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

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Summary

Background Although the addition of the HCV NS3/4A protease inhibitors boceprevir and telaprevir to pegylated interferon (peginterferon) alfa plus ribavirin has improved sustained virological response (SVR) in treatment-naive and treatment-experienced patients infected with hepatitis C virus (HCV) genotype 1, the regimens have a high pill burden and are associated with increased rates and severity of adverse events, such as anaemia and rash. The efficacy and safety of the combination of simeprevir, a one pill, once-daily, oral HCV NS3/4A protease inhibitor, plus peginterferon alfa 2a plus ribavirin were assessed in treatment-naive patients with HCV genotype 1 infection.

Methods In QUEST-1, a phase 3, randomised, double-blind multicentre trial undertaken in 13 countries (Australia, Europe, North America, Puerto Rico, and New Zealand), 394 patients (aged ≥18 years) with chronic HCV genotype 1 infection and no history of HCV treatment, stratified by HCV subtype and host *IL28B* genotype, were randomly assigned in a 2:1 ratio with a computer-generated allocation sequence to receive simeprevir (150 mg once daily, orally) plus peginterferon alfa 2a plus ribavirin for 12 weeks, followed by peginterferon alfa 2a plus ribavirin (simeprevir group), or placebo orally plus peginterferon alfa 2a plus ribavirin for 12 weeks, followed by peginterferon alfa 2a plus ribavirin (placebo group). Treatment duration was 24 weeks or 48 weeks in the simeprevir group according to criteria for response-guided therapy (ie, HCV RNA <25 IU/mL [undetectable or detectable] at week 4 and <25 IU/mL undetectable at week 12) and 48 weeks in the placebo group. Patients, study personnel, and the sponsor were masked to the treatment group assignment. The primary efficacy endpoint was sustained virological response 12 weeks after the planned end of treatment (SVR12) and was assessed with an intention-to-treat analysis. The results of the primary analysis (week 60) are presented for safety and SVR12. This trial is registered with ClinicalTrials.gov, number NCT01289782.

Findings Treatment with simeprevir, peginterferon alfa 2a, and ribavirin was superior to placebo, peginterferon alfa 2a, and ribavirin (SVR12 in 210 [80%] patients of 264 *vs* 65 [50%] of 130, respectively, adjusted difference 29·3% [95% CI 20·1–38·6; p<0·0001). Adverse events in the first 12 weeks of treatment led to discontinuation of simeprevir in two (<1%) patients and discontinuation of placebo in one patient (<1%); fatigue (106 [40%] *vs* 49 [38%] patients, respectively) and headache (81 [31%] *vs* 48 [37%], respectively) were the most common adverse events. The prevalences of anaemia (42 [16%] *vs* 14 [11%], respectively) and rash (72 [27%] *vs* 33 [25%]) were similar in the simeprevir and placebo groups. Addition of simeprevir did not increase severity of patient-reported fatigue and functioning limitations, but shortened their duration.

Interpretation Simeprevir once daily with peginterferon alfa 2a and ribavirin shortens therapy in treatment-naive patients with HCV genotype 1 infection without worsening the adverse event profiles associated with peginterferon alfa 2a plus ribavirin.

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Introduction

Infection with hepatitis C virus (HCV) is one of the leading causes of liver failure worldwide, and resulted in 195 000 deaths in 2010.[1] Every year, 3–4 million individuals become infected with the virus; about 150 million chronically infected patients are at risk of developing liver cirrhosis or liver cancer.[2,3]

For many years, the standard of care for HCV infection was a combination of pegylated interferon (peginterferon) alfa plus ribavirin. However, 50–60% of patients infected with HCV genotype 1 did not have a sustained virological response (SVR) with peginterferon alfa and ribavirin.[4]

The addition of the HCV NS3/4A protease inhibitors boceprevir and telaprevir to peginterferon alfa plus ribavirin combination regimens has improved SVR in treatment-naive and treatment-experienced patients infected with HCV genotype 1, allowing some individuals to have a reduction in the duration of treatment.[5–9]

However, treatment with these agents is limited by increased rates and severity of adverse events, such as anaemia and rash, and challenging dosing schedules with a high pill burden.[10–13]

Simeprevir (TMC435; Janssen and Medivir) is a one pill, once daily, oral HCV NS3/4A protease inhibitor that has been approved in Japan, Canada, the USA, Russia, and Europe for the treatment of patients with chronic HCV infection. Similar to other HCV NS3/4A protease inhibitors, simeprevir acts by inhibiting the protease-mediated cleavage of several of the non-structural proteins of HCV from the polypeptide encoded by the viral genome.[14] Simeprevir has broad genotypic coverage, with antiviral activity against HCV genotypes 1, 2, and 4–6.[15,16] In phase 2a and 2b trials, simeprevir, at a dose of 150 mg for 12 weeks, had potent efficacy and a favourable safety profile in both treatment-naive and treatment-experienced patients with HCV genotype 1 infection.[16–19]

We investigated the efficacy, safety, and tolerability of simeprevir in combination with peginterferon alfa plus ribavirin in treatment-naive patients with HCV genotype 1 infection in the phase 3 QUEST-1 trial. Our aim in this trial was to confirm the safety profile and superior efficacy of simeprevir in combination with peginterferon alfa 2a plus ribavirin compared with just peginterferon alfa 2a plus ribavirin, which was the standard treatment for infection with HCV genotype 1 at the time of initiation of QUEST-1. We present the data from the primary analysis (at week 60) of the final results of the primary endpoint.

See Online for appendix

Methods

Patients and study design

QUEST-1 was a multicentre, randomised, double-blind, parallel-group, placebo-controlled, phase 3 clinical trial to assess the efficacy, safety, and tolerability of simeprevir in combination with peginterferon alfa plus ribavirin (simeprevir group) versus placebo in combination with peginterferon alfa plus ribavirin (placebo group) in treatment-naive patients with HCV genotype 1 infection. In the trial, we also included patient self-assessments of symptoms commonly associated with existing HCV treatments, and routine functioning and health-related quality of life. Overall treatment duration in the simeprevir group was either 24 weeks or 48 weeks according to the response-guided therapy criteria (including 12 weeks of dosing with simeprevir), whereas patients in the control group received placebo plus peginterferon alfa plus ribavirin for 48 weeks. The trial was done between Jan 18, 2011, and Jan 29, 2013, at 71 sites in 13 countries (Australia, Canada, Germany, Italy, Mexico, New Zealand, Puerto Rico, Romania, Russia, Spain, Ukraine, the UK, and the USA).

Eligible patients were aged 18 years and older with confirmed chronic HCV genotype 1 infection, screening plasma HCV RNA concentration greater than 10 000 IU/mL, and no history of treatment for HCV infection. Patients with cirrhosis were eligible if an ultrasound within the previous 6 months showed no signs of hepatocellular carcinoma.

