBV alone.

Results of the PROtease inhibitor TMC435 In patientS who have previously rElapsed on IFN/RBV (PROMISE) study, a randomized, double-blind, placebo-controlled, phase 3 trial undertaken to assess the efficacy, safety, and tolerability of simeprevir with PegIFNα-2a/RBV (PR) for the treatment of chronic HCV genotype 1 infection in patients who had relapsed after previous IFN-based therapy, are presented.

Materials and Methods

Patients

Patients were enrolled at study sites in 14 countries across North America, Europe, and the Asia–Pacific region. Eligible patients were adults (≥18 y) with confirmed genotype 1 HCV infection and screening plasma HCV-RNA levels greater than 10,000 IU/mL, who had relapsed after 24 weeks or more of IFN-based therapy (undetectable HCV-RNA at end of treatment [EOT] or within 2 months after EOT, with documented relapse within 1 year after therapy). A liver biopsy specimen obtained within 3 years of screening showing histology consistent with chronic HCV infection was required, according to the 2010 Food and Drug Administration (FDA) Guidance for Industry on developing DAAs (available from the FDA). Biopsy specimens indicating a METAVIR score of F0–F3 within 3 years of screening, or a score of F4 at any previous time, were acceptable. In total, 68% of patients had a biopsy within a year of screening. Subjects with bridging fibrosis (F3) or cirrhosis (F4) were eligible if they had an ultrasound performed within 6 months before screening (or between the screening and baseline visit) with no findings suspicious for hepatocellular carcinoma. Patients with hepatic decompensation; non–HCV-related liver disease; co-infection with human immunodeficiency virus, hepatitis B virus, or non–genotype 1 HCV; defined laboratory abnormalities (Supplementary Materials and Methods section); any other active disease; or who were either pregnant or planning pregnancy were excluded.

Study Design

This was a randomized, multicenter, double-blind, parallel-group, placebo-controlled, phase 3 clinical trial (NCT01281839), conducted between January 2011 and January 2013. Institutional review boards of all participating institutions approved the study and written informed consent was obtained from all participants according to local regulations. All authors had access to the study data, critically reviewed the manuscript at each draft, and approved the final draft for submission.

After stratification by HCV 1 subtype (1a, 1b, and other) and *IL28B* genotype (rs12979860; CC, CT, or TT), participants were randomized centrally in a 2:1 ratio to receive either simeprevir (150 mg once daily) plus PegIFNα-2a/RBV (180 μg/wk and 1000 or 1200 mg/day depending on body weight, respectively) (PR) for 12 weeks followed by RGT with PR alone for 12 or 36 weeks, or placebo with PR for 12 weeks followed by PR alone for 36 weeks (Supplementary Figure 1). Patients, study personnel, and the sponsor were blinded to the treatment groups. According to RGT criteria, PR therapy was completed at week 24 in simeprevir-treated patients with HCV-RNA levels less than 25 IU/mL at week 4 and undetectable levels at week 12. For patients not meeting these criteria and all patients in the placebo group, treatment with PR was continued until week 48. Patients in both groups were followed-up for 72 weeks after treatment initiation.

According to virologic stopping rules, simeprevir/placebo was discontinued if HCV-RNA level was greater than 1000 IU/mL at week 4. PR also was discontinued if the reduction in HCV RNA compared with baseline was less than 2 $\log_{10}$ IU/mL at week 12, or if HCV RNA was 25 IU/mL or greater at week 24 or 36. Investigators were formally blinded to HCV-RNA data until week 48 and to treatment group until week 72. An external HCV-RNA monitor (who was unblinded to treatment and to HCV-RNA measurements results) informed the investigator if a virologic stopping rule or the RGT criteria were met.

Assessments

Plasma HCV RNA was determined using the Roche COBAS TaqMan HCV/HPS assay version 2.0 (Roche Molecular Diagnostics, Pleasanton, CA). Standard population-based sequencing of the HCV NS3/4A protease domain was performed on baseline samples to determine the presence of naturally occurring baseline polymorphisms, including Q80K, and those from selected time points (based on HCV-RNA changes).

Standard HCV genotyping assays, the Siemens Versant HCV LiPA v2 assay (Siemens Healthcare Diagnostics, Tarrytown, NY) or, if that failed, the Trugene 5′NC genotyping assay, were used

to determine HCV genotype 1 subtype at screening. In addition, HCV genotype/subtype was determined at baseline using an NS5B sequence-based assay. The results of the NS5B-based assay were used for study analyses. Determination of the patients' *IL28B* genotype (SNP rs12979860) was performed on human genomic DNA by a real-time polymerase chain reaction on the ABI 7900HT platform.

AEs were monitored throughout the study. During study visits, patients completed questionnaires to document changes in fatigue severity (Fatigue Severity Scale),[35] as well as productivity and daily activity impairment and work absenteeism (Work Productivity and Activity Impairment questionnaire for Hepatitis C).[36]

Additional details are provided in the Supplementary Materials and Methods section.

Statistical Analysis

This primary analysis was performed when all randomized and treated subjects had completed the week 60 visit or discontinued earlier. All analyses were performed on the intent-to-treat population, which comprised all subjects who received at least one dose of simeprevir or placebo. The primary study end point was the proportion of patients achieving SVR (HCV RNA $<$25 IU/mL undetectable at actual EOT and HCV RNA $<$25 IU/mL) 12 weeks after planned EOT (SVR12). SVR12 rates in the 2 groups were compared using the Cochran–Mantel–Haenszel test controlling for stratification factors (HCV 1 subtype and *IL28B* genotype). A Breslow–Day test for homogeneity of odds ratios based on this model also was performed and the 95% confidence interval (CI) was constructed around each response rate. Phase 3 data for telaprevir and boceprevir show a strong correlation between SVR12 and SVR at 24 weeks after planned EOT (SVR24). Similarly, a good correlation also was observed in phase 2b studies with simeprevir. Sample size calculation based on SVR24 rates therefore was regarded as applicable for SVR12. Based on published data,[37] the SVR24 rate in the placebo group was expected to be approximately 20%. It was calculated that 250 patients in the simeprevir group and 125 patients in the placebo group were needed to provide more than 90% power to detect a significant difference between the 2 treatment groups with a 5% significance level (2-sided).

