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Simeprevir Plus Sofosbuvir (12 and 8 Weeks) in Hepatitis C Virus Genotype 1-Infected Patients Without Cirrhosis: OPTIMIST-1, a Phase 3, Randomized Study

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Effective antiviral therapy is essential for achieving sustained virological response (SVR) in hepatitis C virus (HCV)-infected patients. The phase 2 COSMOS study reported high SVR rates in treatment-naive and prior null-responder HCV genotype (GT) 1-infected patients receiving simeprevir+sofosbuvir±ribavirin for 12 or 24 weeks. OPTIMIST-1 (NCT02114177) was a multicenter, randomized, open-label study assessing the efficacy and safety of 12 and 8 weeks of simeprevir+sofosbuvir in HCV GT1-infected treatment-naive and treatment-experienced patients without cirrhosis. Patients were randomly assigned (1:1; stratified by HCV GT/subtype and presence or absence of NS3 Q80K polymorphism [GT1b, GT1a with Q80K, GT1a without Q80K]), prior HCV treatment history, and *IL28B* GT [CC, non-CC]) to simeprevir 150 mg once daily+sofosbuvir 400 mg once daily for 12 or 8 weeks. The primary efficacy endpoint was SVR rate 12 weeks after end of treatment (SVR12). Superiority in SVR12 was assessed for simeprevir+sofosbuvir at 12 and 8 weeks versus a composite historical control SVR rate. Enrolled were 310 patients, who were randomized and received treatment (n = 155 in each arm). SVR12 with simeprevir+sofosbuvir for 12 weeks (97% [150/155; 95% confidence interval 94%-100%]) was superior to the historical control (87%). SVR12 with simeprevir+sofosbuvir for 8 weeks (83% [128/155; 95% confidence interval 76-89%]) was not superior to the historical control (83%). The most frequent adverse events were nausea, headache, and fatigue (12-week arm: 15% [23/155], 14% [22/155], and 12% [19/155]; 8-week arm: 9% [14/155], 17% [26/155], and 15% [23/155], respectively). No patients discontinued treatment due to an adverse event. One (1%, 12-week arm) and three (2%, 8-week arm) patients experienced a serious adverse event (all unrelated to study treatment). *Conclusion:* Simeprevir+sofosbuvir for 12 weeks is highly effective in the treatment of HCV GT1-infected patients without cirrhosis, including those with Q80K. (HEPATOLOGY 2016;64:370-380)

Abbreviations: AE, adverse event; CI, confidence interval; DAA, direct-acting antiviral agent; EOT, end of treatment; GT, genotype; HCV, hepatitis C virus; IFN, interferon; OPTIMIST, Optimal Treatment with a sIMeprevIr and Sofosbuvir Therapy; pegIFN, pegylated interferon; PRO, patient-reported outcome; QD, once daily; RBV, ribavirin; SVR, sustained virological response; SVR4, SVR at 4 weeks after end of treatment; SVR12, SVR at 12 weeks after end of treatment; SVR24, SVR at 24 weeks after end of treatment.

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The rapid development of new all-oral therapeutic agents for the treatment of hepatitis C virus (HCV) infection has quickly led to the development of combination treatment options that are interferon (IFN)-free and ribavirin (RBV)-free.[1-3] This advance has resulted in reduced severity and incidence of adverse events (AEs) and simpler regimens, thereby increasing adherence.[1] Combination regimens comprising all-oral direct-acting antiviral agents (DAAs) have demonstrated high efficacy, with good safety/tolerability profiles.[4-6]

One of the first IFN-free DAA combination regimens studied was simeprevir+sofosbuvir±RBV in the phase 2 COSMOS study, the outcomes of which led to the approval of simeprevir+sofosbuvir for HCV genotype (GT)1-infected patients.[7] In COSMOS, HCV GT1-infected prior (pegylated interferon [pegIFN] and RBV) null responders (METAVIR scores F0-F2), as well as null responders and treatment-naive patients (METAVIR scores F3-F4), achieved high rates of sustained virological response (SVR) 12 weeks after end of treatment (EOT; SVR12) (90% [72/80] and 94% [82/87], respectively), following simeprevir+sofosbuvir±RBV treatment for 12 or 24 weeks.[7]

Simeprevir is a once-daily (QD), multigenotypic, HCV NS3/4A protease inhibitor approved in combination with pegIFN/RBV for chronic HCV GT1 and GT4 infection in the United States and the European Union. Simeprevir is also approved in the United States and the European Union as part of an IFN-free combination with sofosbuvir for HCV GT1 infection. In addition, simeprevir+sofosbuvir is approved for HCV GT4 infection and HCV/human immunodeficiency virus coinfection in the European Union.

