Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial

Michael Manns, Patrick Marcellin, Fred Poordad, Evaldo Stanislau Affonso de Araujo, Maria Buti, Yves Horsmans, Ewa Janczewska, Federico Villamil, Jane Scott, Monika Peeters, Oliver Lenz, Sivi Ouwerkerk-Mahadevan, Guy De La Rosa, Ronald Kalmeijer, Rekha Sinha, Maria Beumont-Mauviel

Summary

Background Pegylated interferon (peginterferon) alfa 2a or 2b plus ribavirin regimens were the standard of care in patients with hepatitis C virus (HCV) infection, but the sustained virological response can be suboptimum in patients with HCV genotype 1 infection. The efficacy, safety, and tolerability of the combination of simeprevir, a one-pill, once-daily, oral HCV NS3/4A protease inhibitor versus placebo, plus peginterferon alfa 2a or 2b plus ribavirin was assessed in treatment-naive patients with HCV genotype 1 infection.

Methods In the QUEST-2, phase 3 study, done at 76 sites in 14 countries (Europe, and North and South Americas), patients with confirmed chronic HCV genotype 1 infection and no history of HCV treatment were randomly assigned with a computer-generated allocation sequence in a ratio of 2:1 and stratified by HCV genotype 1 subtype and host *IL28B* genotype to receive simeprevir (150 mg once daily, orally), peginterferon alfa 2a (180 µg once weekly, subcutaneous injection) or 2b (according to bodyweight; 50 µg, 80 µg, 100 µg, 120 µg, or 150 µg once weekly, subcutaneous injection), plus ribavirin (1000–1200 mg/day or 800–1400 mg/day, orally; simeprevir group) or placebo (once daily, orally), peginterferon alfa 2a or 2b, plus ribavirin (placebo group) for 12 weeks, followed by just peginterferon alfa 2a or 2b plus ribavirin. Total treatment duration was 24 weeks or 48 weeks (simeprevir group) based on criteria for response-guided therapy (ie, HCV RNA <25 IU/mL undetectable or detectable at week 4 and undetectable week 12) or 48 weeks (placebo). Patients, study personnel, and the sponsor were masked to treatment assignment. The primary efficacy endpoint was sustained virological response at 12 weeks after the planned end of treatment (SVR12). Analyses were by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT01290679. Results from the primary (SVR12, week 60) analysis are presented.

Findings 209 (81%) of 257 patients in the simeprevir group and 67 (50%) of 134 in the placebo group had SVR12 (adjusted difference 32·2%, 95% CI 23·3–41·2; p<0·0001). The incidences of adverse events were similar in the simeprevir and placebo groups at 12 weeks (246 [96%] *vs* 130 [97%]) and for the entire treatment (249 [97%] *vs* 132 [99%]), irrespective of the peginterferon alfa used. The most common adverse events were headache, fatigue, pyrexia, and influenza-like illness at 12 weeks (95 [37%] *vs* 45 [34%], 89 [35%] *vs* 52 [39%], 78 [30%] *vs* 48 [36%], and 66 [26%] *vs* 34 [25%], respectively) and for the entire treatment (100 [39%] *vs* 49 [37%], 94 [37%] *vs* 56 [42%], 79 [31%] *vs* 53 [40%], and 66 [26%] *vs* 35 [26%], respectively). Rash and photosensitivity frequencies were higher in the simeprevir group than in the placebo group (61 [24%] *vs* 15 [11%] and ten [4%] *vs* one [<1%], respectively). There was no difference in the prevalence of anaemia between the simeprevir and placebo groups (35 [14%] *vs* 21 [16%], respectively, at 12 weeks, and 53 [21%] *vs* 37 [28%], respectively, during the entire treatment).

Interpretation Addition of simeprevir to either peginterferon alfa 2a or peginterferon alfa 2b plus ribavirin improved SVR in treatment-naive patients with HCV genotype 1 infection, without worsening the known adverse events associated with peginterferon alfa plus ribavirin.

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Medizinische Hochschule Hannover, Department of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany (Prof M Manns MD); **Service d'Hépatologie, Hôpital Beaujon, University Paris-Diderot and INSERM CRB3, Clichy, France** (Prof P Marcellin MD); **Texas Liver Institute, University of Texas Health Science Center, San Antonio, TX, USA** (Prof F Poordad MD); **LIM-47 Hospital das Clinicas of the University of São Paulo School of Medicine, Faculty of Medicine, University of São Paulo, São Paulo, Brazil** (E S Affonso de Araujo PhD); **Hospital Vall d'Hebron and Ciberhed del Instituto Carlos III, Barcelona, Spain** (Prof M Buti MD); **Université Catholique de Louvain St Luc, Brussels, Belgium** (Prof Y Horsmans PhD); **ID Clinic, Myslowice, Poland** (E Janczewska MD); **CIPREC, Buenos Aires, Argentina** (Prof F Villamil MD); **Janssen Global Services, High Wycombe, UK** (J Scott PhD); **Janssen Infectious Diseases, Beerse, Belgium** (M Peeters MSc, O Lenz PhD, R Sinha PhD), M Beumont-Mauviel PhD); **Janssen Research and Development, Beerse, Belgium** (S Ouwerkerk-Mahadevan PhD); **and Janssen Global Services, Titusville, NJ, USA** (G De La Rosa MD, R Kalmeijer MD)

Introduction

Hepatitis C virus (HCV) infection is a major public health concern, with about 150 million individuals infected worldwide, and 3–4 million new cases of infection reported every year.[1–3] HCV infection is the leading cause of liver cirrhosis, hepatocellular carcinoma, and liver transplantation, and is associated with an increasing mortality rate in infected individuals.[1–3]

In the past decade, the standard of care for HCV infection has been a combination of pegylated interferon (peginterferon) plus ribavirin. Either peginterferon alfa 2a or peginterferon alfa 2b is used in combination with ribavirin for the treatment of HCV infection. The peginterferon plus ribavirin regimens have important limitations, including suboptimal sustained virological response (SVR) in patients infected with HCV genotype 1

Correspondence to:
Prof Michael Manns, Department of Gastroenterology, Hepatology and Endocrinology, Medical School of Hannover, Carl-Neuberg Str 1, 30625, Hannover, Germany
manns.michael@mh-hannover.de

(about 40% of the infected population in North America and about 50% in western Europe).[1,4–7] Despite these limitations, the combination of peginterferon plus ribavirin is still the standard of care for some patient populations—eg, French guidelines recommend peginterferon plus ribavirin in some treatment-naive populations with minimal hepatic complications.[8]

Two direct-acting antiviral agents boceprevir and telaprevir, which inhibit the HCV NS3/4A viral protease were approved by regulatory agencies in 2011.[9] The addition of these direct-acting antiviral agents to peginterferon plus ribavirin in response-guided therapy has improved SVR rates and shortened treatment in some patients infected with HCV genotype 1.[10–14] Despite high SVR rates and shortened treatment with peginterferon plus ribavirin in 45–65% of patients, boceprevir and telaprevir are associated with an increased incidence of adverse events (eg, anaemia and rash) and a high pill burden;[15–18] therefore, simpler and safer treatments are needed.

Simeprevir (TMC435; Janssen, Beerse, Belgium, and Medivir, Stockholm, Sweden) is a one-pill, once-daily, oral HCV NS3/4A protease inhibitor approved in Japan, Canada, the USA, Russia, and Europe for the treatment of chronic HCV infection. It has antiviral activity in patients infected with HCV genotypes 1, 2, 4, 5, and 6.[19,20] Simeprevir showed favourable efficacy and safety in phase 2a and 2b trials.[19,21–23]

We investigated the efficacy, safety, and tolerability of simeprevir versus placebo in combination with peginterferon alfa 2a plus ribavirin or peginterferon alfa 2b plus ribavirin in treatment-naive patients who had chronic HCV genotype 1 infection in the phase 3 QUEST-2 trial. We report the results from the primary analysis.