Exclusion criteria included hepatic decompensation or any non-HCV-related liver disease; co-infection with HIV, hepatitis B virus, or non-genotype 1 HCV infection; significant laboratory abnormalities; any other active disease; and male or female patients who had, or were planning to conceive.

Institutional review boards of all participating institutions approved the study. Written informed consent was obtained from all participants according to local regulations.

Patients received simeprevir (150 mg once daily, orally) or placebo orally in combination with peginterferon alfa 2a (180 µg/week, subcutaneously) plus ribavirin (1000 mg/day or 1200 mg/day, orally, depending on bodyweight [<75 kg or ≥75 kg, respectively]). Patients in the simeprevir group received simeprevir plus peginterferon alfa 2a plus ribavirin for 12 weeks, followed by peginterferon alfa 2a plus ribavirin without simeprevir for 12 weeks or 36 weeks. According to criteria for response-guided therapy, treatment was stopped at week 24 if HCV RNA was less than 25 IU/mL (undetectable or detectable) at week 4 and less than 25 IU/mL undetectable at week 12 or continued with peginterferon alfa 2a plus ribavirin until week 48. Patients in the placebo group received placebo plus peginterferon alfa 2a plus ribavirin for the first 12 weeks, followed by peginterferon alfa 2a plus ribavirin for 36 weeks. All patients in the placebo group continued this combination until week 48. Patients in both groups were followed up for up to 72 weeks after the start of treatment (appendix p 3).

In accordance with the virological stopping rules, simeprevir or placebo was discontinued if HCV RNA concentration was greater than 1000 IU/mL at week 4, whereas the peginterferon alfa 2a plus ribavirin combination was continued. Peginterferon alfa 2a plus ribavirin was discontinued if a reduction of smaller than 2 $\log_{10}$ IU/mL in HCV RNA from baseline was detected at week 12, or if HCV RNA was confirmed to be at least 25 IU/mL at week 24 or week 36.

Randomisation and masking

After stratification according to HCV genotype 1 subtype (1a, 1b, or other) and *IL28B* genotype (SNP rs12979860; CC, CT, or TT) to optimise the balance between treatment groups, patients were randomly assigned to the simeprevir or placebo group in a 2:1 ratio. We used a computer-generated randomisation schedule 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. This interactive web-based or voice-response system assigned a unique code that dictated the treatment assignment and matching study drug kit for each patient. The patients, study personnel, and the sponsor were masked to the treatment group assignment.

The randomisation codes were maintained within the interactive web-based or voice-response system. HCV RNA levels were monitored by an external person who was not masked and was responsible for informing the investigators of any required changes to treatment.

Procedures

Blood samples were obtained at screening, days 1, 7, 14, and 28, every 4 weeks thereafter until week 28, and 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.

HCV RNA was then measured using the HCV/High Pure System assay (version 2.0, Roche COBAS TaqMan, Pleasanton, CA, USA; lower limit of quantification 25 IU/mL and limit of detection 15 IU/mL). In patients who discontinued study medication early, HCV RNA measurements were obtained at the time of withdrawal, during the 4 weeks after withdrawal, and every 12 weeks until week 72.

Standard population sequencing to assess for resistant variants of the HCV NS3/4A protease domain of HCV was done on baseline samples and those from patients in whom treatment failed at selected timepoints (based on HCV RNA changes and sensitivity limit of the sequencing assay). *IL28B* genotyping was done on blood samples obtained at screening.

Adverse events were monitored throughout the trial. Blood samples for biochemical and haematological analyses were obtained at screening and during scheduled visits. Electrocardiogram, vital sign assessment, and physical examination were also done at scheduled visits.

We gathered data for fatigue and productivity (including activity impairment and absenteeism) using the Fatigue Severity Score (FSS)[20] and the Work Productivity and Activity Impairment questionnaire for hepatitis C (WPAI)[21] at baseline and throughout the study. The Centre for Epidemiologic Studies Depression Scale (CES-D)[22] questionnaire was used to assess the effect of treatment on depression, with data gathered at baseline and all the way through the study. Perceived health status and quality of life at baseline and during treatment were assessed through the EuroQol 5-dimension questionnaire (EQ-5D).[23] The five health dimensions measured with the EQ-5D were mobility, self-care, usual activities, pain or discomfort, and anxiety or depression.

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. The secondary endpoints were comparison of SVR 24 weeks after the planned end of treatment (SVR24); percentage of patients meeting criteria for response-guided therapy to complete treatment at week 24; rapid virological response (RVR), defined as HCV RNA less than 25 IU/mL undetectable at week 4; on-treatment failure, defined as confirmed detectable HCV at end of treatment; incidence of viral breakthrough, defined as HCV RNA increase of more than 1 $\log_{10}$ IU/mL from the lowest level noted or an HCV RNA concentration more than 100 IU/mL when previously less than 25 IU/mL, or viral relapse (presence of HCV RNA ≥25 IU/mL during follow-up or at the time of SVR assessments after achieving undetectable levels at the end of the treatment); incidence of adverse events and laboratory abnormalities; and patient-reported symptoms and functioning. We also assessed polymorphisms at baseline and their correlation with simeprevir efficacy. We also report data for the effect of baseline characteristics on treatment response and data from assessment of depression severity, and health status. Data were also gathered for the following endpoints, but are not reported because they were not available at the time of this analysis or the endpoints were not within the scope of this report: SVR at week 72, pharmacokinetics of simeprevir or the relation between simeprevir pharmacokinetics and efficacy or safety, gathering of data for medical resource use, and the effect of CYP3A4, CYP2C19, and drug transporter genotypes on pharmacokinetics, treatment response, and selected safety endpoints.

A total of three amendments were made to the trial protocol, on Nov 10, 2010, May 26, 2011, and Dec 14, 2011. In the first amendment, the primary efficacy