Sofosbuvir is a QD, pangenotypic HCV nucleotide analog NS5B polymerase inhibitor, approved in combination with pegIFN/RBV, RBV, and the NS5A inhibitors ledipasvir and daclatasvir.

Data from the phase 3 ION-3 study evaluating sofosbuvir+ledipasvir in treatment-naive HCV GT1-infected patients without cirrhosis showed that patients randomized to the shorter 8-week treatment achieved a similarly high SVR12 rate to those treated for 12 weeks (94% versus 95%, respectively), although relapse rates in the 8-week arm were slightly higher (5% versus 1%, respectively), indicating that some patients may benefit from a longer 12-week regimen.[8]

The phase 3 OPTIMIST-1 (Optimal Treatment with a sIMeprevIr and Sofosbuvir Therapy) trial further evaluated the efficacy, safety, and tolerability of both a 12-week and a shorter 8-week treatment regimen of simeprevir+sofosbuvir in treatment-naive and

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treatment-experienced patients with chronic HCV GT1 infection without cirrhosis.

Patients and Methods

PATIENTS AND STUDY DESIGN

OPTIMIST-1 was a phase 3, multicenter, randomized, open-label study initiated on April 17, 2014, at 48 sites in the United States and Canada (Supporting Fig. S1). The cutoff date for the primary analysis from which data are presented was January 26, 2015. The study was approved by the institutional review board or independent ethics committee at each participating center and met the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Treatment-naive or treatment-experienced (including IFN-intolerant) adults (age 18-70 years) with chronic HCV GT1a/GT1b infection with documented absence of cirrhosis, plasma HCV RNA >10,000 IU/mL at screening, and documented *IL28B* GT were eligible for inclusion. Treatment-experienced patients included in the study must have had at least one documented previous course of IFN-based therapy with or without RBV. Absence of cirrhosis in enrolled patients was defined as (1) FibroScan (in countries where locally approved) result ≤12.5 kPa within ≤6 months of screening or between screening and day 1, (2) FibroTest score ≤0.48 and aspartate aminotransferase to platelet ratio index ≤1 at screening, or (3) liver biopsy within 2 years of screening, or biopsy between screening and day 1. If only inflammation was present, laboratory evidence of chronic HCV infection (anti-HCV antibody or HCV RNA for at least 6 months prior to baseline) had to be provided (Supporting Information).

Exclusion criteria included hepatic decompensation; liver disease of non-HCV etiology; infection/coinfection with HCV non-GT1a/GT1b, hepatitis B, or human immunodeficiency virus; and significant laboratory abnormalities or presence of other clinically significant disease. Patients were also excluded if they had previously been treated with any direct-acting anti-HCV agent (approved or investigational) for chronic HCV infection (Supporting Information).

The study consisted of a screening period of up to 6 weeks, followed by 12 or 8 weeks of treatment with simeprevir (150 mg QD capsule)+sofosbuvir (400 mg QD tablet). Patients were followed until 24 weeks after EOT (Supporting Fig. S1 and Supporting Information).

Dynamic central randomization was implemented. Patients were randomly assigned 1:1 to 12 or 8 weeks of treatment (Supporting Information). Randomization was stratified according to HCV GT/subtype combined with presence or absence of the NS3 Q80K polymorphism in GT1a patients (1b, 1a without Q80K, 1a with Q80K), prior HCV treatment history (treatment-naive/relapsers, nonresponders, IFN-intolerant/other), and *IL28B* GT (CC, non-CC) based on a polymorphism on chromosome 19 (single-nucleotide polymorphism rs12979860).