Secondary end points included comparison of virologic response rates at other time points (SVR24 [data are presented in the Supplementary Results section] and rapid virologic response [RVR] rate, defined as the proportion of patients with undetectable HCV RNA at week 4 of treatment) and in different patient subgroups (including METAVIR score, HCV 1 subtype, and *IL28B* genotype), the proportion of simeprevir-treated patients meeting RGT criteria to complete treatment at week 24, the incidence of viral breakthrough (HCV-RNA increase of >1 $\log_{10}$ IU/mL from the lowest level observed or HCV RNA $>$100 IU/mL when previously $<$25 IU/mL), on-treatment failure (confirmed detectable HCV RNA at EOT), or viral relapse (presence of detectable HCV RNA during follow-up or at the time of SVR assessments after achieving undetectable levels at EOT), the incidence of AEs and laboratory abnormalities, and quality-of-life measures. The 95% CIs were constructed around the observed response rates and for the differences in response rates between treatment groups.

Patient-reported fatigue and impairment in productivity, daily activities, and missed work time were analyzed as change from baseline using a piecewise linear model comparing the area under the score–time curve from baseline with week 60, allowing slopes to change over time for each treatment arm. These end points were prespecified in the statistical analysis plan in the order presented as part of a closed testing procedure to address multiple testing of secondary end points. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Inc, Cary, NC).

Results

Patients

A total of 462 patients were screened; of these, 394 were randomized and 393 were treated (260 in the simeprevir/PR group and 133 in the placebo/PR group) (Supplementary Figure 2). At the time of this primary analysis, all patients had reached the time point at which the primary end point (SVR12) was assessed (ie, week 60), or had discontinued earlier. In addition, 184 patients (46.8%) had completed the final week 72 visit, and 24 (6.1%) had discontinued the study prematurely. The main reasons for study discontinuation were withdrawal of consent (14 patients; 3.6%) and loss to follow-up evaluation (8 patients; 2.0%).

Most (93.1%) patients in the simeprevir/PR group completed their assigned treatment regimen (compared with 25.6% in the placebo/PR group). The proportion of patients who discontinued simeprevir/placebo intake early was 3.5% and 72.2% in the simeprevir/PR and placebo/PR groups, respectively. The main reason for discontinuation was meeting the week 4 virologic stopping rule for simeprevir or placebo in both arms, with a large proportion of patients in the placebo group (69.9%) stopping placebo at week 4. The proportion of patients who completed PR treatment was 93.5% in the simeprevir/PR group (24 or 48 weeks) and 72.2% in the placebo/PR group (48 weeks).

Baseline demographic and disease characteristics were comparable between groups (Table 1; Supplementary Results section). The median times (in months) between the end of previous (Peg)IFN-based therapy and the start of treatment in this study were as follows: 31.0 (4; 141) and 31.0 (5; 115) for the simeprevir and placebo groups.

Efficacy

In the simeprevir/PR arm, an SVR12 rate of 79.2% (206 of 260) was observed compared with 36.1% (48 of 133) with placebo/PR (Table 2, Figure 1*A*). The difference between the 2 groups (controlling for HCV 1 subtype and *IL28B* genotype as stratification factors) was statistically significant at 43.8% (95% CI, 34.6–53.0; $P < .001$).

The majority of simeprevir-treated patients (92.7%; 241 of 260) met RGT criteria to complete treatment at week 24, of whom 83.0% (200 of 241) achieved SVR12. Among simeprevir-treated patients who did not meet RGT criteria, 40.0% (6 of 15) achieved SVR12.

The RVR rate was 77.2% (200 of 259) in the simeprevir/PR group compared with 3.1% (4 of 129) treated with placebo/PR. Among simeprevir-treated patients who achieved RVR, 86.5% (173 of 200) subsequently achieved

Table 1. Baseline Demographics and Disease Characteristics

	Simeprevir 150 mg 12 weeks + PR (n = 260)	Placebo + PR (n = 133)
Sex, %		
Male	68.8	59.4
Female	31.2	40.6
Race, %		
White	93.5	96.2
Black/African American	2.7	3.0
Native Hawaiian or Other Pacific Islander	0.4	0.0
Asian	3.1	0.8
Multiple	0.4	0
Ethnicity, %		
Hispanic or Latino	7.7	4.5
Median age, *y* (range)	52.0 (20–70)	52.0 (21–71)
Median body mass index (range)	27.2 (14.3–47.7)	26.8 (18.5–41.6)
IL28B genotype, %		
TT	11.9	12.0
CT	64.2	62.4
CC	23.8	25.6
METAVIR fibrosis score, %[a]		
F0–F1	34.8	35.6
F2	32.0	38.6
F3	17.6	11.4
F4	15.6	14.4
Median baseline HCV RNA, log_{10} *IU/mL* (range)	6.42 (4.6–7.7)	6.54 (3.1–7.5)
HCV genotype, %		
1	0.4	0
1a	42.3	40.6
1b	57.3	59.4
Previous HCV therapy, %		
PegIFNα-2a/RBV	68.5	66.2
PegIFNα-2b/RBV	26.9	27.1
Other	4.6	6.8
FSS score		
N	250	131
Mean score (SE)	3.6 (0.10)	3.3 (0.12)
WPAI productivity		
N	246	129
Mean score (SE)	19.0 (1.53)	15.6 (1.88)
WPAI daily activity impairment		
N	246	129
Mean score (SE)	19.4 (1.55)	15.4 (1.84)
WPAI absenteeism		
N	129	60
Mean (SE)	1.2 (0.60)	5.8 (2.60)

FSS, Fatigue Severity Scale; WPAI, work productivity and activity impairment: hepatitis C questionnaire.
[a]Liver biopsy obtained within 3 years of screening (or between the screening and baseline visit) with histology consistent with chronic HCV infection.

SVR12. At week 4, 5% (12 of 260) of simeprevir-treated patients had HCV-RNA level of 25 IU/mL or greater.