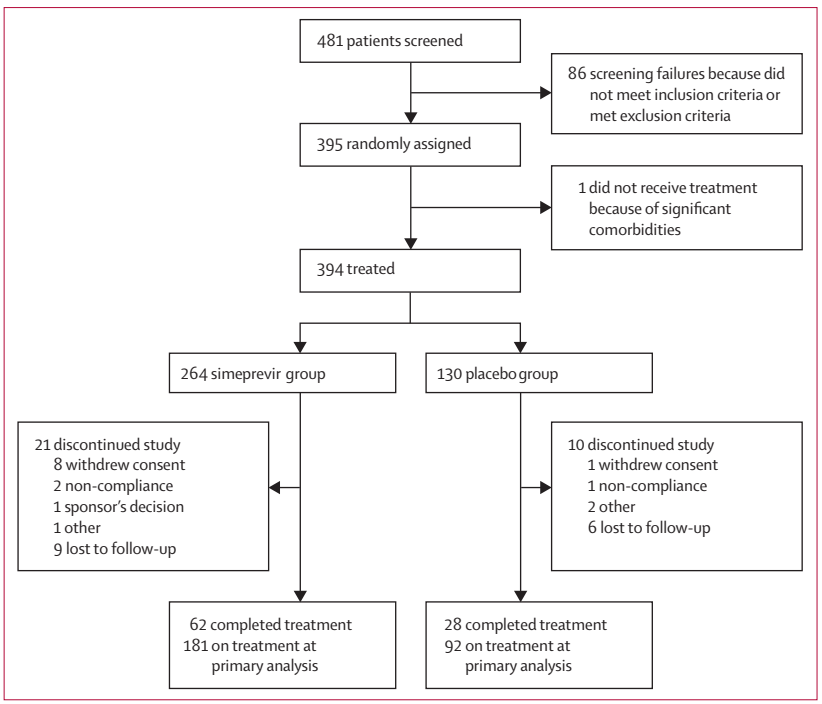

Figure 1: **Trial profile**
Patients in the simeprevir group received simeprevir, pegylated interferon alfa 2a, and ribavirin; patients in the placebo group received placebo, pegylated interferon alfa 2a, and ribavirin.

endpoint was changed from the percentage of patients with SVR at week 60 to the percentage of patients with SVR24. In the second amendment, the sponsor clarified the guidelines for the unmasking of patients to ensure that those in whom treatment failed had alternative treatment options or were rolled over into the TMC435-TiDP16-C213 (ClinicalTrials.gov identifier NCT01323244) study without delay if needed. This protocol amendment also allowed for the use of methadone. In the third amendment, because of the strong correlation shown descriptively between SVR12 and SVR24 in simeprevir phase 2b studies (PILLAR[19] and ASPIRE[17]), and in phase 3 trials of telaprevir[7] and boceprevir,[8] and in agreement with health authorities, the primary endpoint was changed from SVR24 to SVR12 and SVR24 was changed to a secondary endpoint. No change in sample size was judged to be necessary to achieve statistical power for the trial because of the strong correlation between SVR12 and SVR24.

	Simeprevir group (n=264)	Placebo group (n=130)
Women	116 (44%)	56 (43%)
Age (years; median, IQR)	48 (39–54)	48 (36–54)
Ethnic origin		
White	227 (86%)	122 (94%)
Black or African-American	27 (10%)	4 (3%)
Asian	5 (2%)	3 (2%)
BMI (kg/m^2; median, range)	26·6 (16·5–45·2)	26·7 (17·0–53·5)
HCV subtype (NS5B)		
1a	147 (56%)	74 (57%)
1b	117 (44%)	56 (43%)
Baseline HCV RNA concentration >800 000 IU/mL	218 (83%)	96 (74%)
HCV with baseline Q80K*	61 (23%)	30 (23%)
HCV subtype 1a*	60 (41%)	30 (41%)
HCV subtype 1b*	1 (<1%)	0
METAVIR score[26]		
F0–F1	118 (45%)	50 (38%)
F2	65 (25%)	40 (31%)
F3	46 (17%)	23 (18%)
F4	31 (12%)	17 (13%)
IL28B genotype		
CC	77 (29%)	37 (28%)
CT	150 (57%)	76 (58%)
TT	37 (14%)	17 (13%)
FSS	n=263	n=130
Mean (SE)	3·5 (0·10)	3·3 (0·13)
WPAI Productivity score	n=259	n=128
Mean (SE)	18·7 (1·59)	19·2 (2·09)
WPAI Daily Activity Impairment score	n=259	n=128
Mean (SE)	18·6 (1·60)	18·5 (2·08)
WPAI Absenteeism	n=128	n=71
Mean (SE)	3·6 (1·29)	6·1 (2·18)

Data are number (%), unless otherwise indicated. Patients in the simeprevir group received simeprevir, pegylated interferon alfa 2a, and ribavirin; patients in the placebo group received placebo, pegylated interferon alfa 2a, and ribavirin. BMI=body-mass index. HCV=hepatitis C virus. FSS=Fatigue Severity Score. WPAI=Work Productivity and Activity Impairment: hepatitis C questionnaire. *Patients for whom sequencing data were available: 262 of 264 patients in the simeprevir group overall, 129 of 130 in the placebo group overall, 146 of 147 in the simeprevir group HCV subtype 1a, 73 of 74 in the placebo group HCV subtype 1a, 116 of 117 in the simeprevir group HCV subtype 1b, and all 56 in the placebo group HCV subtype 1b.

Table 1: **Baseline characteristics of patients**

Statistical analysis

SGS Life Sciences Services (Mechelen, Belgium) did the statistical analyses using SAS (version 9.1). According to the null hypothesis, there was no significant difference between the active treatment (simeprevir plus peginterferon alfa 2a plus ribavirin) and the control treatment (placebo plus peginterferon alfa 2a plus ribavirin) for the primary efficacy endpoint (SVR12). We used the 5% significance level for the comparison of treatment groups for the primary efficacy endpoint. Because SVR12 in the control group was estimated to be 45%,[24,25] at 5% significance (two-sided p value), with 125 patients in the control group and 250 in the simeprevir group, the power to detect a significant difference of at least 20% between the two treatment groups was expected to be greater than 90%.

Patients' baseline demographics and disease characteristics were summarised descriptively. For the primary endpoint, we compared SVR rates in the simeprevir and placebo groups using the Cochran-Mantel-Haenszel test adjusted for the stratification factors. Additionally, a 95% CI was calculated for the response rate in each treatment group. As a sensitivity analysis, the SVR12 in the simeprevir group was compared with that in the placebo group with a logistic regression model including baseline HCV RNA ($\log_{10}$ IU/mL, included as a continuous variable) and the stratification factors HCV genotype 1 subtype and *IL28B* genotype. The 95% CI for the difference in the percentages of patients in the two groups who had SVR12 was calculated according to this model. For secondary efficacy response measures, 95% CIs were calculated for response rates and for the difference in response rates between groups.

All analyses were done on the intention-to-treat population, defined as patients who received at least one dose of investigational drug (simeprevir or placebo). According to the statistical analysis plan, if the percentage of patients with a major protocol deviation was less than or equal to 10% there was no need for a per-protocol analysis of the primary endpoint based on data from all patients in the intention-to-treat population with exclusion of patients with a major protocol deviation. Further details about the statistical analyses are provided in the appendix.

This trial is registered with ClinicalTrials.gov, number NCT01289782.

Role of the funding source

The funder of the study designed the trial, analysed, and interpreted the data, and helped write and review the

report. All authors had full access to all the data in the study and are responsible for the completeness of the data. All the authors had final responsibility for the decision to submit for publication.