As this was an open-label study, all patients and investigators were aware of treatment allocations.

PROCEDURES

Blood samples for HCV RNA level determination were collected at screening; baseline; day 3; weeks 1, 2, 3, 4, 8, and 12; and weeks 4, 12, and 24 of follow-up. HCV RNA was measured using the Roche COBAS TaqMan HCV/HPS assay version 2.0 (lower limit of quantification 25 IU/mL, limit of detection 15 IU/mL). Standard Sanger population-based sequencing (assay sensitivity ~20%-25%) of HCV NS3/4A (considering positions 43, 80, 122, 155, 156, and 168), NS5A (considering positions 28, 30, 31, 32, and 93), and NS5B (considering positions 96, 142, 159, 282, 316, 320, 321, 390, and 415) regions was done at baseline for all patients. Postbaseline sequencing of HCV NS3/4A and NS5B was done for those patients not achieving SVR12. Laboratory (hematology, biochemistry, and urinalysis) tests, vital signs, and physical examinations were performed regularly during treatment and follow-up. Electrocardiogram assessments were performed at screening.

AEs were monitored throughout the study and up to 4 weeks after planned EOT (Supporting Information).

Patient-reported outcomes (PROs) were assessed using three well-validated PRO instruments—the Fatigue Severity Scale,[9] the Center for Epidemiologic Studies Depression Scale,[10] and the EuroQoL 5-Dimensions questionnaire[11]—in addition to a new PRO tool specifically designed for HCV-infected patients—the Hepatitis C Symptom and Impact Questionnaire version 4 (Supporting Information).

OUTCOMES

The primary efficacy endpoints were to (1) demonstrate superiority of 12 weeks' simeprevir (150 mg QD)+sofosbuvir (400 mg QD) versus a historical control rate, which was a composite of the highest SVR rates for approved DAA regimens available at the time of study design (see below, Statistical Analysis); (2) demonstrate superiority of 8 weeks' simeprevir+sofosbuvir versus a historical control; and (3) (if the first two objectives were met) evaluate noninferiority of 8 weeks' versus 12 weeks' treatment with simeprevir+sofosbuvir, all with respect to the proportion of patients achieving SVR12 in the overall population.

Predefined secondary endpoints included SVR rate 4 and 24 weeks after EOT (SVR4 and SVR24, respectively); on-treatment virological response (HCV RNA <25 IU/mL or undetectable at all time points); on-treatment failure including viral breakthrough, which was a stopping rule and defined as confirmed >1.0 $\log_{10}$ increase in HCV RNA from nadir or confirmed HCV RNA >100 IU/mL in patients who had previously achieved HCV RNA <25 IU/mL; viral relapse; SVR12 by prior treatment history and by selected characteristics (including baseline HCV RNA); changes from baseline in the HCV NS3/4A and NS5B sequence in patients not achieving SVR12; safety and tolerability of 12 or 8 weeks' simeprevir+sofosbuvir; and change from baseline for PRO assessments at all time points.

An exploratory analysis to investigate SVR12 by baseline NS5A polymorphisms was also undertaken.

STATISTICAL ANALYSIS

All analyses were performed on the intent-to-treat population (all randomized patients who received at least one dose of study drug). The primary analysis was performed when all patients had completed the SVR12 visit or had discontinued earlier.

The historical control SVR rates for the 12-week and 8-week treatment arms (87% and 83%, respectively) were a composite of the highest historical SVR rates of approved DAA regimens in the subpopulations (available at the time the OPTIMIST-1 study was designed) depending on the proportion of treatment-naive, prior relapser, prior nonresponder, IFN-intolerant, and other patients enrolled in the study. The SVR rates predefined for each subpopulation are shown in Supporting Table S1.