Methods

Patients and study design

QUEST-2 was a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial to assess the efficacy, safety, and tolerability of simeprevir in combination with peginterferon alfa 2a plus ribavirin or peginterferon alfa 2b plus ribavirin (simeprevir group) versus placebo in combination with peginterferon alfa 2a plus ribavirin or peginterferon alfa 2b plus ribavirin (placebo group) in treatment-naive patients with chronic HCV genotype 1 infection. The study was done during Jan 18, 2011, and Feb 5, 2013, at 76 sites in 14 countries in Europe, North America, and South America (appendix).

See **Online** for appendix

Eligible patients were men and women aged 18 years and older with confirmed chronic HCV genotype 1 infection, plasma HCV RNA concentration at screening of greater than 10 000 IU/mL, and no history of treatment of HCV infection with an approved or an investigational drug. Patients with cirrhosis were eligible if an ultrasound assessment within the 6 months before the study did not show any signs of hepatocellular carcinoma. Patients were excluded if they had hepatic decompensation, any non-HCV-related liver disease, or co-infection with HIV, hepatitis B virus, or non-genotype 1 HCV.

In accordance with the 2008 Declaration of Helsinki, institutional review boards of all participating institutions approved the study. Written informed consent was obtained from all participants according to local regulations.

Randomisation and masking

After stratification by HCV genotype 1 subtype (1a, 1b, or other) and *IL28B* genotype (CC, CT, or TT), patients were randomly assigned in a 2:1 ratio to the simeprevir or placebo group. We used a computer-generated randomisation schedule that was prepared by or under the supervision of the sponsor before the study, balanced using randomly permuted blocks, and implemented using an interactive web-based or voice response system. Sponsors, investigators, and patients were masked to treatment assignment. In Europe, where randomisation to peginterferon alfa 2b was allowed, patients were randomly assigned in a 1:1 ratio to peginterferon alfa 2a (Pegasys, Hoffmann-La Roche, Basel, Switzerland) plus ribavirin or peginterferon alfa 2b (PegIntron, Merck Sharp and Dohme, Whitehouse Station, NJ, USA) plus ribavirin with the aim of a maximum 30% of the overall population assigned to the regimen containing peginterferon alfa 2b. The remaining patients were not randomly assigned and received peginterferon alfa 2a plus ribavirin. Administration of the two types of peginterferon was open label. PegIntron could only be used within European Medicines Agency (EMA) countries for regulatory reasons, and as such this randomisation was only done in these countries. We provide further details about randomisation and masking in the appendix p 1.

Procedures

Patients were given simeprevir (150 mg once daily, orally) plus peginterferon plus ribavirin or placebo (once daily, orally) plus peginterferon plus ribavirin for 12 weeks, followed by just peginterferon plus ribavirin for 12 weeks or 36 weeks, depending on criteria for response-guided treatment. Peginterferon alfa 2a (180 µg in prefilled syringes) and peginterferon alfa 2b (prefilled pens containing 0·5 mL solution with 50 µg, 80 µg, 100 µg, 120 µg, or 150 µg administered at 1·5 µg/kg bodyweight) were administered as once-weekly subcutaneous injections. Ribavirin was administered as CoPegus (Hoffmann-La Roche, Basel, Switzerland; 1000–1200 mg/day) or as Rebetol (Merck Sharp and Dohme, Whitehouse Station, NJ, USA; 800–1400 mg/day) in combination with peginterferon alfa 2a and peginterferon alfa 2b, respectively. Treatment duration with simeprevir was response-guided and treatment was stopped at week 24 in patients with HCV RNA less than 25 IU/mL undetectable or detectable at

week 4 and less than 25 IU/mL undetectable at week 12. Patients in the simeprevir group who did not meet these criteria continued peginterferon plus ribavirin until week 48, as did all patients in the placebo group. Patients in both groups were followed up for up to 72 weeks after the start of treatment (appendix p 6).

In accordance with virological stopping rules, simeprevir and placebo were discontinued if HCV RNA concentration was greater than 1000 IU/mL at week 4, whereas peginterferon plus ribavirin were continued. All treatment was discontinued if the reduction in HCV RNA concentration compared with baseline was less than 2 $\log_{10}$ IU/mL at week 12 or if HCV RNA was confirmed detectable and 25 IU/mL or greater at week 24 or week 36.

Standard population sequencing of HCV NS3/4A was done on baseline samples and on those from patients in whom treatment failed at selected timepoints (based on HCV RNA changes and sensitivity limit of the sequencing assay). *IL28B* genotyping (locus rs12979860) was done on blood samples taken at screening with real-time PCR.

Blood samples were obtained at screening, days 1, 7, 14, and 28, at 4-week intervals thereafter until week 28, and then at weeks 36 and 48 for those receiving 24 weeks of treatment, and at weeks 36, 42, 48, and 52 for those continuing treatment until week 48.

In patients who discontinued all study medication early, HCV RNA measurements were done at withdrawal, 4 weeks after withdrawal, and 12-week intervals (from baseline) until week 72.

According to the statistical analysis plan, if the percentage of patients with a major protocol deviation was less than 10%, there was no need for a per-protocol analysis of the primary endpoint based on data from patients in the intention-to-treat population with exclusion of patients with major protocol violations.

Adverse events were monitored during the trial. Blood samples for biochemical and haematological analyses were obtained at screening and during scheduled visits.

Data for fatigue and productivity (including activity impairment and absenteeism) were gathered with the Fatigue Severity Score (FSS) and Work Productivity and Activity Impairment: Hepatitis C (WPAI) questionnaires (appendix pp 1–2), respectively, which were completed by patients at regular intervals. The Center for Epidemiologic Studies Depression Scale (CES-D) questionnaire (appendix pp 1–2) was used to assess the effect of treatment on depression, with data gathered at baseline and throughout the trial. Perceived health status and quality of life at baseline and during treatment were assessed with the EuroQol 5-dimension (EQ-5D) questionnaire (appendix pp 1–2). The five health dimensions measured with EQ-5D were mobility, self-care, usual activities, pain or discomfort, and anxiety or depression (additional details are provided in the appendix pp 1–2).

Plasma HCV RNA concentration was measured with the Roche COBAS TaqMan HCV/HPS assay (Roche Molecular Diagnostics, Pleasanton, CA, USA) system (version 2.0), which has a limit of quantification of 25 IU/mL and a limit of detection of 15 IU/mL.

Outcomes

The primary efficacy endpoint was the proportion of patients achieving SVR12—defined as HCV RNA concentration of less than 25 IU/mL undetectable at end of treatment and less than 25 IU/mL detectable or undetectable 12 weeks after the planned end of treatment. Data from the week 60 primary analysis are presented for the final results of the primary endpoint of the study—SVR12. Three amendments were made to the protocol, which are described in detail in the appendix p 1. Secondary efficacy endpoints included the proportion of patients meeting criteria for response-guided therapy to complete treatment at week 24, rapid virological response (RVR; HCV RNA concentration <25 IU/mL undetectable at week 4), activity, safety, and tolerability of simeprevir in the two subpopulations of patients who were given peginterferon alfa 2a or 2b, on-treatment failure (confirmed detectable HCV RNA concentration at the end of treatment), incidence of viral relapse (HCV RNA concentration ≥25 IU/mL during follow-up or at the time of SVR assessments in patients with undetectable levels at the end of treatment), incidence of adverse events and laboratory abnormalities, and quality-of-life measures. SVR at 24 weeks after the planned end of treatment (SVR24) are reported in the supplemental results (appendix p 3). We also assessed polymorphisms (HCV NS3 protease domain) at baseline and their correlation with the efficacy of simeprevir plus peginterferon plus ribavirin and the effect of baseline characteristics on treatment response. Data for depression severity and health status are also presented.

Statistical analysis

SGS Life Sciences Services (Mechelen, Belgium) did the statistical analyses with SAS (version 9.1). All statistical analyses were done at the 5% two-sided significance level. Efficacy and safety analyses were done on the intention-to-treat population, which comprised all the randomly assigned patients who received at least one dose of the study medication.

Because SVR12 in the control group was expected to be about 45%,[24,25] at 5% significance (two-sided), with 125 patients in the control group and 250 in the simeprevir group, the power needed to detect a significant difference of at least 20% between the two treatment groups was greater than 90%.