Results

395 (82%) of 481 patients who were screened were randomly assigned to treatment. 394 patients who were randomly assigned to treatment received at least one dose of study drug (264 in the simeprevir group and 130 in the placebo group; figure 1). Major protocol deviations were reported in nine (3%) of 264 patients in the simeprevir group and five (4%) of 130 in the placebo group.

Similar numbers of patients were enrolled from Europe and North America (Canada, Mexico, Puerto Rico, and the USA), and baseline characteristics were generally similar between the treatment groups (table 1), except for a higher proportion of black or African-American patients in the simeprevir group versus placebo group (10% *vs* 3%, respectively).

SVR12 was achieved in a higher percentage of patients in the simeprevir group than in the placebo group (80% *vs* 50%), and the difference stratified by HCV genotype 1 subtype and *IL28B* genotype was significant (29·3%, 95% CI 20·1–38·6; p<0·0001; table 2). RVR was higher in the simeprevir group than in the placebo group (80% *vs* 12%; table 2). In the simeprevir group, 181 (90%) of 202 patients with RVR achieved SVR12.

A higher proportion of patients in the simeprevir group had SVR24 than in the placebo group (205 [83%] of 247 *vs* 18 [60%] of 30; weighted difference 18·1%, 95% CI –0·4 to 36·6; p=0·0253). At the time of the primary analysis, SVR24 data were available for 247 patients in the simeprevir group and 30 in the placebo group. These findings are in line with SVR12 data.

Most of the patients in the simeprevir group (85%) met criteria for response-guided therapy to complete treatment at week 24 (table 3). Of these patients, 91% subsequently achieved SVR12 (table 3). 21% of the patients who did not meet the criteria for response-guided treatment achieved SVR12 (table 3). 73% of the patients who met the criteria had undetectable HCV RNA at week 4 and 92% of these patients achieved SVR12 (table 3). Of the 28 patients meeting the criteria for response-guided treatment but with HCV RNA less than 25 IU/mL detectable at week 4, 79% subsequently achieved SVR12 (table 3). 12 (5%) of 264 patients discontinued treatment before the assessment for response-guided therapy. Two patients did not have a week 4 HCV RNA result. However, based on other measurements, these patients were judged to meet criteria for response-guided therapy, and therefore were included in the met criteria for response-guided therapy, but were excluded from the week 4 subanalysis.

Figure 2 shows the subpopulation analyses. Baseline HCV RNA, HCV genotype (1a or 1b), METAVIR[26] score (F0–F2, F3, or F4), and *IL28B* genotype (CC, CT, or TT) had an effect on SVR12; however, the rates were consistently higher in the simeprevir group than in the placebo group and most differences were significant (table 4). Sex did not have an effect on SVR12 in the simeprevir group (figure 2). Q80K is a naturally occurring NS3 polymorphism that confers low-level resistance to simeprevir (7·7 times change in 50% maximal effective concentration as a single aminoacid substitution in a genotype 1b replicon).[26] The presence of the Q80K polymorphism at baseline in patients infected with HCV genotype 1a given simeprevir was associated with a lower SVR12 than in patients without this polymorphism at baseline (table 4). 38 (63%) of 60 simeprevir-treated patients infected with HCV genotype 1a with the Q80K polymorphism at baseline achieved RVR and 28 (74%) of these 38 patients achieved SVR12. 64 (74%) of 86 patients infected with HCV genotype 1a without the Q80K polymorphism at baseline achieved RVR with simeprevir, and 59 (92%) of these 64 achieved SVR12. 99 (85%) of 117 patients with HCV genotype 1b in the simeprevir group

	Simeprevir group (n=264)	Placebo group (n=130)	Difference (95% CI)
Week 4			
<25 IU/mL undetectable (RVR)	202/254 (80%)	15/127 (12%)	68·0 (60·5 to 75·4)
<25 IU/mL undetectable or detectable	230/254 (91%)	25/127 (20%)	70·3 (62·4 to 78·1)
SVR12	210/264 (80%)	65/130 (50%)	29·3 (20·1 to 38·6)
On-treatment failure*	24 (9%)	44 (34%)	–24·9 (–33·7 to –16·0)
Met virological stopping rule at week 12, 24, or 36	14 (5%)	36 (28%)	–23·2 (–31·7 to –14·8)
Viral relapse†	21/234 (9%)‡	18/84 (21%)	–12·5 (–22·1 to –3·0)

Data are n/N (%) or number (%), unless otherwise indicated. Patients in the simeprevir group received simeprevir, pegylated interferon alfa 2a, and ribavirin; patients in the placebo group received placebo, pegylated interferon alfa 2a, and ribavirin. RVR=rapid virological response. SVR12=sustained virological response at 12 weeks defined as an undetectable HCV RNA concentration (<25 IU/mL undetectable) at the end of treatment and HCV RNA less than 25 IU/ml detectable or undetectable at 12 weeks after the planned end of treatment. HCV=hepatitis C virus. 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 the on-treatment virological response. *HCV RNA was confirmed to be detectable at end of treatment. †Patients with undetectable HCV RNA at the end of treatment. ‡Viral relapse occurred within 12 weeks of the end of treatment in 20 patients in the simeprevir group and in 16 patients in the placebo group. Relapse occurred after week 12 of follow-up but before the SVR12 assessment in one simeprevir-treated patient, who prematurely discontinued treatment with all study drugs because of non-compliance.

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

	Simeprevir group (n=264)	SVR12
Met criteria for response-guided treatment*	224/264 (85%)	203/224 (91%)
HCV RNA <25 IU/mL (undetectable) at week 4	194/264 (73%)	179/194 (92%)
HCV RNA <25 IU/mL (detectable) at week 4	28/264 (11%)	22/28 (79%)
Did not meet criteria for response-guided treatment	28/264 (11%)	6/28 (21%)

Data are n/N (%). Patients in the simeprevir group received simeprevir, pegylated interferon alfa 2a, and ribavirin. *12 patients could not be classified in accordance with the criteria for response-guided treatment and discontinued study treatment before the assessment of their eligibility—ie, they discontinued before the HCV measurement at week 4, or they discontinued before measurement at week 12 if they had HCV RNA concentration less than 25 IU/mL detectable or undetectable at week 4.