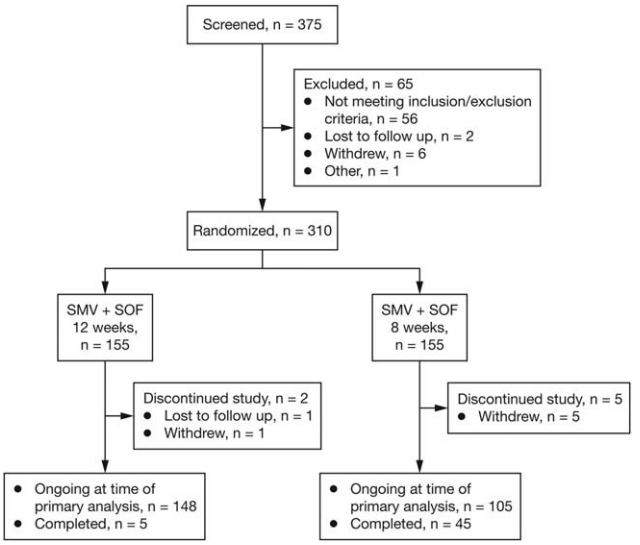

FIG. 1. OPTIMIST-1 study profile. At the time of the primary analysis, 100% of patients had achieved SVR12 or had discontinued earlier. Abbreviations: SMV, simeprevir; SOF, sofosbuvir.

It was determined that a sample size of 150 patients per treatment group would provide 90% power to show superiority in SVR12 rate for the 12-week simeprevir+sofosbuvir group versus the composite historical control rate, provided the SVR12 threshold did not exceed 84%. In addition, the same sample size was estimated to provide 90% power to show noninferiority in SVR12 of no more than -12% of the 8-week versus the 12-week simeprevir+sofosbuvir arm.

The primary objective was tested by means of a closed testing procedure. To establish that the SVR12 rate achieved with 12 weeks' simeprevir+sofosbuvir was superior to the historical control rate, the lower limit of the 95% confidence interval (CI) for the SVR12 rate among patients treated for 12 weeks had to exceed the composite historical control rate of 87% (Supporting Table S1). Superiority of the 8-week arm versus the composite historical control rate of 83% was determined in a similar manner if superiority of the 12-week arm had been established (Supporting Information).

Secondary efficacy outcomes were analyzed using descriptive statistics and 95% CIs. All safety data were summarized descriptively.

Regarding the effect of baseline HCV RNA on SVR12 rates, the statistical analysis plan identified 6,000,000 IU/mL and ≥6,000,000 IU/mL as two categories of interest. In addition, a post hoc analysis was

TABLE 1. Baseline Demographics and Disease Characteristics (Intent-to-Treat Population)

Characteristic	Simeprevir 150 mg QD+Sofosbuvir 400 mg QD	
	12 Weeks (n = 155)	8 Weeks (n = 155)
Age (years)	56 (19-70)	56 (21-70)
Male	82 (53%)	87 (56%)
Body mass index (kg/m^2)	28.0 (16.5-54.5)	26.9 (16.9-56.4)
Race*		
White	120 (78%)	125 (81%)
Black/African American	31 (20%)	24 (16%)
Asian	2 (1%)	4 (3%)
Other	1 (<1%)	1 (<1%)
Ethnicity		
Hispanic or Latino	24 (15%)	24* (16%)
Prior HCV treatment history†		
Treatment-naive	115 (74%)	103 (66%)
Treatment-experienced‡	40 (26%)	52 (34%)
HCV genotype/subtype and baseline NS3 Q80K polymorphism		
1a	116 (75%)	116 (75%)
1a with Q80K§	46 (40%)	49 (42%)
1a without Q80K§	70 (60%)	67 (58%)
1b	39 (25%)	39 (25%)
Baseline HCV RNA (log_{10} IU/mL)		
Median (range)	6.83 (3.9-7.9)	6.85 (4.8-7.8)
<4,000,000 IU/mL	56 (36%)	48 (31%)
IL28B genotype‖		
CC	43 (28%)	41 (26%)
CT	86 (55%)	86 (55%)
TT	26 (17%)	28 (18%)
METAVIR score#		
F0-F2	66 (43)	58 (37)
F3	15 (10)	12 (8)
F4	0	0
PRO scores		
FSS**	3.2 (0.14)	2.9 (0.13)
CES-D††	10.2 (0.71)	8.8 (0.72)
EQ-5D VAS‡‡	76.7 (1.48)	79.3 (1.53)
HCV-SIQv4 OBSS‡‡	13.3 (1.01)	10.8 (0.94)