Irrespective of factors such as baseline HCV-RNA level, *IL28B* genotype, METAVIR score, and HCV subtype, SVR12 rates were significantly higher in the simeprevir/PR group than in the placebo/PR group (all $P < .001$) (Table 3, Figure 1*B*). In simeprevir-treated patients with HCV genotype 1a infection, the presence of the Q80K polymorphism at baseline was associated with a lower SVR12 rate compared with those without this polymorphism at baseline (46.7% [14 of 30] vs 78.5% [62 of 79], respectively). However, the SVR12 rate was high among the 13 simeprevir-treated patients with baseline Q80K polymorphism who achieved RVR (76.9% vs 23.5% among patients without RVR). Only one simeprevir-treated patient with HCV genotype 1b infection had Q80K polymorphism at baseline; this patient achieved SVR12. The possible effect of baseline characteristics and early response parameters on SVR12 in the simeprevir/PR group is presented in Supplementary Table 1.

Table 2. Virologic Response Over Time (RVR and SVR12), Proportion of Patients Meeting RGT Criteria and Corresponding SVR12 Rate, and Rates of On-Treatment Failure and Relapse

	Simeprevir 150 mg + PR (n = 260)	Placebo + PR (n = 133)
RVR	200/259 (77.2)	4/129 (3.1)
SVR12	206/260 (79.2)	48/133 (36.1)
Met RGT criteria	241/260 (92.7)	N/A
SVR12 in patients who met RGT criteria	200/241 (83.0)	N/A
SVR12 in patients who did not meet RGT criteria	6/15 (40.0)	N/A
On-treatment failure[a]	8 (3.1)	36 (27.1)
Virologic stopping rule met at weeks 12, 24, or 36	5 (1.9)	15 (11.3)
Viral relapse[b]	46/249 (18.5)	45/93 (48.4)

NOTE. All differences between the simeprevir and placebo groups: $P < .001$. SVR12 was defined as HCV RNA <25 IU/mL undetectable at the actual EOT and HCV RNA <25 IU/mL 12 weeks after the planned end of treatment.
N/A, not applicable.
[a]Confirmed detectable HCV-RNA levels at actual EOT.
[b]Among patients with undetectable HCV-RNA levels at actual EOT.

The rate of on-treatment failure was 3.1% (8 of 260) for simeprevir/PR and 27.1% (36 of 133) for placebo/PR (Table 2). Five patients (1.9%) in the simeprevir/PR group and 93 patients (69.9%) in the placebo/PR group met the virologic stopping rule at week 4, which dictated stopping simeprevir/placebo only and continuing with PR. Respective proportions of patients meeting a virologic stopping rule requiring discontinuation of all treatment at weeks 12, 24, or 36 were 1.9% (5 of 260) and 11.4% (15 of 133) in the simeprevir/PR and placebo/PR groups. Viral breakthrough occurred in 2.3% (6 of 260) of simeprevir-treated patients; this rate was similar in patients infected with genotype 1a/other (2.7%) and genotype 1b (2.0%). No placebo-treated patients had viral breakthrough. Viral breakthrough occurred mainly during the first 12 weeks of treatment with simeprevir/PR, and 5 of 6 simeprevir-treated patients with viral breakthrough also met a virologic stopping rule. Among patients with undetectable HCV RNA at EOT, 18.5% (46 of 249) in the simeprevir/PR group and 48.4% (45 of 93) in the placebo/PR group had experienced viral relapse. With simeprevir, this occurred less frequently in patients infected with genotype 1b (17 of 144; 11.8%) than in those with genotype 1a/other (29 of 105; 27.6%).

NS3 sequencing data were available for 52 of the 59 simeprevir-treated patients who did not achieve SVR12 (n = 54) or who relapsed after the SVR12 time point (n = 5). Most of these patients (considering NS3 positions 43, 80, 122, 155, 156, and 168) had emerging mutations in the NS3 protease domain at the time of failure (90.4%). In genotype 1a–infected patients, this was mainly R155K alone or with other amino acid substitutions at positions 80 or 168. For genotype 1b, this was mainly D168V or other mutations at position 168 (Table 4).

Safety and Tolerability

During the first 12 weeks of treatment, the most frequent AEs in the simeprevir/PR group (>25% of patients) were headache, fatigue, and influenza-like illness (Table 5). AEs were mainly grades 1/2. Grades 3/4 AEs were reported in 20.0% of patients in the simeprevir/PR group and in 21.1% in the placebo/PR group, with serious AEs (SAEs) reported in 1.2% and 2.3% of patients, respectively. Grades 2/3 photosensitivity reaction was reported as an SAE in 2 simeprevir-treated patients (0.8%). No other SAE was reported in more than 1 patient in either group. No patient discontinued simeprevir or placebo alone owing to AEs. During the first 12 weeks of treatment, AEs led to permanent discontinuation of all study drugs in 0.4% of simeprevir-treated and no placebo-treated patients. The same discontinuation rates were reported during the entire treatment phase for each of the treatment groups.

Two deaths have been reported, both after the first 12 weeks of treatment (Table 5). One patient in the simeprevir/PR group (METAVIR score F4 at baseline) died 5 days after consent withdrawal owing to SAEs considered unrelated to simeprevir by the investigator (pancytopenia, bradycardia, pyrexia, pneumonia, septic shock, confusional state, dyspnea, and respiratory acidosis). One patient in the placebo group also died of an SAE considered unrelated to treatment (primary liver cancer with lung metastasis).

Isolated mild and reversible increases in bilirubin (direct, indirect, and total) were observed in the simeprevir/PR group during the first 2 weeks of treatment, but were not accompanied by changes in any other liver parameters. During the first 12 weeks of treatment, increased bilirubin AEs (mainly grades 1/2) were reported in 5.8% of simeprevir-treated and in 2.3% of placebo-treated patients. Grades 3 or 4 increased bilirubin AEs occurred in 1.5% and 0.4% of simeprevir-treated patients, respectively, but none led to discontinuation of simeprevir. Grades 3/4 hyperbilirubinemia (laboratory reported) occurred in 6.2% of simeprevir-treated and in 3.1% of placebo-treated patients.