Table 3: **Proportion of patients meeting criteria for response-guided treatment in the simeprevir, peginterferon alfa 2a and ribavirin group and corresponding SVR12 in the intention-to-treat population**

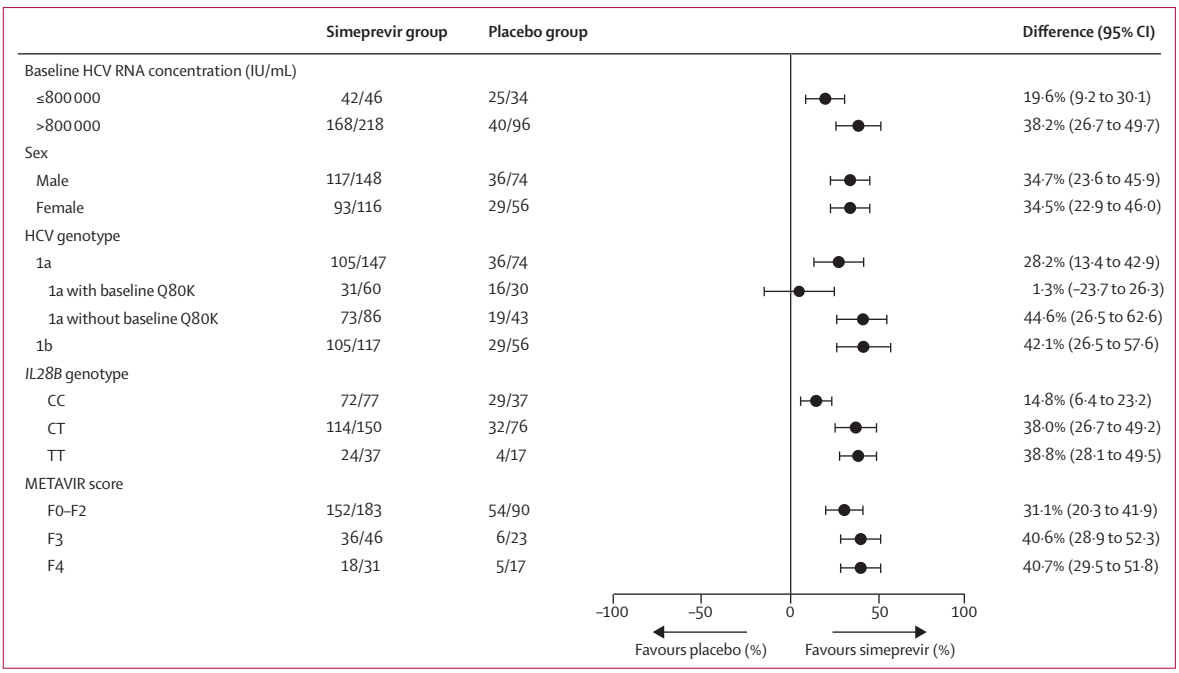

Figure 2: **Difference in SVR12 between treatment groups by demographic and baseline characteristics of patients**
Data are n/N, unless otherwise indicated. Patients in the simeprevir group received simeprevir, pegylated interferon alfa 2a, and ribavirin; patients in the placebo group received placebo, pegylated interferon alfa 2a, and ribavirin. SVR12=sustained virological response at 12 weeks defined as HCV RNA undetectable (<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.

	Simeprevir group (n=264)	Placebo group (n=130)	Difference (95% CI)	p value
HCV subtype				
1a	105/147 (71%)	36/74 (49%)	28·2 (13·4 to 42·9)	0·0002
With baseline Q80K	31/60 (52%)	16/30 (53%)	1·3 (–23·7 to 26·3)	0·9199
Without baseline Q80K	73/86 (85%)	19/43 (44%)	44·6 (26·5 to 62·6)	<0·0001
1b	105/117 (90%)	29/56 (52%)	42·1 (26·5 to 57·6)	<0·0001
METAVIR score				
F0–F2	152/183 (83%)	54/90 (60%)	31·1 (20·3 to 41·9)	<0·0001
F3–F4	54/77 (70%)	11/40 (28%)	40·9 (29·5 to 52·2)	<0·0001
F3	36/46 (78%)	6/23 (26%)	40·6 (28·9 to 52·3)	<0·0001
F4	18/31 (58%)	5/17 (29%)	40·7 (29·5 to 51·8)	<0·0001
***IL28B* genotype**				
CC	72/77 (94%)	29/37 (78%)	14·8 (6·4 to 23·2)	0·0006
CT	114/150 (76%)	32/76 (42%)	38·0 (26·7 to 49·2)	<0·0001
TT	24/37 (65%)	4/17 (24%)	38·8 (28·1 to 49·5)	<0·0001
Baseline HCV RNA concentration (IU/mL)				
≤800 000	42/46 (91%)	25/34 (74%)	19·6 (9·2 to 30·1)	0·0003
>800 000	168/218 (77%)	40/96 (42%)	38·2 (26·7 to 49·7)	<0·0001
Sex				
Male	117/148 (79%)	36/74 (49%)	34·7 (23·6 to 45·9)	<0·0001
Female	93/116 (80%)	29/56 (52%)	34·5 (22·9 to 46·0)	<0·0001

Data are n/N (%), unless otherwise indicated. Patients in the simeprevir group received simeprevir, pegylated interferon alfa 2a, and ribavirin; patients in the placebo group received placebo, pegylated interferon alfa 2a, and ribavirin. 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 HCV RNA less than 25 IU/mL detectable or undetectable 12 weeks after the planned end of treatment.

Table 4: **SVR12 according to HCV genotype, METAVIR score, *IL28B* genotype, baseline HCV RNA, and sex**

had RVR and 93 (94%) of these 99 patients achieved SVR12. 59 (22%) of 264 patients in the simeprevir group had dose reductions in ribavirin compared with 30 (23%) of 130 in the placebo group. SVR12 values were similar in the simeprevir group irrespective of whether or not the patients had a dose reduction in ribavirin (50 [85%] of 59 and 160 [78%] of 205, respectively). 17 (63%) of 27 black or African-American patients in the simeprevir group achieved SVR12 compared with one (25%) of four in the placebo group. 16 (59%) of 27 black or African-American patients treated with simeprevir had RVR and 15 (94%) of these individuals achieved SVR12.

On-treatment failure (ie, detectable HCV RNA at end of treatment) was noted in 9% of patients in the simeprevir group and 34% in the placebo group (table 2). A lower percentage of patients in the simeprevir group met the virological stopping rule requiring discontinuation of all treatment at week 12, 24, or 36, than in the placebo group (5% *vs* 28%, respectively; table 2). Similarly, a lower percentage of patients in the simeprevir group met the virological stopping rule at week 4 (ie, cessation of simeprevir or placebo and continuation of peginterferon alfa 2a plus ribavirin) than in the placebo group (12 [5%] of 264 *vs* 83 [64%] of 130, respectively). Viral relapse was less common in the simeprevir group than in the placebo group (9% *vs* 21%, respectively; table 2), and occurred within 12 weeks of the end of treatment in 20 (95%) of 21 patients with relapse in the simeprevir group and 16 (89%) of 18 in the placebo group.

Data for paired baseline sequencing and treatment failure in patients treated with simeprevir who did not achieve SVR12 showed emergent mutations at the time of failure in 35 (92%) of 38 patients for whom sequencing data were available. For patients infected with genotype 1a, these emergent mutations were mainly R155K alone or with other aminoacid substitutions at positions 80 or 168 (the six NS3 positions of interest are 43, 80, 122, 155, 156, and 168). For patients infected with genotype 1b, the mutations were mainly D168V.