Data are median (range) or n (%) except for PRO scores, which are mean (standard error).
*n = 154.
†Randomization was stratified by prior HCV treatment history, as follows: treatment-naive/relapsers, nonresponders, IFN-intolerant/other. Patients were classified as "other" if they had received previous pegIFN-based therapy with no on-treatment HCV RNA data available or undetectable HCV RNA levels within 2 months after end of prior treatment, or had received previous pegIFN-based therapy for <12 weeks and did not discontinue previous therapy due to pegIFN-related and/or RBV-related AEs, or had received non-pegIFN-based therapy (IFN with or without RBV), regardless of prior treatment response.
‡Treatment-experienced patients included prior relapsers, prior nonresponders, IFN-intolerant, and other patients (n = 8, 14, 2, and 16 for the 12-week arm; n = 13, 10, 11, and 18 for the 8-week arm, respectively). Prior nonresponders included prior null responders, prior partial responders, and unknown patients (n = 8, 4, and 2 for the 12-week arm; n = 5, 1, and 4 for the 8-week arm, respectively).
§Among HCV GT1a-infected patients.
‖Based on a polymorphism on chromosome 19 (single-nucleotide polymorphism rs12979860).
#Missing METAVIR score data: n = 74 for the 12-week arm; n = 85 for the 8-week arm.
**Normal reference value 2.3, range 1-7.
††Normal reference value 16 (lower threshold for depression), range 0-60.
‡‡Normal reference value not available, range 0-100.
Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; EQ-5D VAS, EuroQoL 5-Dimensions questionnaire visual analog scale; FSS, Fatigue Severity Scale; HCV-SIQv4, Hepatitis C Symptom and Impact Questionnaire; OBSS, overall body system score.

performed to identify a possible baseline HCV RNA cutoff that was predictive of achieving a high SVR12 rate (i.e., 95% in patients with baseline HCV RNA $\geq$ the cutoff point). A univariate logistic regression model was fitted, and a receiver operating characteristic curve was used to determine the predictive value. In patients treated for 12 weeks, baseline HCV RNA was not associated with achieving SVR12; and therefore,

TABLE 2. Virological Response Over Time (Including SVR12) and On-Treatment Failure and Viral Relapse Rates (Intent-to-Treat Population)

	Simeprevir 150 mg QD+Sofosbuvir 400 mg QD			
Response	12 Weeks	95% CI	8 Weeks	95% CI
Week 4 HCV RNA level*				
<25 IU/mL undetectable (RVR)	134/153 (88%)	81%-92%	127/154 (82%)	76%-88%
<25 IU/mL detectable	17/153 (11%)	7%-17%	25/154 (16%)	11%-23%
≥25 IU/mL	2/153 (1%)	0%-5%	2/154 (1%)	0%-5%
SVR4[†]	150/155 (97%)	93%-99%	130/155 (84%)	77%-89%
SVR12[†]	150/155 (97%)	94%-100%	128/155 (83%)	76%-89%
On-treatment failure[‡]	0	—	0	—
Viral breakthrough[§]	0	—	0	—
Viral relapse[‖]	4/154 (3%)	1%-7%	27/155[#] (17%)	12%-24%

Data are n/N (%) or 95% CI.
*Missing data due to patients having discontinued all study drugs before week 4 or having missing data at the week 4 time point.
[†]SVR4 and SVR12 defined as HCV RNA <25 IU/mL detectable or undetectable 4 weeks or 12 weeks, respectively, after EOT.
[‡]Confirmed HCV RNA <25 IU/mL detectable or ≥25 IU/mL at EOT.
[§]Confirmed >1.0 $\log_{10}$ increase in HCV RNA from nadir or confirmed HCV RNA >100 IU/mL in patients who had previously achieved HCV RNA <25 IU/mL.
[‖]Failure to achieve SVR with HCV RNA <25 IU/mL undetectable at EOT and HCV RNA ≥25 IU/mL during the follow-up period. The incidence of viral relapse was only calculated for patients with undetectable HCV RNA levels at EOT and with at least one follow-up HCV RNA measurement.
[#]In the 8-week arm, viral relapse was detected at the first follow-up visit (follow-up week 4) for 24/27 (89%) patients, and at the next follow-up visit (follow-up week 12) for 3/27 (11%) patients.
Abbreviation: RVR, rapid virological response.