Rash, pruritus, neutropenia, and anemia AEs were comparable between the simeprevir and placebo groups (Table 5). For rash and pruritus, all AEs were grades 1/2, except for 1 case of grade 3 rash in the simeprevir group

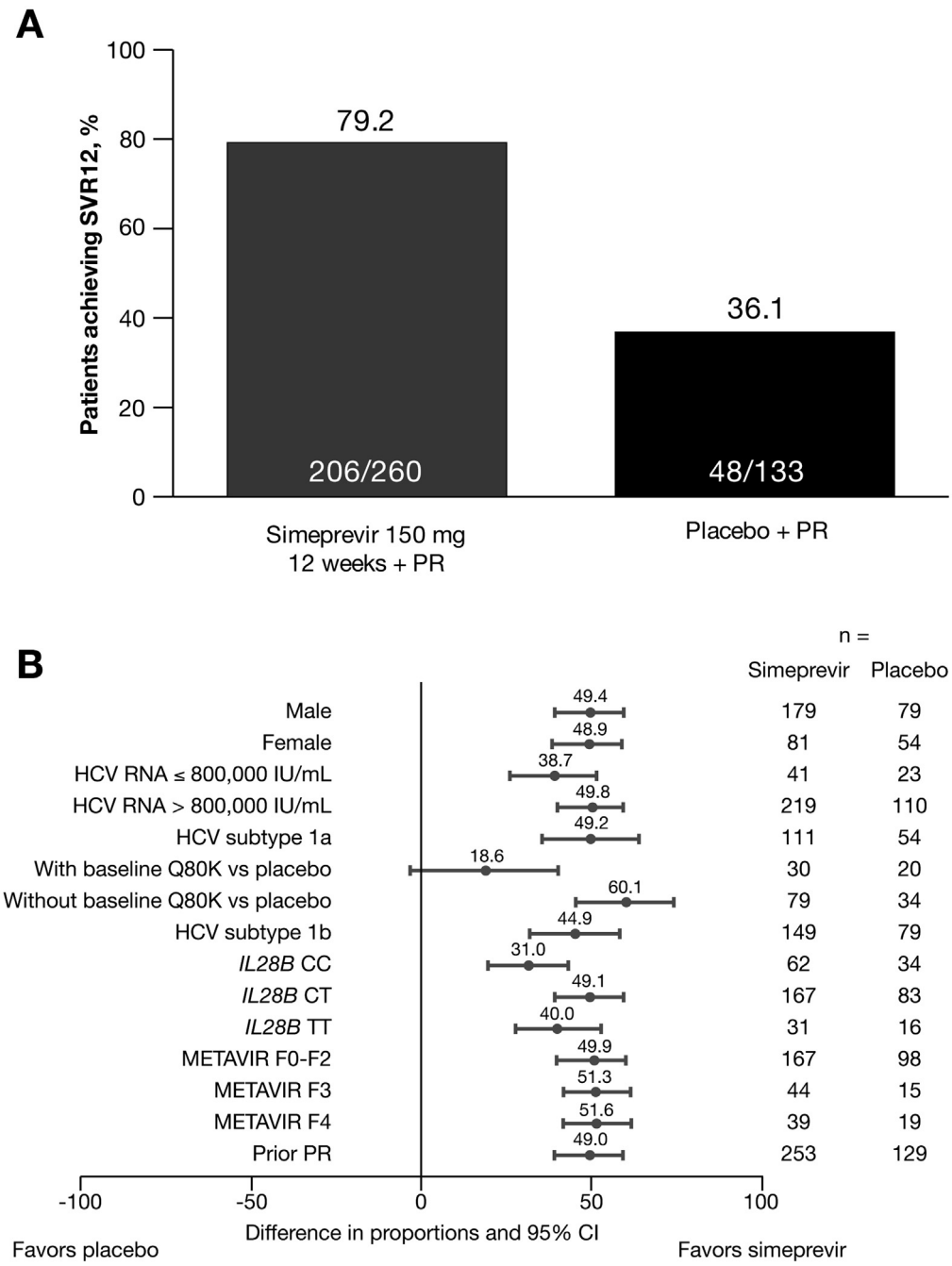

Figure 1. (*A*) SVR12 rates. (*B*) Differences in SVR12 by patient subgroup. Differences in the proportions and their respective CIs are derived from a logistic regression model including factors for treatment group, baseline HCV RNA (log_{10} IU/mL), HCV 1 subtype, and *IL28B*.

(a grade 3 photosensitivity reaction was considered possibly related to simeprevir), and did not lead to treatment discontinuation. Photosensitivity AEs were reported in 3.5% of simeprevir-treated and in no placebo-treated patients. With the exception of the case of grade 3 photosensitivity in the simeprevir group, these were grades 1/2 and did not lead to treatment discontinuation. Most anemia AEs were grades 1/2 and did not lead to treatment discontinuation, with grade 3 anemia occurring in 1.2% of simeprevir-treated and in 2.3% of placebo-treated patients. No cases of grade 4 anemia were reported.

In terms of laboratory abnormalities, decreases in hemoglobin were observed in 16.5% of simeprevir-treated and in 13.0% of placebo-treated patients. These were of grade 3 severity in 0.8% of simeprevir-treated and in 1.5% of placebo-treated patients, with no grade 4 decreases in hemoglobin in either group. No differences were observed for any other laboratory abnormalities between the 2 groups. The only grades 3/4 laboratory abnormality observed in more than 10% of simeprevir-treated patients was a decrease in absolute neutrophil count (14.6% with simeprevir and 17.6% with placebo).

Table 3. SVR12 Rates According to *IL28B* Genotype, METAVIR Score, and HCV Genotype

	Simeprevir 150 mg + PR (n = 260)	Placebo + PR (n = 133)	Difference between groups (simeprevir–placebo, 95% CI)[a]
IL28B genotype, %			
TT	20/31 (64.5)	3/16 (18.8)	40.0 (27.4–52.7)
CT	131/167 (78.4)	28/83 (33.7)	49.1 (38.9–59.4)
CC	55/62 (88.7)	18/34 (52.9)	31.0 (18.9–43.1)
METAVIR fibrosis score, %			
F0–F2	137/167 (82.0)	40/98 (40.8)	49.9 (39.6–60.3)
F3–F4	61/83 (73.5)	8/34 (23.5)	51.4 (41.5–61.3)
F3	32/44 (72.7)	3/15 (20.0)	51.3 (41.4–61.1)
F4	29/39 (74.4)	5/19 (26.3)	51.6 (41.5–61.6)
HCV genotype, %			
1a/other	78/111 (70.3)	15/54 (27.8)	49.2 (34.8–63.7)
With baseline Q80K	14/30 (46.7)	6/20 (30.0%)	18.6 (-7.5 to 44.7)
Without baseline Q80K	62/79 (78.5)	9/34 (26.5%)	60.1 (43.9–76.3)
1b	128/149 (85.9)	34/79 (43.0)	44.9 (31.6–58.2)

[a]The difference in proportions and respective 95% CIs are derived from a logistic regression model.