The primary analysis for comparison of SVR12 in the simeprevir and placebo groups was the Cochran-Mantel-Haenszel test adjusted for stratification factors. The 95% CIs were calculated for the response rate in each group. For the sensitivity analysis, a logistic regression model, which included baseline HCV RNA concentration and

the stratification factors HCV genotype 1 subtype and *IL28B* genotype, was used to compare SVR12 between the simeprevir and placebo groups. The 95% CI for the difference in response proportions was calculated with this model.

For all secondary response measures, 95% CIs were calculated for the response rates and for the difference in response rates between the simeprevir and placebo groups. The logistic regression model used for the primary efficacy analysis was applied for the analysis of secondary efficacy response measures. Descriptive statistics were calculated for the change in $\log_{10}$ HCV RNA from baseline. Further details of the statistical analyses are provided in the appendix p 2.

This trial is registered with ClinicalTrials.gov, number NCT01290679.

Role of the funding source

The study funder designed the trial, analysed and interpreted the data, and helped write and review the report. All authors had full access to all the study data and are responsible for the completeness of the data. The corresponding author had final responsibility for the decision to submit for publication.

Results

474 patients were screened and 393 were randomly assigned to treatment; 391 patients received at least one dose of study drug (257 in simeprevir group and 134 in placebo group; figure 1). Similar numbers of patients were randomly assigned to treatment with peginterferon alfa 2a (122 [31%] of 391) or peginterferon alfa 2b (123 [31%]). 146 (37%) of 391 patients were not randomly assigned to peginterferon alfa 2a or peginterferon alfa 2b and received peginterferon alfa 2a. 235 (91%) of 257 patients completed all study treatments in the simeprevir group. 237 (92%) of 257 patients in the simeprevir group and 81 (60%) of 134 in the placebo group completed peginterferon and ribavirin. Table 1 shows the patients' baseline characteristics. There were no major demographic differences between the various groups of patients. The patients were mostly white, had high viral load, and 4–14% had METAVIR[26] score of F4. Major protocol deviations were noted in 18 (7%) of 257 patients in the simeprevir group and seven (5%) of 134 patients in the placebo group.

Significantly more patients achieved SVR12 in the simeprevir group than in the placebo group (209 [81%] of 257 *vs* 67 [50%] of 134; table 2)—the adjusted difference weighted by HCV subtype, *IL28B* genotype, and peginterferon type as stratification factors was 32·2% [95% CI 23·3–41·2]; p<0·0001).

On-treatment response rates were higher in the simeprevir group than in the placebo group. Most patients in the simeprevir group (235 [91%] of 257) met criteria for response-guided therapy, and of these 202 (86%) achieved SVR12 (table 3). In patients who met criteria for response-guided therapy in the simeprevir group, SVR12 was higher in the subgroup with an HCV RNA concentration of less than 25 IU/mL undetectable at week 4 (178 [91%] of 195) than in the subgroup with an HCV RNA concentration less than 25 IU/mL detectable at week 4 (24 [60%] of 40; table 3). Importantly, similar proportions of patients with high and low METAVIR scores in the simeprevir group met the criteria for response-guided therapy (F3–F4 50 [94%] of 53, and F0–F2 177 [91%] of 195). All 17 (100%) patients with a METAVIR score of F4 met criteria for response-guided therapy in the simeprevir group; 11 (65%) of these achieved SVR12 (table 4). 202 (79%) of 255 patients in the simeprevir group compared with 17 (13%) of 133 in the placebo had an RVR (table 2). In the simeprevir group, a higher

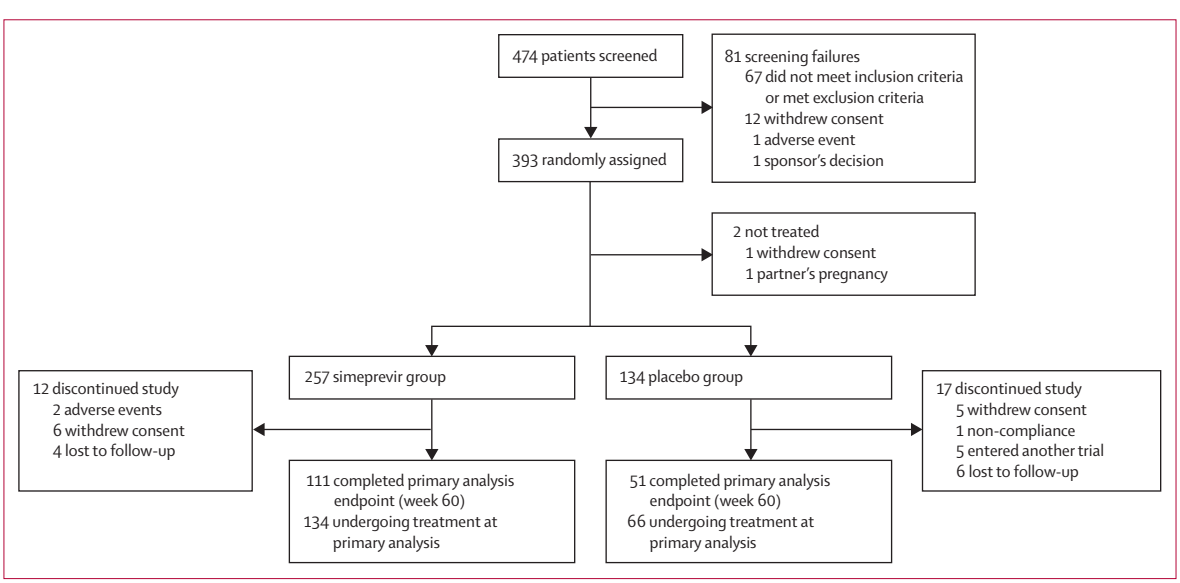

Figure 1: **Trial profile**

proportion of patients with METAVIR scores F0–F2 had an RVR than did those with scores F3–F4 (160 [83%] of 193 *vs* 36 [68%] of 53).

A significantly higher percentage of patients achieved SVR12 in the simeprevir group than in the placebo group, irrespective of the type of peginterferon they were given (table 4): 68 (88%) of 77 patients in the simeprevir group randomly assigned to peginterferon alfa 2a achieved SVR12 compared with 28 (62%) of 45 in the placebo group (difference 33·9% [95% CI 21·0–46·8]; p<0·0001; table 4). Of the patients randomly assigned to peginterferon alfa 2b, 62 (78%) of 80 patients in the simeprevir group versus 18 (42%) of 43 in the placebo group achieved SVR12 (46·1% [33·9–58·3]; p<0·0001; table 4). Of the patients who were not randomly assigned to a peginterferon and were given peginterferon alfa 2a, SVR12 was achieved in 79 (79%) of 100 patients in the simeprevir group and 21 (46%) of 46 in the placebo group (41·4% [28·6–54·2]; p<0·0001; table 4). The percentage of patients meeting criteria for response-guided therapy in the simeprevir group was similar in patients randomly assigned to peginterferon alfa 2a (75 [97%] of 77) or peginterferon alfa 2b (70 [88%] of 80]). RVR was also similar in patients in the simeprevir group randomly assigned to peginterferon alfa 2a (60 [78%] of 77 patients) or peginterferon alfa 2b (63 [80%] of 79 patients).