establishing a cutoff in this group was not pursued. In the 8-week arm, a relation between baseline HCV RNA and achieving SVR12 was observed; and after exploring a range of cutoff points graphically, baseline HCV RNA 4,000,000 IU/mL was identified as the optimal cutoff predictive of response in patients treated with simeprevir in combination with sofosbuvir for 8 weeks.

Descriptive statistics were used to display the actual value and change from baseline for each PRO assessment at each time point (including baseline). In addition, mean changes from baseline in specific subgroups were assessed (Supporting Information).

SAS software (version 9.2; SAS Institute Inc., Cary, NC) was used for all analyses. For the primary endpoint, all statistical tests and 95% CIs were two-sided with a significance level of 0.05.

This trial is registered with clinicaltrials.gov number NCT02114177.

Results

In total, 375 patients were screened; 310 were randomized and received at least one dose of treatment (155 in each arm). At the time of the primary analysis, all patients had achieved SVR12 or had discontinued earlier (Fig. 1; Supporting Information).

Baseline demographics and disease characteristics were well balanced between the treatment arms (Table 1; Supporting Information).

A total of 150 of 155 patients (97%; 95% CI 94%-100%) in the 12-week simeprevir+sofosbuvir arm achieved SVR12 (Table 2 and Fig. 2). As the lower limit of the 95% CI of the SVR12 rate in the 12-week arm was greater than the historical control rate (94% > 87%), superiority was demonstrated (Fig. 2). In the 8-week simeprevir+sofosbuvir arm, 128 of 155 patients (83%; 95% CI 76%-89%) achieved SVR12. However, superiority over the historical control was not demonstrated, as the lower limit of the 95% CI was not greater than the historical control rate (76% <83%; Fig. 2). As superiority of the 8-week regimen versus the historical control was not demonstrated, noninferiority of this regimen versus 12 weeks of simeprevir+sofosbuvir was not assessed.

Results for the key secondary efficacy outcomes are presented in Table 2. There was high concordance between SVR4 and SVR12 rates in both arms (Table 2). At the time of the primary analysis, five of five (100%) and 39 of 46 (85%) patients in the 12-week and 8-week arms, respectively, had achieved SVR24.

Table 3 shows SVR12 rates by subgroups of interest. In the 12-week arm, high SVR12 rates were observed irrespective of subgroup. In the 8-week arm, treatment-naive patients achieved SVR12 at a