Mean scores for patient-reported fatigue, productivity impairment, and impairment in daily activities increased by similar amounts from baseline to week 4 in the 2 treatment groups, and remained increased through week 24 in both groups. Fatigue, productivity impairment, and activity impairment improved to levels at or below baseline in the simeprevir/PR group after week 24, when most simeprevir-treated patients were able to complete therapy owing to

Table 4. Emerging Mutations at Time of Failure in Patients Not Achieving SVR

	Proportion of patients with emerging mutations among patients not achieving SVR	Emerging mutations at time of failure (overview), n/N (%)	Emerging mutations at time of failure
Overall	47/52 (90.4)		
GT1a[a] with Q80K	12/14 (85.7)	8/12 (66.7) R155K	
		3/12 (25.0) D168E	
		1/12 (8.3) S122R	S122R (n = 1)
GT1a without Q80K	18/18 (100)	7/18 (38.9) R155K	
		4/18 (22.2) R155K in combination with mutations at NS3 positions 80 or 168	R155K+D168E (n = 1), R155K+D168A (n = 1, Q80K+ R155K (n = 2)
		7/18 (38.9) D168V, A, A/V, E or H	D168V (n = 2), D168A (n = 2), D168A/V (n = 1), D168E (n = 1), D168H (n = 1)
GT1b	17/20 (85.0)	8/17 (47.1) D168V	
		7/17 (41.2) D168A, E, T or E/V	D168A (n = 3), D168E or E/V (n = 3), D168T (n = 1)
		2/17 (11.8) Other	Q80R+D168E/V(n = 1), Q80R+S122T+D168E (n = 1)

NOTE. Data shown take into consideration NS3 positions 43, 80, 122, 155, 156, and 168. Specific amino acid changes at 1 or more of these positions are either known to confer reduced susceptibility to simeprevir in vitro or have emerged during in vitro selection experiments. Considering a longer list of 18 NS3 amino acid positions that also includes NS3 positions that have been associated with resistance to other HCV NS3/4A protease inhibitors or that were considered of interest based on observations in simeprevir in vitro or in vivo studies (18 NS3 amino acid positions of interest: 36, 41, 43, 54, 55, 80, 107, 122, 132, 138, 155, 156, 158, 168, 169, 170, 174, and 175), 4 patients had additional mutations: 1 HCV genotype 1a patient with Q80K at baseline had a single emerging mutation I170T. I170T also was observed in another HCV genotype 1a patient without baseline Q80K in combination with emerging R155K. One HCV genotype 1b patient had emerging V107I in combination with D168V and another S174F in combination with D168V. Similar mutations were observed at other time points in patients not achieving SVR. Emerging mutations beyond the 18 positions of interest in the NS3 protease domain were infrequent, the same mutation was observed in no more than 1 patient and always in combination with emerging mutations at positions 80, 155, and/or 168.
GT1a, HCV genotype 1a; GT1b, HCV genotype 1b.
[a]Genotype 1a might include a few patients with non-1a/1b HCV genotype.

Table 5. Adverse Events During the First 12 Weeks of Treatment (Simeprevir/Placebo Plus PR Treatment Phase)

	Patients, %		Patients, %	
	Simeprevir 150 mg 12 weeks + PR (n = 260)	Placebo + PR (n = 133)	Simeprevir 150 mg 12 weeks + PR (n = 260)	Placebo + PR (n = 133)
	First 12 weeks		Entire treatment phase	
Any AE	95.4	92.5	97.3	94.0
Grade 1 or 2 AE	75.4	71.4	69.6	63.9
Grade 3 AE	18.1	18.0	24.2	25.6
Grade 4 AE	1.9	3.0	3.5	4.5
AE with fatal outcome	0	0	1	1
SAE	1.2	2.3	5.4	7.5
AE leading to permanent discontinuation of:				
At least 1 study drug	1.2	1.5	2.3	5.3
Simeprevir/placebo and PR	0.4	0	0.4	0
Simeprevir/placebo only	0	0	0	0
PegIFNα-2a and/or RBV	0.8	1.5	1.9	5.3
PegIFNα-2a only	0	0	0	0
RBV only	0	0	0	0.8
Most common AEs[a]				
Fatigue	31.9	42.1	32.3	43.6
Headache	31.9	36.1	33.1	36.1
Influenza-like illness	29.6	20.3	30.0	20.3
AEs of clinical interest				
Rash	18.5	14.3	23.1	22.6
Pruritus	23.5	16.5	27.7	27.8
Neutropenia	14.6	16.5	17.7	21.8
Photosensitivity	3.5	0	3.5	0
Anemia	10.8	6.0	16.9	20.3

[a]AEs occurring in more than 25% of patients in the simeprevir group in the first 12 weeks and during the entire treatment phase.

meeting RGT criteria, but remained increased through week 48 in the placebo/PR group (Figure 2*A–C*). As a result, significantly lower fatigue, productivity impairment, and activity impairment was observed in simeprevir-treated compared with placebo-treated patients over the entire study period ($P < .001$). Similar trends were not observed for patient-reported time missed from work. Absenteeism scores for the subset of patients in the labor force at baseline showed no significant difference between groups ($P = .701$; Figure 2*D*).

Discussion

This study was performed to assess the efficacy and safety of simeprevir in combination with PR in patients with chronic HCV genotype 1 infection who had relapsed after previous IFN-based therapy. Oral, once-daily treatment with simeprevir 150 mg for 12 weeks in combination with PR followed by treatment for 12–36 weeks with PR was associated with a significant improvement in SVR12 in this patient population compared with that seen in the placebo control group. SVR in this study was defined as HCV RNA less than 25 IU/mL undetectable at actual EOT and less than 25 IU/mL detectable/undetectable 12 weeks after planned EOT; all simeprevir-treated patients who achieved SVR12 had undetectable levels at the SVR12 time point. Overall, 79.2% of simeprevir-treated patients achieved SVR12 compared with 36.1% of those who received PR alone. In this study, an RGT strategy was used to allow individualized shortening of PR treatment duration to 24 weeks based on early virologic response. A shorter overall treatment duration is highly desirable in patients with chronic HCV infection because it reduces exposure to PR, resulting in reduced costs and a lower incidence of treatment-related AEs.[38–40] Almost all simeprevir-treated patients (92.7%) met RGT criteria and were eligible to stop PR at week 24. The SVR12 rate in these patients was 83.0%, supporting this treatment approach. Among the 77.2% of simeprevir-treated patients with RVR (HCV RNA <25 IU/mL undetectable at week 4), 86.5% achieved SVR12. As expected, the relapse rate in patients treated with simeprevir/PR was lower than in those who received PR alone (18.5% compared with 48.4%).