Overall frequencies of adverse events were similar in the two groups during the first 12 weeks of treatment and for the entire treatment (table 5). In the first 12 weeks of treatment, grade 3 adverse events were reported in 20% versus 26% of patients, grade 4 adverse events in 3% versus 3% of patients, and serious adverse events in 3% versus 4% of patients in the simeprevir and placebo groups, respectively. The adverse events resulted in less than 1% of patients permanently discontinuing simeprevir or placebo in the first 12 weeks and during the entire treatment period. In the first 12 weeks, 3% of patients in the simeprevir group discontinued all study drugs compared with 2% in the placebo group. No deaths occurred during the trial. Fatigue and headache were the most common adverse events in the simeprevir and placebo groups, occurring in more than 25% of patients (table 5).

Adverse events of clinical interest in the first 12 weeks of treatment were pruritus in 24% and 13% of patients in the simeprevir and placebo groups, respectively; most cases of pruritus were grade 1 or 2 and occurred early in treatment, with rare discontinuations of study drugs (table 5). Rash (any type) during the first 12 weeks occurred with a similar frequency in both groups (simeprevir 27% and placebo

	First 12 weeks		Entire treatment	
	Simeprevir group (n=264)	Placebo group (n=130)	Simeprevir group (n=264)	Placebo group (n=130)
Any adverse event	250 (95%)	123 (95%)	255 (97%)	125 (96%)
Most frequently reported adverse events*				
Fatigue	106 (40%)	49 (38%)	110 (42%)	53 (41%)
Headache	81 (31%)	48 (37%)	88 (33%)	51 (39%)
Grade 1 or 2 adverse events	189 (72%)	85 (65%)	181 (69%)	75 (58%)
Grade 3 adverse events	54 (20%)	34 (26%)	65 (25%)	43 (33%)
Grade 4 adverse events	7 (3%)	4 (3%)	9 (3%)	7 (5%)
Serious adverse events	7 (3%)	5 (4%)	10 (4%)	8 (6%)
Adverse events leading to permanent discontinuation of simeprevir or placebo	2 (<1%)†	1 (<1%)	2 (<1%)	1 (<1%)
Adverse events leading to permanent discontinuation of all study drugs	7 (3%)‡	3 (2%)	7 (3%)	3 (2%)
Adverse events of special interest				
Increased bilirubin§	24 (9%)	5 (4%)	24 (9%)	6 (5%)
Grade 1 or 2	17 (6%)	3 (2%)	17 (6%)	3 (2%)
Grade 3	6 (2%)	2 (2%)	6 (2%)	2 (2%)
Grade 4	1 (<1%)	0	1 (<1%)	0
Leading to permanent stop¶	1 (<1%)‖	0	1 (<1%)‖	0
Adverse events of clinical interest				
Rash (any type)**	72 (27%)	33 (25%)	89 (34%)	42 (32%)
Grade 1 or 2	70 (27%)	33 (25%)	87 (33%)	42 (32%)
Grade 3	2 (<1%)	0	2 (<1%)	0
Grade 4	0	0	0	0
Leading to permanent stop¶	4 (2%)	1 (<1%)	4 (2%)	1 (<1%)
Pruritus††	63 (24%)	17 (13%)	79 (30%)	26 (20%)
Grade 1 or 2	62 (23%)	17 (13%)	77 (29%)	26 (20%)
Grade 3	1 (<1%)	0	2 (<1%)	0
Grade 4	0	0	0	0
Leading to permanent stop¶	1 (<1%)	0	2 (<1%)	0
Photosensitivity reactions	7 (3%)	1 (<1%)	7 (3%)	1 (<1%)
Grade 1 or 2	7 (3%)	1 (<1%)	7 (3%)	1 (<1%)
Grade 3 or 4	0	0	0	0
Leading to permanent stop¶	0	0	0	0

(Table 5 continues on next page)

	First 12 weeks		Entire treatment	
	Simeprevir group (n=264)	Placebo group (n=130)	Simeprevir group (n=264)	Placebo group (n=130)
(Continued from previous page)				
Neutropenia	49 (19%)	14 (11%)	64 (24%)	23 (18%)
Grade 1 or 2	21 (8%)	5 (4%)	26 (10%)	7 (5%)
Grade 3	23 (9%)	9 (7%)	32 (12%)	15 (12%)
Grade 4	5 (2%)	0	6 (2%)	1 (<1%)
Leading to permanent stop¶	0	0	0	1 (<1%)
Haemoglobin decrease (any grade)	67 (25%)	34 (26%)	98 (37%)	58 (45%)
Grade 1	48 (18%)	26 (20%)	68 (26%)	37 (28%)
Grade 2	16 (6%)	5 (4%)	26 (10%)	17 (13%)
Grade 3	3 (1%)	3 (2%)	4 (2%)	4 (3%)
Grade 4	0	0	0	0
Anaemia (any grade)	42 (16%)	14 (11%)	53 (20%)	27 (21%)
Grade 1 or 2	40 (15%)	10 (8%)	51 (19%)	22 (17%)
Grade 3	2 (<1%)	3 (2%)	2 (<1%)	4 (3%)
Grade 4	0	1 (<1%)	0	1 (<1%)
Leading to permanent stop¶	0	2 (2%)	1 (<1%)	2 (2%)

Data are number (%), unless otherwise indicated. Patients in the simeprevir group received simeprevir, peginterferon alfa 2a, and ribavirin; patients in the placebo group received placebo, peginterferon alfa 2a, and ribavirin. A comparison of the frequency of adverse events in the first 12 weeks in patients who received treatment with simeprevir, peginterferon alfa 2a, and ribavirin with patients who received peginterferon alfa 2a plus ribavirin (with or without placebo) shows any toxicities related to simeprevir. The investigators graded the adverse events, and information about the severity grading of adverse events is provided in the appendix p 2. Peginterferon=pegylated interferon. MedDRA=Medical Dictionary for Regulatory Activities. *In more than 25% of patients during the first 12 weeks of treatment and during the entire treatment period in the simeprevir group. †Adverse events in these two patients were rash and increased bilirubin concentration in the blood. ‡Adverse events in these seven patients were major depression, overdose, psoriasis, positive pregnancy test, rash, rash and skin burning sensation, or rash and pruritus. §Increased bilirubin concentration included MedDRA preferred terms . ¶Permanent cessation of at least one study drug. ||Grade 2 jaundice. **Rash MedDRA high-level terms: erythemas; papulosquamous disorders; rashes, eruptions, and exanthemas not elsewhere classified; photosensitivity conditions; standardised MedDRA query severe cutaneous adverse reaction: narrow scope and selected terms of the broad scope. ††Pruritus included MedDRA high-level term pruritus not classified elsewhere.