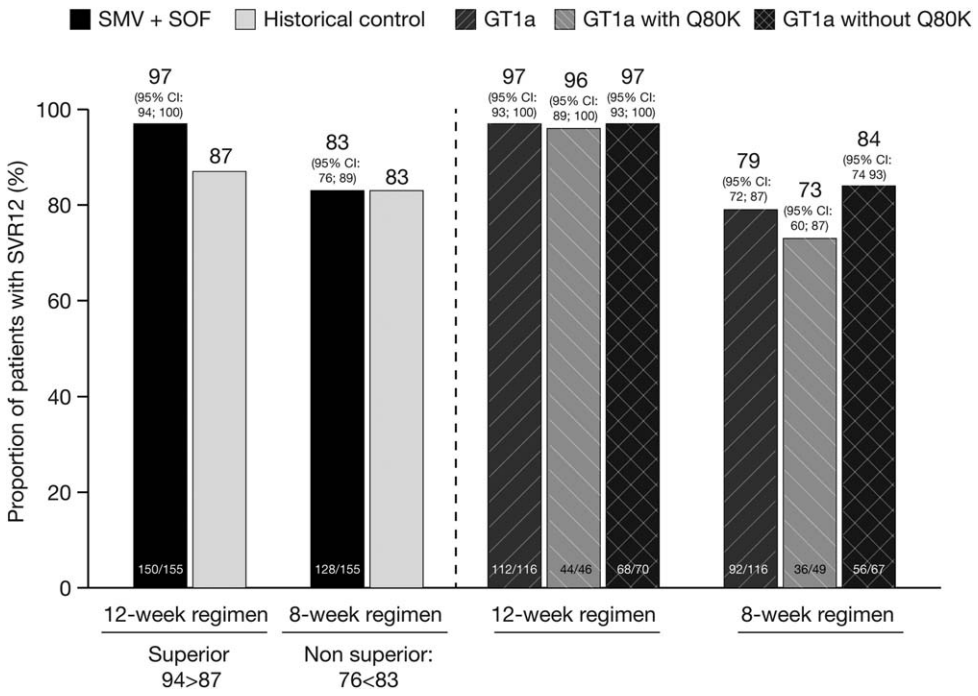

FIG. 2. SVR12 rates for patients receiving simeprevir +sofosbuvir for 12 and 8 weeks versus historical control rates (intent-to-treat population). The primary objective was tested by means of a closed testing procedure. The 95% Cls were constructed using a normal approximation with continuity correction. To conclude superiority of the SMV+SOF arm versus the historical data, the lower limit of the 95% CI of the SMV+SOF arm had to be greater than the historical control rate. Abbreviations: SMV, simeprevir; SOF, sofosbuvir.

numerically higher rate than treatment-experienced patients (88 of 103 [85%] versus 40 of 52 [77%], respectively). GT1b-infected patients and patients with *IL28B* CC GT had high SVR12 rates of 92% (36 of 39 patients) and 93% (38 of 41 patients), respectively. Analyses regarding baseline HCV RNA level showed that patients with HCV RNA ≤4,000,000 IU/mL achieved an SVR12 rate of 96% (46 of 48 patients) in the 8-week arm (Table 3). Race, ethnicity, and body mass index at baseline did not appear to impact SVR12 rates in either treatment arm (Supporting Information).

A total of 95/232 (41%) GT1a-infected patients had an NS3 Q80K polymorphism at baseline, a naturally occurring polymorphism known to confer low-level resistance to simeprevir *in vitro* (Table 1).[12] In the 12-week arm, 44/46 (96%) GT1a-infected patients with baseline Q80K achieved SVR12 compared with 36/49 (73%) in the 8-week arm (Table 3). Baseline NS3 polymorphisms associated with simeprevir resistance *in vitro* other than Q80K were uncommon (n = 8) and did not affect outcome; all seven patients with a baseline NS3 Q80R polymorphism (12-week arm, n = 5; 8-week arm, n = 2) and the one patient (12-week arm) with an NS3 D168E polymorphism at baseline achieved SVR12. NS5B substitution S282T or other polymorphisms associated with resistance to sofosbuvir were not observed at baseline. Baseline NS5A polymorphisms had no effect on SVR12 rates in the 12-week arm, and a numerical difference in SVR12 rates was observed in the 8-week arm between patients with and without baseline NS5A polymorphisms (Supporting Information).

Among patients who did not achieve SVR12 and with sequencing data available, emerging NS3 mutations associated with simeprevir resistance were observed in one of three (33%; R155K+D168E+I170T) and one of 25 (4%; I170T) patients in the 12-week and 8-week arms, respectively (Table 4). Both of these patients were GT1a-infected and had an NS3 Q80K polymorphism at baseline. The patient in the 8-week arm also had an emerging NS5B S282T mutation. No other emerging NS5B mutations considering the nine NS5B positions of interest were observed in any other patient not achieving SVR12.

On-treatment failure, including viral breakthrough, was not observed in either treatment arm (Table 2). The main reason for not achieving SVR12 was viral relapse, which occurred in four of 155 (3%) and 27 of 155 (17%) patients in the 12-week and 8-week arms, respectively, and was primarily detected at the first follow-up visit 4 weeks after EOT (Table 2).