In this study, more than 30% of patients had bridging fibrosis or cirrhosis (given that a 3-year biopsy window was allowed, the proportion of patients with cirrhosis may have

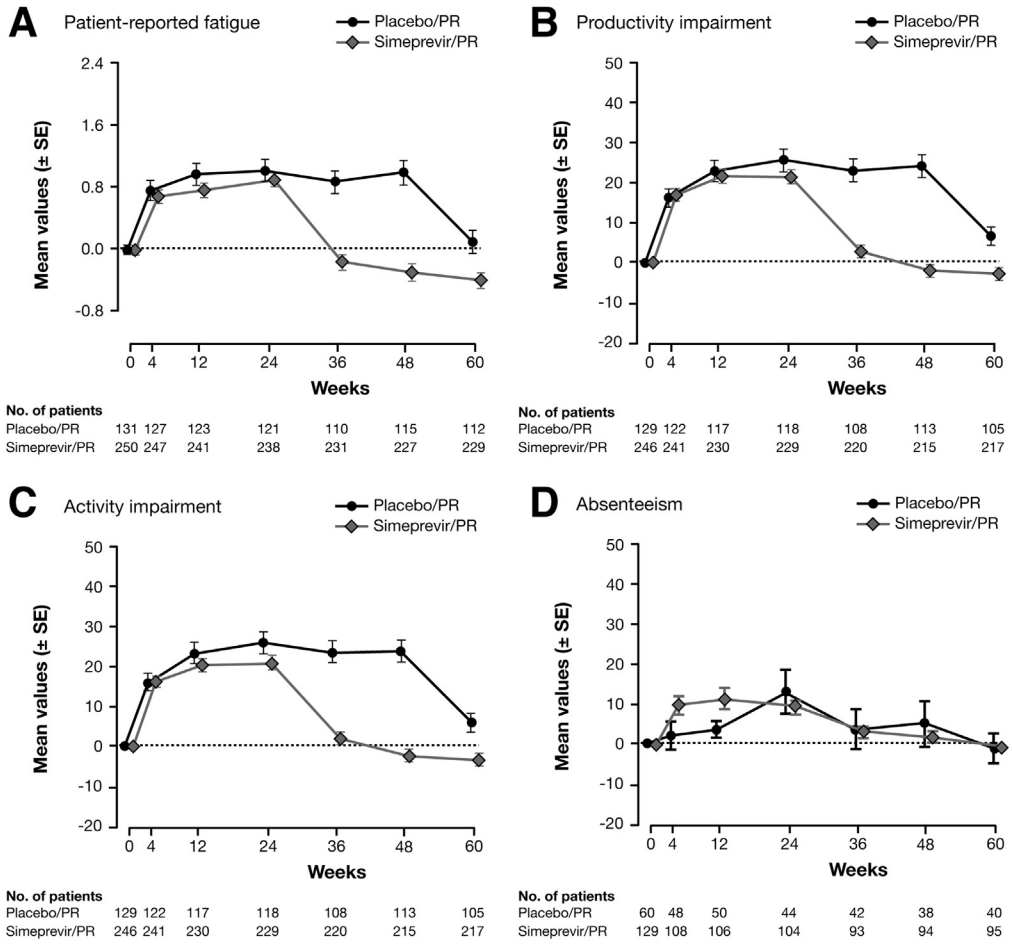

Figure 2. Change in score from baseline in (*A*) patient-reported fatigue, (*B*) productivity impairment, (*C*) activity impairment, and (*D*) absenteeism.

been underestimated; however, this approach was based on FDA guidance that was current at the time of patient enrolment in this trial). In patients with baseline METAVIR F3–F4 scores, SVR12 rates were significantly higher in those treated with simeprevir/PR than in those who received placebo/PR (73.5% vs 23.5%, respectively; $P < .001$). The SVR12 rates in simeprevir-treated patients were also higher than in those who received placebo/PR across *IL28B* genotypes (88.7% vs 52.9% for CC, 78.4% vs 33.7% for CT, and 64.5% vs 18.8% for TT; all $P < .001$). The SVR12 rates with simeprevir were lower in HCV genotype 1a patients who had the Q80K polymorphism at baseline compared with those without this polymorphism (46.7% vs 78.5%). The impact of the Q80K polymorphism on SVR varied depending on the presence of baseline characteristics associated with poor treatment outcome. As seen with patients with Q80K, the SVR rates differed based on week 4 virologic response. For example, among simeprevir-treated patients harboring Q80K who had RVR (13 of 29), most achieved SVR12 (76.9%). Although the Q80K variant itself only has limited effect on simeprevir activity, the resistance barrier for Q80K-carrying variants appears to be lower. This potentially facilitates the emergence of additional mutations, resulting in a higher treatment failure rate in Q80K patients compared with patients without Q80K when treated with simeprevir in combination with PR.[41]

Results of this study are consistent with those of previous studies of simeprevir in combination with PR in treatment-experienced[30] and treatment-naive patients.[27,33,34] SVR24 rates of 75% and 83% have been reported for boceprevir and telaprevir, respectively, in combination with PegIFN/RBV in patients who relapsed after prior IFN-based therapy.[11,14] The SVR24 rates in the placebo control groups in these studies were 24% and 29%, respectively. The SVR24 rate was 69% in boceprevir-treated patients who were HCV RNA negative at weeks 8 and 12 and therefore eligible for a shorter overall duration of PegIFN/RBV (36 weeks).[11] No data concerning the potential for RGT with telaprevir in relapsed patients have been reported.