	All patients		Patients randomly assigned to peginterferon alfa 2a (European countries)			Patients randomly assigned to peginterferon alfa 2b (European countries)		
	Simeprevir group (n=257)	Placebo group (n=134)	Simeprevir group (n=77)	Placebo group (n=45)	Total (n=122)	Simeprevir group (n=80)	Placebo group (n=43)	Total (n=123)
Women	117 (46%)	57 (43%)	32 (42%)	16 (36%)	48 (39%)	37 (46%)	22 (51%)	59 (48%)
Age (years; median, IQR)	46 (18–73)	47 (18–73)	45 (18–67)	47 (19–65)	46 (18–67)	42 (18–73)	46 (21–67)	44 (19–73)
Ethnic origin								
White	237 (92%)	123 (92%)	75 (97%)	43 (96%)	118 (97%)	78 (98%)	41 (95%)	119 (97%)
Black or African-American	16 (6%)	10 (7%)	1 (1%)	1 (2%)	2 (2%)	1 (1%)	2 (5%)	3 (2%)
Asian	2 (<1%)	1 (<1%)	1 (1%)	1 (2%)	2 (2%)	1 (1%)	0	1 (<1%)
Other	2 (<1%)*	0	NA	NA	NA	NA	NA	NA
Body-mass index (kg/m^2; median, IQR)†	25·8 (17·5–53·5)	26·2 (18·1–51·6)	24·6 (17·5–31·9)	25·6 (18·1–32·9)	24·9 (17·5–32·9)	25·1 (19·1–42·1)	24·9 (19·0–32·4)	25·1 (19·0–42·1)
HCV subtype (NS5B)‡								
1a	105 (41%)	54 (41%)	28 (36%)	9 (20%)	37 (30%)	23 (29%)	18 (43%)	41 (33%)
1b	150 (58%)	77 (58%)	48 (62%)	34 (76%)	82 (67%)	56 (70%)	24 (57%)	80 (65%)
Other	2 (<1%)	2 (2%)	1 (1%)	2 (4%)	3 (2%)	1 (1%)	0	1 (<1%)
Baseline HCV RNA concentration >800 000 IU/mL	199 (77%)	98 (73%)	56 (73%)	31 (69%)	87 (71%)	63 (79%)	28 (65%)	91 (74%)
HCV with baseline Q80K								
Subtype 1a or other	24 (23%)	14 (26%)	5 (18%)	2 (22%)	7 (19%)	2 (8%)	4 (22%)	6 (14%)
Subtype 1b	1 (<1%)	0	0	0	0	1 (2%)	0	1 (1%)
METAVIR score§[26]								
F0–F1	130 (52%)	60 (45%)	39 (53%)	23 (51%)	62 (53%)	44 (59%)	16 (37%)	60 (51%)
F2	65 (26%)	42 (31%)	19 (26%)	14 (31%)	33 (28%)	19 (25%)	15 (35%)	34 (29%)
F3	36 (15%)	17 (13%)	12 (16%)	4 (9%)	16 (14%)	9 (12%)	6 (14%)	15 (13%)
F4	17 (7%)	15 (11%)	3 (4%)	4 (9%)	7 (6%)	3 (4%)	6 (14%)	9 (8%)
IL28B genotype								
CC	75 (29%)	42 (31%)	20 (26%)	14 (31%)	34 (28%)	22 (28%)	11 (26%)	33 (27%)
CT	142 (55%)	71 (53%)	48 (62%)	22 (49%)	70 (57%)	47 (59%)	28 (65%)	75 (61%)
TT	40 (16%)	21 (16%)	9 (12%)	9 (20%)	18 (15%)	11 (14%)	4 (9%)	15 (12%)
Fatigue Severity Score (mean, SE)¶	3·1 (0·1)	3·1 (0·1)	NA	NA	NA	NA	NA	NA
WPAI: Productivity Score (mean, SE)‖	15·1 (1·50)	14·0 (2·1)	NA	NA	NA	NA	NA	NA
WPAI: Daily Activity Impairment Score (mean, SE)**	14·7 (1·5)	13·7 (2·1)	NA	NA	NA	NA	NA	NA
WPAI: Absenteeism Score (mean, SE)††	4·0 (1·6)	4·3 (2·3)	NA	NA	NA	NA	NA	NA

Data are number (%), unless otherwise indicated. Q80K results are given only for patients for whom sequencing data were available. HCV=hepatitis C virus. Peginterferon=pegylated interferon. NA=not applicable or available. WPAI=Work Productivity Activity Impairment: hepatitis C. *One patient was an American Indian or Alaskan Native and the other patient was of mixed ethnic origin. †Data were missing for two patients in the placebo group. ‡Data were missing for one patient in the placebo group. §Data were missing for nine patients in the simeprevir group. ¶Data were missing for four patients (two in each of the simeprevir and placebo groups). ‖Data were missing for seven patients (five in the simeprevir group and two in the placebo group). **Data were missing for seven patients (two in the simeprevir group and five in the placebo group). ††Data were missing for 179 patients (112 in the simeprevir group and 67 in the placebo group).

Table 1: **Baseline characteristics of patients**

	Simeprevir group (n=257)	Placebo group (n=134)	Adjusted difference (95% CI)	p value
Week 4				
<25 IU/mL undetectable (RVR)	202/255 (79%)	17/133 (13%)	NA	NA
<25 IU/mL undetectable or detectable	244/255 (96%)	29/133 (22%)	NA	NA
SVR12*	209/257 (81%)	67/134 (50%)	32·2% (23·3–41·2)	<0·0001
On-treatment failure†	18/257 (7%)	43/134 (32%)	NA	NA
Met virological stopping rule at weeks 12, 24, or 36	11/257 (4%)	38/134 (28%)	NA	NA
Viral relapse‡	30/236 (13%)§	21/88 (24%)	NA	NA

Data are n/N (%), unless otherwise indicated. HCV=hepatitis C virus. RVR=rapid virological response. NA=not applicable or available. SVR12=sustained virological response at 12 weeks defined as HCV RNA less than 25 IU/mL undetectable at the end of treatment and less than 25 IU/mL detectable or undetectable 12 weeks after the planned end of treatment. SVR24=sustained virological response at 24 weeks defined as HCV RNA less than 25 IU/mL undetectable at the end of treatment and less than 25 IU/mL detectable or undetectable 24 weeks after the planned end of treatment. *The denominators for the SVR12 data are the number of patients in the intention-to-treat population per treatment group; the week 4 response data are for on-treatment virological response. †HCV RNA was confirmed to be detectable at end of treatment. ‡Patients with undetectable HCV RNA at end of treatment. §Of the 30 patients in the simeprevir group who had a relapse, five relapsed after SVR12: one patient completed treatment at week 24 and relapsed at the SVR12 assessment, two patients relapsed at SVR24 (after achieving SVR12), and two patients relapsed after SVR24 (after achieving SVR12 and SVR24), but one of these patients did not have confirmed viral relapse at the cutoff date for this analysis and confirmatory HCV RNA testing thereafter showed undetectable HCV RNA; all 21 patients in the placebo group relapsed before week 12 of the follow-up.

Table 2: **Virological response with time (RVR and SVR12), on-treatment failure, and relapse in the intention-to-treat population**

	Simeprevir group (n=257)	SVR12
Met criteria for response-guided therapy*	235 (91%)	202/235 (86%)
HCV RNA <25 IU/mL undetectable at week 4	195 (76%)	178/195 (91%)
HCV RNA <25 IU/mL detectable at week 4	40 (16%)	24/40 (60%)
Did not meet criteria for response-guided therapy	16 (6%)	5/16 (31%)

Data are number (%). SVR12=sustained virological response at 12 weeks defined as HCV RNA less than 25 IU/mL undetectable at the end of treatment and less than 25 IU/mL detectable or undetectable 12 weeks after the planned end of treatment. *Six patients could not be classified in accordance with the criteria for response-guided treatment and discontinued study treatment before measurement of HCV at week 4, or before week 12 if they had HCV RNA of less than 25 IU/mL detectable or undetectable at week 4.

Table 3: **Patients meeting criteria for response-guided therapy in the simeprevir group and corresponding SVR12 in the intention-to-treat population**

Consistently, significantly more patients in the simeprevir group than in the placebo group had SVR12, irrespective of *IL28B* genotype (CC, CT, or TT), HCV genotype (1a or 1b), or METAVIR score (F0–F2, F3–F4, F3, or F4; table 4). In the simeprevir group, 12 (71%) and 11 (65%) of 17 patients with cirrhosis achieved RVR and SVR12, respectively, compared with four (27%) and six (40%) of 15 patients, respectively, in the placebo group. Q80K is a naturally occurring NS3 polymorphism that confers low-level resistance to simeprevir (7·7 times change in median maximal effective concentration as a single aminoacid substitution in a genotype 1b replicon).[27] In patients with genotype 1a with and without Q80K polymorphism at baseline, 18 (75%) of 24 and 65 (82%) of 79, respectively, had SVR12 in the simeprevir group versus seven (50%) of 14 and 17 (43%) of 40 patients, respectively, in the placebo group (table 4). In the simeprevir group, 24 (23%) of 103 patients with genotype 1a for whom sequencing data were available had Q80K at baseline, 15 (63%) of 24 achieved RVR; 14 (93%) of 15 achieved SVR12. In nine (38%) of 24 patients with HCV genotype 1a with Q80K polymorphism who did not achieve RVR, four (44%) achieved SVR12. Moreover, with the exception of the Q80K subgroup, significantly more patients had SVR12 in the simeprevir group than in the placebo group in each of the demographic and baseline characteristic subgroups (figure 2). Similar proportions of patients had SVR12 in the simeprevir group with and without a dose reduction in ribavirin (53 [85%] of 62 and 156 [80%] of 195, respectively). 62 (24%) of 257 patients in the simeprevir group had dose reductions in ribavirin versus 41 (31%) of 134 in the placebo group.