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

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

25%) and was mostly grade 1 or 2, with the exception of grade 3 rash in less than 1% of patients treated with simeprevir (table 5). Treatment (with at least one study drug) was discontinued due to rash in 2% and less than 1% of patients who received simeprevir and placebo, respectively (table 5).

Mean concentrations of haemoglobin were similar in the two treatment groups until week 24; thereafter, haemoglobin concentrations in the simeprevir group returned to baseline levels (appendix p 4). Most reductions in haemoglobin concentrations were of grade 1 or 2 (table 5).

19% of patients in the simeprevir group had neutropenia during the first 12 weeks of treatment compared with 11% in the placebo group, but the incidences of grade 3 and 4 neutropenia were similar in both groups (9% and 2% with simeprevir, respectively, and 7% and zero with placebo, respectively; table 5). No occurrences of neutropenia were serious (table 5).

Mild, transient increases in bilirubin were noted in the simeprevir group in the first 12 weeks of treatment, with 2% of patients having a grade 3 bilirubin increase and less than 1% a grade 4 increase (table 5). Bilirubin increases were rapidly reversible after the end of simeprevir dosing (appendix p 4) and mainly attributable to increases in indirect (unconjugated) bilirubin. Increased bilirubin concentration was an adverse event in 9% of patients in the simeprevir group in the first 12 weeks of treatment compared with 4% of those in the placebo group (table 5). Only one patient discontinued treatment due to increased bilirubin concentration in the simeprevir group (table 5). This patient did not have any increase in transaminases, and simeprevir was stopped according to a protocol-defined toxicity management guideline. Increases in alanine aminotransferase and aspartate aminotransferase were infrequent and similar between the treatment groups, and were not associated with increased bilirubin (data not shown).

Patient-reported fatigue severity, impairment in productivity, and daily activity impairment scores increased (worsened) by similar amounts in both treatment groups from baseline to week 4 and remained increased in both groups until the end of week 24 (appendix p 5). Scores returned to values that were similar to baseline between weeks 24 and 36 in the simeprevir group and weeks 48 and 60 in the placebo group (appendix p 5). According to a piecewise linear mixed model, scores for fatigue (p=0·0008), productivity impairment (p=0·0296), and daily activity impairment (p=0·0097) were significantly lower in patients who received simeprevir than in those who received placebo, in agreement with the shorter treatment duration in the

simeprevir group (appendix p 5). Differences in terms of absenteeism between the two treatment groups were not significant (appendix p 5).

Mean CES-D scores for depression severity were similar at baseline in both groups (appendix p 6). During the first 24 weeks of treatment, mean CES-D scores were increased compared with baseline in both groups (indicating increased symptoms of depression), but were slightly lower in patients in the placebo group than in the simeprevir group (appendix p 6). Between weeks 36 and 48, mean CES-D scores in the patients in the simeprevir group fell and remained at baseline values throughout follow-up, whereas those in the placebo group remained increased until the end of week 48, returning to baseline values at week 60 (appendix p 6). Similar trends were captured with the EQ-5D questionnaire (data not shown).

Discussion

In this trial, a significantly higher percentage of treatment-naive patients with chronic hepatitis C virus genotype 1 infection who were receiving simeprevir in combination with peginterferon alfa 2a and ribavirin (simeprevir group) achieved SVR12 (primary efficacy endpoint) than did those receiving placebo in combination with peginterferon alfa 2a and ribavirin (placebo group), and had lower on-treatment failure and relapse rates. 85% of patients in the simeprevir group met criteria for response-guided therapy and were eligible to complete treatment at week 24, and 91% of these subsequently achieved SVR12 (table 2).

Reduction of the overall treatment duration is beneficial for several reasons, including a shorter mean exposure to peginterferon alfa and ribavirin, thus leading to a reduced frequency of adverse events related to peginterferon alfa and ribavirin, reduction in costs, and improvements in quality-adjusted life-years.[28,29] An additional advantage is that once-daily, oral dosing of simeprevir is a simplified, easy-to-adhere-to regimen for patients (panel).

In QUEST-1, patients in the simeprevir group had a significantly higher on-treatment virological response than did those in the placebo group, with 80% achieving RVR (HCV RNA <25 IU/mL undetectable at week 4; table 2), and 91% achieving SVR with 24 weeks of treatment. Of the patients who met the criteria for response-guided treatment, we noted higher SVR12 in patients with HCV RNA of less than 25 IU/mL undetectable at week 4 than in those with HCV RNA less than 25 IU/mL detectable (table 3).

In patients treated with peginterferon alfa plus ribavirin, HCV genotype 1a,[30] *IL28B* non-CC genotype,[31] and cirrhosis or advanced fibrosis[32,33] are associated with lower SVR rates. These classic baseline predictors of response also have an effect on SVR rates in patients treated with simeprevir in combination with peginterferon alfa 2a plus ribavirin. However, in QUEST-1, SVR12 in the simeprevir group was significantly higher than in the placebo group, irrespective of *IL28B* genotype (CC, CT, or TT), HCV genotype (1a or 1b), or METAVIR score (F0–F4). In terms of the *IL28B* genotype, the highest SVR12 was noted in patients in the simeprevir group with the CC genotype (94%; table 4), although the difference in SVR12 between patients with this genotype and those without this genotype was substantially smaller than in the placebo group, indicating that there is a weaker correlation between *IL28B* genotype and efficacy of simeprevir than the association with just peginterferon alfa plus ribavirin.[34] Simeprevir also resulted in higher SVR12 in patients with cirrhosis (F4) than did placebo. SVR12 frequencies in the simeprevir group were similar in patients with HCV genotype 1a without the Q80K polymorphism at baseline and with genotype 1b. However, in patients with HCV genotype 1a who had the Q80K polymorphism at baseline (a factor that does not affect the response to peginterferon alfa 2a plus ribavirin), SVR12 was not significantly higher with simeprevir than with placebo (table 4). Most patients treated with simeprevir who did not achieve SVR12 had emergent mutations at the time of failure; these mutations were similar to those previously reported with simeprevir.[27]

Generally, the safety and tolerability profile of simeprevir was similar to that established for peginterferon alfa plus ribavirin regimens. The reported adverse events in the simeprevir group were clinically manageable, and most were grade 1 or 2. A lower percentage of patients in the simeprevir group discontinued treatment than did those in the placebo group, and this difference might be attributable to the shorter treatment duration in the simeprevir group. Treatment with simeprevir did not lead to an increased incidence of rash or anaemia, as noted with other protease inhibitors.[5,7,8,10,11,13,35,36] Unlike with telaprevir and boceprevir, mean reductions in haemoglobin concentrations were similar between the simeprevir and placebo groups during the study and they were matched by similar patterns and degree of anaemia (a study of the comparison of simeprevir with telaprevir is in progress). Of note, rash (seen with telaprevir) seldom led to discontinuation of treatment. Simeprevir was associated with increases in bilirubin concentrations; however, these increases were mild and transient and were not associated with concomitant increases in other laboratory markers of liver function. Simeprevir-associated bilirubin increases are mainly driven by increases in unconjugated bilirubin because it is an inhibitor of organic anion transporting polypeptide 1B1 and multidrug resistance protein 2 in vitro.[37]