The safety and tolerability profile of simeprevir/PR in the present study was generally similar to that of PR alone,[42] with no additional treatment-related AEs reported. The improved virologic response rates achieved by addition of simeprevir to PR allowed a reduction in total treatment duration for most patients, which significantly reduced exposure to PR and time with treatment-related side effects overall for simeprevir-treated compared with placebo-treated patients. AEs were generally mild and clinically

manageable, with few grades 3/4 AEs or SAEs reported, and no patient discontinued simeprevir because of AEs. No increased incidence for simeprevir/PR compared with PR alone was seen for rash, pruritus, neutropenia, or anemia AEs, despite the fact that use of erythropoiesis-stimulating agents was not allowed in this study. These events were considered of clinical interest because an increased incidence has been reported with boceprevir and telaprevir.[11–14,22] Mild and transient bilirubin increases were seen in simeprevir-treated patients; however, no concomitant increases in other laboratory liver parameters were observed. This finding may be associated with inhibition of bilirubin transporters OATP1B1 and MRP2 by simeprevir,[43] although RBV-induced hemolysis also may cause bilirubin increases. The addition of simeprevir to PR did not increase patient-reported fatigue, productivity impairment, or activity impairment beyond what was observed in patients who received PR alone, but did shorten the duration of these treatment-related problems.

In conclusion, the addition of simeprevir 150 mg once daily to PR substantially improved SVR rates in HCV genotype 1–infected patients who had relapsed after previous IFN-based therapy, irrespective of *IL28B* genotype, METAVIR score, HCV 1 subtype, or the presence of baseline polymorphisms. The majority of simeprevir-treated patients met RGT criteria, enabling a shorter, 24-week overall duration of PR treatment. The addition of simeprevir to PR generally was well tolerated, with safety and tolerability similar to PR alone. Ongoing studies are investigating simeprevir in both PegIFNα and IFN-free combinations, including all oral regimens.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2014.02.051.

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Reprint requests
Address requests for reprints to: Xavier Forns, MD, Liver Unit, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Barcelona, Spain. e-mail: xforns@clinic.ub.es; fax: (+34) 93 227 1779.

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Conflicts of interest
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Supplementary Materials and Methods

Patients

Patients with the following defined laboratory abnormalities were excluded from the trial: platelets less than 90,000/mm^3, absolute neutrophil count less than 1500/mm^3, white blood cell count less than 3000/μL, hemoglobin level less than 12 g/dL for women and less than 13 g/dL for men, creatinine level greater than 1.5 mg/dL, alanine aminotransferase and/or aspartate aminotransferase level greater than 10 times the upper limit of laboratory normal range, total serum bilirubin level 1.5 times or more the upper limit of laboratory normal range, and α-fetoprotein level greater than 50 ng/mL in subjects with cirrhosis (METAVIR fibrosis score, F4).

Assessments

Blood samples were collected at screening, on days 1, 3, 7, 14, and 28, at 4-week intervals thereafter until week 28, at weeks 36, 42 and 48, and during follow-up evaluation (weeks 52, 60, and 72).

Blood samples for biochemical and hematologic analyses were obtained at screening and during scheduled visits, when electrocardiogram, vital signs, and physical examination assessments also were performed.

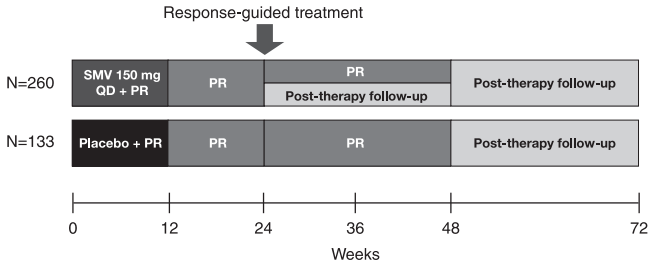
Supplementary Results

Patients

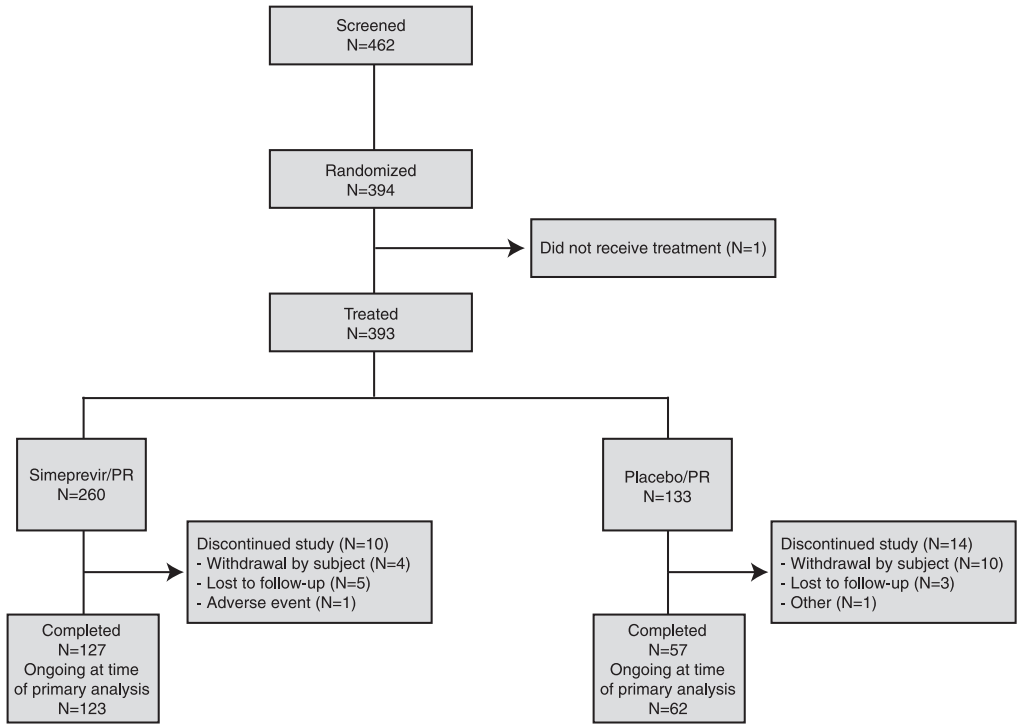
Approximately 70% of patients were enrolled in Europe, 22% in North America, and 8% in Australia and New Zealand. The majority of patients were male (65.6%), 94.4% were white, their median age was 52 years, and their median body mass index was 27.0 kg/m^2. A significant proportion of patients had bridging fibrosis (METAVIR F3 [15.4%]) or cirrhosis (METAVIR F4 [15.2%]). All patients were infected with HCV genotype 1 (41.7% with HCV genotype 1a, and 58.0% with HCV genotype 1b). In terms of IL28B genotype, 24.4% had CC, 63.6% had CT, and 12.0% had TT. Most patients had received prior PegIFN-based therapy (67.7% had received PegIFNα-2a/RBV and 27.0% had received PegIFNα-2b/RBV). The median baseline HCV-RNA level was 6.5 $\log_{10}$ IU/mL (range, 3.1–7.7 $\log_{10}$ IU/mL), with 83.7% of patients having baseline HCV-RNA levels greater than 800,000 IU/mL. The Q80K polymorphism was present at baseline in 13.1% of patients (12.1% [31 of 257] in the simeprevir/PR group and 15.0% [20 of 133] in the placebo/PR group). Among the 51 patients with Q80K at baseline, only 1 was infected with HCV genotype 1b (enrolled in the simeprevir arm). The prevalence of Q80K at baseline among patients infected with HCV genotype 1a was 30.7% (50 of 163).