18 (7%) of 257 patients in the simeprevir group had on-treatment failure versus 43 (32%) of 134 in the placebo group (table 2). The proportion of patients who met a virological stopping rule for discontinuation of all treatment at weeks 12, 24, or 36 was lower in the simeprevir group than in the placebo group (11 [4%] of 257 *vs* 38 [28%] of 134, respectively; table 2). Viral relapse was also lower in the simeprevir group than in the placebo group (30 [13%] of 236 *vs* 21 [24%] of 88, respectively; table 2).

Paired data for sequence analysis of the NS3 protease domain at baseline and treatment failure were available for 42 (81%) of 52 patients in simeprevir group with treatment failure. 41 (98%) of these patients had emerging mutations at NS3 positions 80, 122, 155, or 168 at the time of treatment failure (considering the six NS3 positions of interest 43, 80, 122, 155, 156, and 168; see appendix p 3 for details of the types of mutations noted).

Overall, the proportions of patients who had adverse events in the first 12 weeks of treatment were similar in the simeprevir and placebo groups, and the proportions were similar in the two groups for the entire treatment (table 5). The incidence and severity of adverse events in the simeprevir group for the entire treatment period were similar irrespective of the type of peginterferon used (table 6). Adverse events led to permanent discontinuation of simeprevir and placebo in two (<1%)

patients and one (<1%) patient, respectively, in the first 12 weeks of treatment and during the entire treatment (table 5). In the first 12 weeks, two (<1%) patients in the simeprevir group discontinued all study treatment versus none of the patients in the placebo group (table 5). Two deaths (due to colon cancer and an unknown cause, most likely pulmonary embolism or sudden cardiac arrest) occurred 1 month and 4 months after completion of treatment in the simeprevir group, but were not thought to be related to the study drug. No deaths occurred in the placebo group.

The most common adverse events (reported in >25% of patients) in the simeprevir group were headache, fatigue, pyrexia, and influenza-like illness (table 5), all of which are well known adverse events associated with peginterferon plus ribavirin.

48 (19%) of 257 patients in the simeprevir group and 20 (15%) of 134 in the placebo group had pruritus in the first 12 weeks of treatment (table 5). The pruritus was grade 1 or 2 and did not result in treatment discontinuation. 61 (24%) patients in the simeprevir group and 15 (11%) in the placebo group had rash (all types; table 5). With the exception of grade 3 rash in two (<1%) patients in the simeprevir group, rash was grade 1 or 2, and there were no incidences of serious rash events (table 5). Rash led to treatment discontinuation of at least one study drug in three (1%) patients in the simeprevir group and none in the placebo group (table 5). With the exception of one grade 2 photosensitivity reaction in the simeprevir group, the rest of the reactions reported during the first 12 weeks of simeprevir treatment were grade 1 (nine [4%] of 257 patients in the simeprevir group *vs* one [<1%] of 134 in the placebo group), and did not result in treatment discontinuation (table 5).

Mean haemoglobin values were similar in the two groups until week 24 (appendix p 7); thereafter, haemoglobin values in the simeprevir group returned towards baseline values. Similarly, no differences were noted in reductions in haemoglobin according to grade during treatment between the two groups (table 5).

Mild, transient increases in bilirubin were reported in 23 (9%) patients in the simeprevir group compared with three (2%) in the placebo group (table 5). With

	Simeprevir (n=257)	Placebo (n=134)	Difference (95% CI)*	p value
All patients	209/257 (81%)	67/134 (50%)	32·2 (23·3 to 41·2)	<0·0001
Type of interferon				
Randomly assigned to peginterferon alfa 2a + ribavirin	68/77 (88%)	28/45 (62%)	33·9 (21·0 to 46·8)	<0·0001
Randomly assigned to peginterferon alfa 2b + ribavirin	62/80 (78%)	18/43 (42%)	46·1 (33·9 to 58·3)	<0·0001
Not randomly assigned to peginterferon alfa 2a + ribavirin	79/100 (79%)	21/46 (46%)	41·4 (28·6 to 54·2)	<0·0001
IL28B genotype				
CC	72/75 (96%)	34/42 (81%)	10·5 (3·6 to 17·4)	0·0031
CT	114/142 (80%)	29/71 (41%)	45·5 (33·5 to 57·6)	<0·0001
TT	23/40 (58%)	4/21 (19%)	41·1 (29·3 to 52·9)	<0·0001
HCV subtype				
1a	86/107 (80%)	26/57 (46%)	45·3 (27·6 to 63·0)	<0·0001
With Q80K	18/24 (75%)†	7/14 (50%)	24·6 (−17·3 to 66·6)	0·2492
Without Q80K	65/79 (82%)	17/40 (43%)	58·2 (39·3 to 77·1)	<0·0001
1b	123/150 (82%)	41/77 (53%)	36·7 (21·9 to 51·6)	<0·0001
METAVIR score				
F0–F2	165/195 (85%)	52/102 (51%)	37·8 (26·0 to 49·6)	<0·0001
F3–F4	35/53 (66%)	15/32 (47%)	48·3 (36·4 to 60·3)	<0·0001
F3	24/36 (67%)	9/17 (53%)	47·5 (34·5 to 60·4)	<0·0001
F4	11/17 (65%)	6/15 (40%)	47·5 (35·2 to 59·9)	<0·0001
Sex				
Male	110/140 (79%)	36/77 (47%)	41·8 (29·7 to 53·8)	<0·0001
Female	99/117 (85%)	31/57 (54%)	40·0 (27·2 to 52·9)	<0·0001
Baseline HCV RNA concentration (IU/mL)				
≤800 000	54/58 (93%)	29/36 (81%)	17·8 (7·2 to 28·5)	0·0010
>800 000	155/199 (78%)	38/98 (39%)	48·3 (36·4 to 60·2)	<0·0001

Data are n/N (%), unless otherwise indicated. Peginterferon=pegylated interferon. HCV=hepatitis C virus. SVR12=sustained virological response at 12 weeks defined as HCV RNA less than 25 IU/mL undetectable at the end of treatment and less than 25 IU/mL detectable or undetectable 12 weeks after the planned end of treatment.*Differences in proportions and the respective 95% CIs are derived from a logistic regression model that includes factors for treatment group, baseline HCV RNA (log_{10} IU/mL), HCV subtype, *IL28B*, and type of peginterferon alfa. †Only one patient with genotype 1b HCV had Q80K at baseline in the simeprevir group (and none in the placebo group) and this patient achieved SVR12.