Severity of patient-reported fatigue, productivity impairment, and impairment in daily activities were significantly reduced overall in the simeprevir group compared with the placebo group. Mean scores for patient-reported depressive symptom severity (CES-D) and overall quality of life (EQ-5D) worsened to similar degrees in each group after patients started treatment, and remained at those levels for the duration of treatment with peginterferon alfa 2a plus

Panel: **Research in context**

Systematic review

The direct-acting antiviral agents that have been approved for the treatment of hepatitis C virus (HCV) infection have substantially improved sustained virological response (SVR) in infected patients; however, the associated dosing schedules are challenging and there is an increased incidence of treatment-related toxicity (eg, rash and anaemia). Therefore, an unmet clinical need exists for simplified, well tolerated regimens for patients infected with genotype 1 HCV.

Simeprevir 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 patients chronically infected with HCV. In the PILLAR[19] and ASPIRE[17] phase 2 trials, simeprevir at 150 mg once daily, administered to treatment-naive and treatment-experienced patients, respectively, was more effective than were the lower doses tested (75 mg in PILLAR and 100 mg in ASPIRE), whereas extending simeprevir treatment beyond 12 weeks did not show a consistent benefit. Based on these results, the 150 mg for 12 weeks was selected for further investigation.

Interpretation

In the phase 3 QUEST-1 trial of the efficacy, safety, and tolerability of simeprevir in combination with pegylated interferon (peginterferon) alfa-2a plus ribavirin (simeprevir group) in treatment-naive patients infected with genotype 1 HCV, SVR values at 12 weeks were significantly higher (irrespective of *IL28B* genotype, HCV genotype subtype, and METAVIR score), and lower for on-treatment failure and relapse, in the simeprevir group than in the placebo group. Most patients in the simeprevir group achieved high early response rates and qualified for shortened treatment duration. The safety and tolerability profiles were favourable, with clinically manageable adverse events and significantly reduced severity of patient-reported fatigue and functioning impairments. Taken together, these results suggest that simeprevir represents an excellent candidate for inclusion in triple-therapy regimens in patients with HCV infection.

ribavirin (up to week 24 in the simeprevir group, and up to week 48 in the placebo group). This pattern was consistent with that noted with fatigue, productivity, and activity impairment. The shortened duration of simeprevir-based treatment from 48 weeks to 24 weeks reduces the adverse effect of greater fatigue, lower productivity, and more protracted depression associated with traditional interferon treatment.

A limitation of our study was that recruitment was largely in North America and Europe (175 [44%] and 166 [42%] of 394 patients, respectively), thus potentially reducing the applicability of the results to other geographical regions. Other limitations were that most of the patients were white, with a small proportion of black or African–American and Asian patients, and most patients did not have cirrhosis, with only 12% of patients in the simeprevir group having a METAVIR score of F4 (table 1).

When the QUEST-1 trial was initiated, the standard of care in HCV treatment was peginterferon alfa 2a plus ribavirin and therefore this standard was used as the comparator in the trial as the most appropriate control at the time. While the trial was in progress, the standard of care for HCV genotype 1 infection changed to treatment with direct-acting agents (namely, telaprevir and boceprevir) in combination with peginterferon alfa 2a plus ribavirin. The timeline did not allow for the comparator to represent this change in the standard of care. To address this limitation, a phase 3 non-inferiority trial to assess the efficacy, safety, and tolerability of simeprevir versus telaprevir in combination with peginterferon alfa 2a plus ribavirin in patients with HCV infection who are null or partial responders to previous peginterferon alfa 2a plus ribavirin was initiated and is in progress (NCT01485991). Results from this trial will be available this year.

In conclusion, simeprevir, administered at 150 mg as a single pill once a day, in combination with peginterferon alfa 2a plus ribavirin enhances rates of sustained virological response compared with just peginterferon alfa 2a plus ribavirin, without exacerbating the side-effect profile of peginterferon alfa 2a and ribavirin, and allows for a shortened duration of treatment in most patients. These results also establish a foundation for the assessment of simeprevir as a component of interferon-free direct-acting agent regimens.[38]

Contributors

IMJ was the principal investigator of the trial, was involved in the study setup, was responsible for the clinical supervision of the patients and performance of the study, and contributed to the preparation and writing of the manuscript. GJD, GRF, MWF, MR, VVR, LM, and AC were study investigators, responsible for the treatment of patients, and involved in the acquisition, analysis, and interpretation of the data, and the critical revision of the manuscript. MP participated in the study design and interpretation of the data. 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. JS was responsible for the analysis, interpretation, writing, and editing of descriptions of patient-reported fatigue data, including the supplemental methods related to patient-reported fatigue. 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 into the clinical study and contributed to the writing of the manuscript.

Declaration of interests

IMJ has received research or grant support from AbbVie, Achillion, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Novartis, Roche, Merck, Janssen, and Vertex; has acted as a consultant or adviser for AbbVie, Achillion, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Idenix, Novartis, Roche, Schering, Merck, Janssen, and Vertex; and has been on the speaker's bureau for Bristol-Myers Squibb, Gilead, Janssen, Roche, and Vertex. GJD has received honoraria from Roche, Merck, Janssen, Gilead, Bristol-Myers Squibb, and AbbVie; research grants from Roche, Merck, Janssen, Gilead, Bristol-Myers Squibb, AbbVie, Vertex, and Boehringer Ingelheim; and travel sponsorship from Roche, Merck, Gilead, and Bristol-Myers Squibb. GRF has acted as a speaker and has received consultancy fees from Janssen, Roche, Gilead, Bristol-Myers Squibb, Boehringer Ingelheim, Merck, Chugai, Idenix, and Novartis. MWF has received research or grant support from Janssen, Roche, Merck, Vertex, Tibotec, Gilead, Bristol-Myers Squibb, Anadys, Conatus, and Abbott; and has acted as a consultant for Janssen, Roche, Tibotec, Vertex, Merck, Pharmasset, GlaxoSmithKline, Novartis, Abbott, Gilead, and Bristol-Myers Squibb. MR, VVR, LM, and AC declare that they have no competing interests to disclose with regards to this manuscript. MP, OL, RS, and MB-M are employees of Janssen Infectious Diseases. SO-M, GDLR, and RK are employees of Janssen Research and Development. JS is an employee of Janssen Global Services.

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