Efficacy

At the time of this primary week 60 analysis, the SVR24 assessment time point had been reached by 254 of 260 patients in the simeprevir/PR group and by 64 of 133 patients in the placebo/PR group. The SVR24 rate was higher among simeprevir-treated patients (78.3% [199 of 254] vs 31.3% [20 of 64]; adjusted difference, 47.1%; 95% CI, 34.8–59.5; $P < .001$). All simeprevir-treated patients who achieved SVR24 had HCV-RNA levels less than 25 IU/mL undetectable at the SVR24 time point.



Supplementary Figure 1. Study design. Response-guided treatment in simeprevir (SMV) arm: if HCV-RNA level was less than 25 IU/mL at week 4 and undetectable at week 12, complete treatment at week 24. Stopping rules: if HCV-RNA level was greater than 1000 IU/mL at week 4, stop SMV/placebo; if HCV-RNA level was less than 2 $\log_{10}$ IU/mL reduction at week 12, or confirmed 25 IU/mL or greater at week 24 or 36, stop all treatment. PR, peginterferon α-2a 180 μg/week + ribavirin 1000–1200 mg/day; QD, once daily; SMV, simeprevir.



Supplementary Figure 2. Patient disposition.

Supplementary Table 1. Univariate Analyses of Baseline Characteristics, Pharmacokinetic Exposure Measures, and Early Response Parameters on SVR12 in the Simeprevir/PR Treatment Arm (Intent-to-Treat Population)

	P value (likelihood ratio test)	Significance level[a]
Age, *y*	.455	
Baseline ALT level, *U/L* (nonlinear)	.731	
BMI, kg/m^2 (nonlinear)	.002	**
Baseline HCV-RNA level, log_{10} *IU/mL*	.080	
Height, *cm* (nonlinear)	.633	
Weight, *kg* (nonlinear)	.052	
HCV genotype/subtype	.002	**
Baseline Q80K	<.001	***
Sex	.345	
HCV genotype/subtype, baseline Q80K	<.001	***
IL28B	.023	*
METAVIR score	.299	
Race	.583	
Region	<.001	***
AUC_{24h} (log_{10} ng·h/mL)	.070	
Predose plasma concentration (log_{10} ng/mL)	.081	
cEVR	<.001	***
eRVR	<.001	***
RVR	<.001	***
HCV RNA <25 IU/mL at week 4	<.001	***

NOTE. Generalized additive modeling methodology using cubic spline functions was applied in the analysis. Nonlinear indicates that a cubic spline function with 2 degrees of freedom was used to model SVR12.
ALT, alanine transaminase; AUC, area under concentration-time curve; BMI, body mass index; cEVR, complete early virologic response; eRVR, extended rapid virologic response.
[a]Statistical significance level of likelihood ratio test: *<.05, **<.01, ***<.001.

Appendix

PROMISE Study Investigators

Jacob George, Graeme Macdonald, Martin Weltman, Stuart Roberts, Hugh Harley, Peter Ferenci, Hermann Laferl, Michael Gschwantler, Hans Orlent, Hans Van Vlierberghe, Christophe Moreno, Stefan Bourgeois, Yves Horsmans, Frederik Nevens, Maged Peter Ghali, Curtis Cooper, Eric Yoshida, Sylvie Vezina, Scott Fung, David K H Wong, Vlad Ratziu, Jean-Pierre Bronowicki, Dominique Guyader, Naoky Tsai, Thomas Berg, Peter Buggisch, Hartwig Klinker, Matthias Dollinger, Stefan Mauss, Holger Hinrichsen, Norbert Gruener, Saif Abu-Mouch, Assy Nimer, Yaacov Baruch, Ziv Ben Ari, Elimelech Zuckerman, Rifaat Safadi, Sergio Babudieri, Giampiero Carosi, Gloria Taliani, Pietro Andreone, Ed Gane, Catherine Stedman, Graeme Dickson, Robert Flisiak, Andrzej Horban, Waldemar Halota, Ivan Melendez-Rivera, Vyacheslav Morozov, Elena Bessonova, Dzhamal Abdurakhmanov, Zhanna Kobalava, Natalia Geyvandova, Maria Buti , Jose Luis Calleja, Moises Diago, Xavier Forns, Manuel Romero, Kaushik Agarwal, Andrew Austin, Ashley Brown, Matthew Cramp, David Mutimer, Ray Fox, Edwin DeJesus, Ana Corregidor, Franco Antonio B Felizarta, Norman Gitlin, Michael Jones, Albert Tran, Jean-Pierre Zarski, Fabien Zoulim, Lawrence Serfaty, Christophe Hezode, Jens Rasenack, Stefan Zeuzem, Michael Biermer, Wiesław Kryczka, Ewa Janczewska-Kazek, Barbara Baka-Ćwież, Alexey Yakovlev, Vladimir Rafalskiy, Natalia Zakharova, Igor Nikitin, Pavel Bogomolov, Maribel Rodriguez-Torres, Coleman Smith, James Underwood, Ziad Younes, Gregory Everson, Joseph Galati, Michael E Schwartz and Eric Lawitz.