Table 4: **SVR12 in patients according to subgroups**

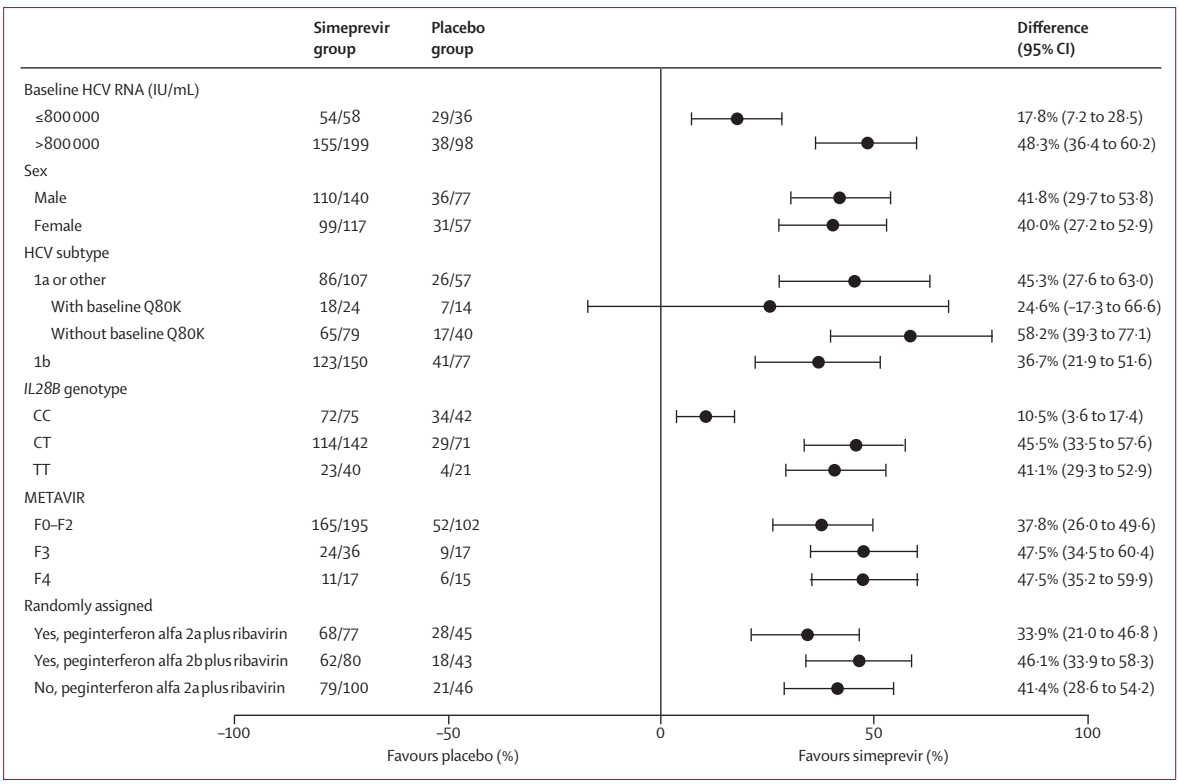

Figure 2: **Difference in SVR12 between treatment groups by demographic and baseline characteristics**
Data are n/N, unless otherwise indicated. SVR12=sustained virological response at 12 weeks, defined as HCV RNA of less than 25 IU/mL undetectable at the end of treatment and HCV RNA less than 25 IU/mL detectable or undetectable 12 weeks after the planned end of treatment. HCV=hepatitis C virus. Peginterferon=pegylated interferon.

simeprevir, laboratory bilirubin increases were rapidly reversible after the end of dosing and were mainly attributable to indirect bilirubin increases (appendix p 7).

Mean scores of patient-reported fatigue, impairment in productivity, and daily activity impairment increased similarly in both treatment groups from baseline to week 4 and remained increased in both groups until the end of week 24 (appendix p 8). Between weeks 24 and 36, mean scores in simeprevir-treated patients returned to values that were similar to baseline levels. Conversely, in the placebo group, reduction in mean scores did not return to baseline levels until week 60 (appendix p 8). Fatigue scores were significantly lower in the simeprevir group than in the placebo group (p=0·0085), in accord with shorter treatment duration in the simeprevir group (appendix p 3). Similar results were noted for impairment in daily activity and productivity (appendix p 3). Differences in absenteeism between the two groups were not significant (appendix p 8).

Mean scores on the CES-D were similar in the simeprevir and placebo groups, with no relevant differences noted until week 36 when mean scores in the simeprevir group decreased, remaining at baseline values throughout follow-up, while those in the placebo group remained increased until the end of week 48, returning to baseline values at week 60 (appendix p 9). The difference in the CES-D area under the curve at 60 weeks between treatment groups was not significant (p=0·079). Similar patterns were captured with the EQ-5D questionnaire (data not shown).

For the **MedDRA preferred terms** see http://www.meddra.org/

Discussion

Simeprevir, as a single pill, once daily, in combination with peginterferon alfa plus ribavirin (simeprevir group), was superior to placebo in combination with peginterferon alfa plus ribavirin (placebo group) in terms of SVR12 (the primary endpoint of the study; table 2). Irrespective of the type of peginterferon alfa used, SVR12 was significantly higher in the simeprevir group than in the placebo group (table 4).

Although the trial was not designed to assess differences between the different types of peginterferon alfa, patients randomly assigned to peginterferon alfa 2a had higher SVR12 than did those randomly assigned to peginterferon alfa 2b. Peginterferon alfa 2a has been reported to be superior to peginterferon alfa 2b in terms of SVR in patients with chronic HCV (panel);[30] however, it has also been shown to be similar with respect to SVR.[31] In QUEST-2, demographic and baseline disease characteristics of patients randomly assigned to peginterferon alfa 2a or peginterferon alfa 2b were balanced (table 1). Differences in SVR12 in patients randomly assigned to peginterferon alfa 2a (Europe)

	First 12 weeks		Entire treatment	
	Simeprevir group (n=257)	Placebo group (n=134)	Simeprevir group (n=257)	Placebo group (n=134)
Any adverse event	246 (96%)	130 (97%)	249 (97%)	132 (99%)
Most frequently reported*				
Headache	95 (37%)	45 (34%)	100 (39%)	49 (37%)
Fatigue	89 (35%)	52 (39%)	94 (37%)	56 (42%)
Pyrexia	78 (30%)	48 (36%)	79 (31%)	53 (40%)
Influenza-like illness	66 (26%)	34 (25%)	66 (26%)	35 (26%)
Grade 1 or 2 adverse events	180 (70%)	98 (73%)	165 (64%)	86 (64%)
Grade 3 adverse events	55 (21%)	29 (22%)	69 (27%)	41 (31%)
Grade 4 adverse events	11 (4%)	3 (2%)	15 (6%)	5 (4%)
Serious adverse event	6 (2%)	2 (1%)	16 (6%)	10 (7%)
Adverse events leading to permanent discontinuation of simeprevir or placebo only	2 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
Adverse events leading to permanent discontinuation of all study drugs	2 (<1%)	0	2 (<1%)	0
Adverse events of special interest				
Increased bilirubin†	23 (9%)	3 (2%)	24 (9%)	3 (2%)
Grade 1 or 2	19 (7%)	3 (2%)	20 (8%)	3 (2%)
Grade 3	4 (2%)	0	4 (2%)	0
Adverse events leading to permanent stop‡	0	0	0	0
Adverse events of clinical interest				
Pruritus§	48 (19%)	20 (15%)	66 (26%)	36 (27%)
Grade 1 or 2	48 (19%)	20 (15%)	66 (26%)	36 (27%)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Adverse events leading to permanent stop‡	0	0	0	0
Rash (any type)¶	61 (24%)	15 (11%)	69 (27%)	27 (20%)
Grade 1 or 2	59 (23%)	15 (11%)	67 (26%)	27 (20%)
Grade 3	2 (<1%)	0	2 (<1%)	0
Grade 4	0	0	0	0
Adverse events leading to permanent stop‡	3 (1%)	0	3 (1%)	1 (<1%)
Photosensitivity reactions	10 (4%)	1 (<1%)	10 (4%)	1 (<1%)
Grade 1 or 2	10 (4%)	1 (<1%)	10 (4%)	1 (<1%)
Grade 3	0	0	0	0
Adverse events leading to permanent stop‡	0	0	0	0
Neutropenia	42 (16%)	24 (18%)	54 (21%)	36 (27%)
Grade 1 or 2	12 (5%)	10 (7%)	13 (5%)	13 (10%)
Grade 3	20 (8%)	12 (9%)	29 (11%)	19 (14%)
Grade 4	10 (4%)	2 (1%)	12 (5%)	4 (3%)
Adverse events leading to permanent stop‡	1 (<1%)	1 (<1%)	1 (<1%)	2 (1%)
Decreased haemoglobin concentration (any grade)	58 (23%)	34 (25%)	89 (35%)	53 (40%)
Grade 1 or 2	57 (22%)	32 (24%)	88 (34%)	50 (37%)
Grade 3	1 (<1%)	2 (1%)	1 (<1%)	3 (2%)
Grade 4	0	0	0	0
Anaemia	35 (14%)	21 (16%)	53 (21%)	37 (28%)
Grade 1 or 2	32 (12%)	20 (15%)	49 (19%)	36 (27%)
Grade 3	3 (1%)	1 (<1%)	3 (1%)	1 (<1%)
Grade 4	0	0	1 (<1%)	0
Adverse events leading to permanent stop‡	0	0	0	0

Data are number (%), unless otherwise indicated. The first 12 weeks are the period during which patients were given simeprevir plus peginterferon alfa plus ribavirin; a comparison of the frequency of adverse events between these patients and those given just peginterferon alfa plus ribavirin (with placebo) during that time provides a clear indication of any additional toxicity that simeprevir might have. The investigators graded the adverse events, and information about the severity grading of adverse events are provided in the appendix p 5. Peginterferon=pegylated interferon. MedDRA=Medical Dictionary for Regulatory Activities. *Adverse events reported in more than 25% of patients in the simeprevir group during the first 12 weeks and during the entire treatment. †Increased bilirubin included MedDRA preferred terms. ‡Permanent cessation of at least one study drug. §Pruritus included MedDRA high-level term: pruritus not elsewhere classified. ¶Rash included MedDRA high-level terms: erythemas; papulosquamous disorders; rashes, eruptions, and exanthemas not elsewhere classified; photosensitivity reactions; standardised MedDRA query severe cutaneous adverse reaction: narrow scope and selected terms of the broad scope.

Table 5: **Summary of adverse events during the first 12 weeks of treatment and during the entire treatment**

	Peginterferon alfa 2a		Peginterferon alfa 2b		Overall	
	Simeprevir group (n=77)	Placebo group (n=45)	Simeprevir group (n=80)	Placebo group (n=43)	Simeprevir group (n=257)	Placebo group (n=134)
Any adverse event	75 (97%)	44 (98%)	78 (98%)	43 (100%)	249 (97%)	132 (99%)
Grade 3 or 4 adverse events	28 (36%)	18 (40%)	23 (29%)	9 (21%)	84 (33%)	46 (34%)
Serious adverse events	7 (9%)	3 (7%)	4 (5%)	4 (9%)	16 (6%)	10 (7%)
Adverse events leading to permanent discontinuation of simeprevir or placebo only	0	0	1 (1%)	0	2 (<1%)	1 (<%)
Adverse events leading to permanent discontinuation of all study drugs	0	0	0	0	2 (<1%)	0

Data are number (%), unless otherwise indicated. Peginterferon=pegylated interferon.

Table 6: **Summary of adverse events during the entire treatment by type of peginterferon alfa**

versus those who were not randomly assigned but were treated with peginterferon alfa 2a (North and South America) could be explained by regional differences.

Most of the patients in the simeprevir group met the criteria for response-guided therapy, and a large percentage of these achieved SVR12 (table 3). Shortened duration of treatment is beneficial both in terms of reducing the time patients have adverse events due to peginterferon alfa plus ribavirin, and by potentially contributing to overall cost reductions in treatment. On-treatment virological response was high in the simeprevir group as assessed with RVR and HCV RNA concentrations less than 25 IU/mL detectable or undetectable at week 4 (table 2). In patients who met the criteria for response-guided therapy, higher SVR12 was noted in those with HCV RNA concentrations less than 25 IU/mL undetectable at week 4 versus those with less than 25 IU/mL detectable (table 3). Similar results were noted for the METAVIR score subgroups F0–F2 versus F3–F4; higher RVR in patients with F0–F2 correlated with higher SVR12.

The presence of cirrhosis or advanced fibrosis,[6,32] HCV genotype 1a,[33] and *IL28B* non-CC genotype[34] are associated with a poor response to peginterferon plus ribavirin. Investigation of the difference between triple therapy with simeprevir and peginterferon plus ribavirin in these subgroups was therefore of particular interest. In the QUEST-2 study, SVR12 was significantly higher in the simeprevir group than in the placebo group irrespective of *IL28B* genotype, suggesting that the addition of simeprevir to peginterferon plus ribavirin regimens might help overcome the association between *IL28B* genotype and response to peginterferon plus ribavirin,[35] or to current triple therapy regimens.[36] As expected, in both treatment groups, *IL28B* CC genotype was associated with higher responses than the CT and TT genotypes (table 4).

In QUEST-2, high SVR12 was achieved in the simeprevir group in patients with HCV genotype 1a or 1b and in those with genotype 1a irrespective of the presence of Q80K polymorphism at baseline (table 4). In additional analyses, the difference between SVR12 in patients with HCV genotype 1a with the Q80K polymorphism at baseline in the simeprevir group and SVR12 in patients with HCV genotype 1a overall (ie, with and without Q80K) in the placebo group was significant (p=0·005). However, pooled data from QUEST-2 and QUEST-1, another phase 3 study, showed no difference in SVR12 in patients with HCV genotype 1a with Q80K in the simeprevir and placebo groups (49 [58%] of 84 *vs* 23 [52%] of 44). Based on this finding, the US Food and Drug Administration recommends that all patients with HCV genotype 1a are screened for the presence of the Q80K polymorphism before beginning triple therapy with simeprevir plus peginterferon plus ribavirin and to consider an alternative treatment if this polymorphic variant is detected.[37]

A significantly higher percentage of patients with cirrhosis achieved SVR12 in the simeprevir group than in the placebo group (table 4). However, SVR12 in the simeprevir group was lower in patients with cirrhosis than in those without cirrhosis and this might partly be due to the lower response to peginterferon plus ribavirin in the patients with HCV infection with cirrhosis or advanced fibrosis.[6,32]

In terms of subgroups, there are few data for black or African–American patients in QUEST-2, but results in these patients were in accordance with those reported for the overall population (data not shown). Neither the pharmacokinetic profile of simeprevir nor its adverse-event profile showed any differences in response to the drug in the white and black or African–American populations (data not shown). However, in view of the small number of these patients who participated in the trial, results should be verified in larger groups of patients. Similarly, the number of patients of Asian or other ethnic origin was small. Additionally, most patients did not have cirrhosis, with only 7% with a METAVIR score of F4 in the simeprevir group (table 1). Another limitation was that recruitment was mostly in Europe (252 [64%] of 391 patients) and America (79 [20%] and 60 [15%] of 391 patients in North and South Americas, respectively) and thus other geographic regions were not represented accurately.

On-treatment failure and relapse rates were lower in the simeprevir group than in the placebo group. Most patients in the simeprevir group with treatment failure had emerging mutations in the HCV NS3 protease domain, which, similar to what has been reported previously for simeprevir,[27] were mainly D168V in patients with HCV genotype 1b or R155K alone or in combination with aminoacid substitutions at positions 80 or 168 in those with genotype 1a.

Treatment with simeprevir in QUEST-2 was generally safe and well tolerated, with an overall adverse-event profile similar to that of peginterferon plus ribavirin, irrespective of whether patients were randomly assigned to peginterferon alfa 2a or peginterferon alfa 2b. Importantly, no difference was noted in the reduction in haemoglobin concentration during the treatment between the simeprevir and placebo groups; hence, the incidence of anaemia, unlike with other protease inhibitor regimens, was similar in the two groups.[10,18,38] Although the incidences of rash (any type) and photosensitivity were increased in the simeprevir group, no grade 4 or serious adverse events were reported and discontinuation of at least one study drug was reported in 1% of patients due to rash, and in none of the patients due to photosensitivity reactions (table 5). These results show the favourable safety profile of simeprevir in terms of anaemia and rash compared with boceprevir and telaprevir. Bilirubin increases were noted at a higher frequency in the simeprevir group; however, the increases were mild and transient (levels returned to baseline values after completion of simeprevir treatment), with most bilirubin-associated adverse events being grade 1 or 2, not associated with increases in other liver parameters, particularly in aspartate aminotransferase and alanine aminotransferase concentrations, no cases of Hy's Law[39,40] (increase of at least three times the upper limit of normal in aspartate aminotransferase or alanine aminotransferase concentrations and more than two times the upper limit of normal in bilirubin concentration), a predictor of drug-induced severe hepatocellular injury, and no cases leading to treatment discontinuation. In-vitro data suggest that simeprevir-associated bilirubin increases are mainly driven by increases in unconjugated bilirubin because simeprevir is an inhibitor of OATP1B1 and MRP2.[41] In a study of simeprevir plus sofosbuvir in an all-oral combination therapy without ribavirin, hyperbilirubinaemia did not occur.[29] Hyperbilirubinaemia in QUEST-2 was possibly caused by ribavirin-induced haemolytic anaemia and inhibition of the OATP1B1 transporter. Hyperbilirubinaemia might not occur when simeprevir is used in the absence of ribavirin or other haemolysis-inducing drugs.

In QUEST-2, mean scores for fatigue at baseline were greater than the population normal reference value (2·3) by amounts that are clinically relevant.[42] In both treatment groups, mean fatigue scores increased similarly, showing clinically important worsening during the masked phase of treatment that persisted as long as patients were receiving peginterferon plus ribavirin (appendix p 3). The addition of simeprevir did not increase fatigue beyond what was noted with just peginterferon alfa plus ribavirin and reduced the duration of treatment-related fatigue and limitations in productivity, and daily activities for most of the patients. The QUEST-2 findings are consistent with those of the ViraHep-C study[43] and help emphasise the value to patients of shorter treatment both in terms of reduced time with fatigue and reduced impairment in routine functioning. Mean scores for patient-reported depression and overall quality of life, as measured with the CES-D and EQ-5D questionnaires, worsened by similar amounts in the two groups at treatment initiation, and remained at levels that indicated clinically important worsening for most patients who were receiving treatment (until the end of week 24 in the simeprevir group, and until the end of week 48 in the placebo group); this pattern was consistent with fatigue, productivity, and activity impairment results. A limitation of the data for patient-reported outcomes is that both clinician and patient knew when the treatment was discontinued. Changes in scores for patient-reported outcomes might therefore indicate relief that treatment has ended, even when stopping treatment signals treatment failure. Additionally, reporting symptoms and functioning from both the clinician's and patient's

***Panel:* Research in context**

Systematic review

We searched PubMed up to May 1, 2014, for reports of clinical trials of treatments for hepatitis C virus (HCV) genotype 1 infection with the terms "HCV" or "hepatitis C".[3,28] We identified several relevant studies.[10–14,18–25,29] Regimens containing pegylated interferons (peginterferons) alfa 2a and 2b plus ribavirin are used to treat patients with HCV infection. Recently, direct-acting antiviral agents have been added to these regimens to improve the sustained virological response (SVR) in patients with genotype 1 infection. However, the improved dosing schedules are not easy to adhere to due to the high pill burden, duration of treatment can be long, and adverse events are frequent.

Interpretation

In the QUEST-2 trial, the combination of simeprevir, peginterferon alfa 2a or 2b, plus ribavirin (simeprevir group) resulted in significantly higher SVR at 12 weeks than did the combination of placebo, peginterferon alfa 2a or 2b, plus ribavirin (placebo group; 81% *vs* 50%). Taken together, these results demonstrate that simeprevir has high efficacy and good safety, while offering patients a straightforward, easier-to-adhere-to regimen. Because of the high rapid virological response (RVR) rates and the high SVR in patients with RVR in the simeprevir group in QUEST-1 and QUEST-2 phase 3 trials, response-guided treatment is no longer used, and our recommendation is that all patients are treated with simeprevir for no longer than 24 weeks.

perspectives might place focus on subjective outcomes that are not the primary objective of HCV treatment. However, a patient's perception of how he or she is feeling or functioning is an important outcome of clinical care and correlates with other outcomes as shown by the association in patient-reported outcomes.

When QUEST-2 was initiated, peginterferon plus ribavirin was the standard of care and therefore was used as the comparator in the study. QUEST-1 is a similar phase 3 study with patients recruited in the same period in different centres and receiving only one pegylated interferon (alfa 2a).[44] While QUEST-2 was in progress, the direct-acting antiviral agents telaprevir and boceprevir were approved for the treatment of HCV infection. To address the HCV community's interest in a head-to-head comparison with the current standard of care (ie, protease inhibitor plus peginterferon plus ribavirin), a phase 3 non-inferiority trial was initiated to assess the efficacy, safety, and tolerability of simeprevir versus telaprevir in combination with peginterferon plus ribavirin in patients with HCV infection who are null or partial responders to previous peginterferon plus ribavirin and is in progress (ATTAIN; TMC435HPC3001; ClinicalTrials.gov number NCT01485991). Results from this trial will be available this year.

In conclusion, a regimen of simeprevir, administered orally, once daily as a single pill, in combination with either peginterferon alfa 2a or peginterferon alfa 2b plus ribavirin could be used to improve SVR in treatment-naive patients with HCV genotype 1 infection, without worsening the known adverse-event profile for peginterferon alfa plus ribavirin, allowing the shortening of treatment in most patients.

Contributors

MM was the principal investigator of the trial, was involved in the study setup, and was responsible for the clinical supervision of the patients and performance of the study. PM, FP, ESAdA, MB, YH, EJ, and FV were investigators in the study, responsible for the treatment of patients, and involved in the acquisition, analysis, and interpretation of the data, and critical revision of the manuscript. JS contributed to the analysis, interpretation, and description of patient-reported fatigue data, including drafting and editing supplemental information about the study method. MP participated in the study design and data analysis. OL provided scientific input in the clinical study, did the virology analysis, and contributed to the writing of the manuscript. SO-M, GDLR, and RK provided scientific input in the clinical study and contributed to the writing of the manuscript. RS was responsible for the conduct and overview of the trial, analysis of the data, and review of the clinical study report. MB-M provided scientific input in the clinical study and contributed to the writing of the manuscript.

Declaration of interests

MM has received financial compensation for consultancy or lecture activities from AbbVie, Roche, Bristol-Myers Squibb, Gilead, Boehringer Ingelheim, Idenix, Vertex, Achillion, Novartis, Merck or Merck Sharp and Dohme, Janssen, and GlaxoSmithKline, and research grants from AbbVie, Roche, Gilead, Novartis, Boehringer Ingelheim, Bristol-Myers Squibb, Merck or Merck Sharp and Dohme, and Janssen. PM has received grant support and has acted as an investigator, speaker, and expert for Roche, Gilead, Bristol-Myers Squibb, Novartis, Janssen, and Merck Sharp and Dohme; as an investigator and expert for Vertex and AbbVie; as an investigator for Boehringer Ingelheim and Pfizer; and has received grant support and acted as an investigator for Alios BioPharma. FP has received research grants from AbbVie, Anadys, Achillion, Bristol-Myers Squibb, Boehringer Ingelheim, Genentech, Idenix, Gilead, Merck, Pharmassett, Vertex, Salix, Tibotec or Janssen, and Novartis; and has acted as an adviser or speaker for AbbVie, Achillion, Bristol-Myers Squibb, Inhibitex, Boeheringer Ingelheim, Pfizer, Genentech, Idenix, Gilead, Merck, Vertex, Salix, Janssen, and Novartis. ESAdA declares no conflicting interests with respect to this manuscript. MB has been on advisory boards for Merck Sharp and Dohme, Janssen, Novartis, and Bristol-Myers Squibb. YH has received grants from Janssen, Merck, and Roche and has been a clinical investigator or consultant for Vertex, Janssen, Bristol-Myers Squibb, Merck, Roche, Gilead, AbbVie, and Boehringer Ingelheim. EJ has acted as a consultant and speaker for Janssen-Cilag. FV has received research grants from Janssen; education grants from Bristol-Myers Squibb; and travel grants from Novartis, Gador, Janssen, Pfizer, and Roche. JS is an employee of Janssen-Cilag and a Johnson & Johnson stockholder. MP and OL are employees and stockholders of Janssen Infectious Diseases. SO-M is an employee of Janssen Research & Development. GDLR and RK are employees of Janssen Global Services. RS and MB-M are employees of Janssen Infectious Diseases.

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