Viral relapse rates were consistently lower in the 12-week versus 8-week arm across all subgroups

TABLE 3. SVR12 and Relapse Rates by Virological Response at Week 4, Prior Treatment History, HCV GT/Subtype and Presence of Baseline NS3 Q80K Polymorphism, *IL28B* Genotype, and Baseline HCV RNA (Intent-to-Treat Population)

	Simeprevir 150 mg QD+Sofosbuvir 400 mg QD							
	SVR12				Viral Relapse*			
	12 Weeks	95% CI	8 Weeks	95% CI	12 Weeks	95% CI	8 Weeks	95% CI
Week 4 HCV RNA†								
<25 IU/mL undetectable	129/134 (96%)	92%-99%	108/127 (85%)	78%-91%	4/133 (3%)	1%-8%	19/127 (15%)	9%-22%
<25 IU/mL detectable	17/17 (100%)	81%-100%	17/25 (68%)	47%-85%	0/17 (0%)	0%-20%	8/25 (32%)	15%-54%
≥25 IU/mL	2/2 (100%)	16%-100%	2/2 (100%)	16%-100%	0/2 (0%)	0%-84%	0/2 (0%)	0%-84%
Prior treatment history								
Treatment-naive	112/115 (97%)	93%-100%	88/103 (85%)	77%-92%	2/114 (2%)	0%-6%	15/103 (15%)	8%-23%
Treatment-experienced	38/40 (95%)	83%-99%	40/52 (77%)	63%-88%	2/40 (5%)	1%-17%	12/52 (23%)	13%-37%
HCV GT/subtype and baseline NS3 Q80K polymorphism								
GT1a	112/116 (97%)	91%-99%	92/116 (79%)	71%-86%	3/115 (3%)	1%-7%	24/116 (21%)	14%-29%
GT1a with Q80K	44/46 (96%)	85%-100%	36/49 (73%)	59%-85%	2/46 (4%)	1%-15%	13/49 (27%)	15%-41%
GT1a without Q80K	68/70 (97%)	90%-100%	56/67 (84%)	73%-92%	1/69 (1%)	0%-8%	11/67 (16%)	9%-28%
GT1b	38/39 (97%)	87%-100%	36/39 (92%)	79%-98%	1/39 (3%)	0%-14%	3/39 (8%)	2%-21%
IL28B								
CC	43/43 (100%)	92%-100%	38/41 (93%)	80%-99%	0/43 (0%)	0%-8%	3/41 (7%)	2%-20%
CT	83/86 (97%)	90%-99%	72/86 (84%)	74%-91%	2/85 (2%)	0%-8%	14/86 (16%)	9%-26%
TT	24/26 (92%)	75%-99%	18/28 (64%)	44%-81%	2/26 (8%)	1%-25%	10/28 (36%)	19%-56%
Baseline HCV RNA (IU/mL)‡								
≤6,000,000	70/73 (96%)	89%-99%	61/68 (90%)	80%-96%	2/72 (3%)	0%-10%	7/68 (10%)	4%-20%
>6,000,000	80/82 (98%)	92%-100%	67/87 (77%)	67%-85%	2/82 (2%)	0%-9%	20/87 (23%)	15%-33%
≤4,000,000	54/56 (96%)	88%-100%	46/48 (96%)	86%-100%	1/55 (2%)	0%-10%	2/48 (4%)	1%-14%
>4,000,000	96/99 (97%)	91%-99%	82/107 (77%)	68%-84%	3/99 (3%)	1%-9%	25/107 (23%)	16%-33%

Data are n/N (%) or 95% CI based upon Clopper Pearson approximation.
*The incidence of viral relapse was only calculated for patients with undetectable HCV RNA levels at EOT and with at least one follow-up HCV RNA measurement.
†Missing data due to patients having discontinued all study drugs prior to, or having missing data at, the week 4 time point.
‡The HCV RNA value of 4,000,000 IU/mL was selected based on a post hoc analysis performed to identify a possible cutoff for baseline HCV RNA that was predictive for achieving SVR12 in patients treated with 8 weeks of simeprevir+sofosbuvir.

(Table 3). In the 8-week arm, among patients with baseline HCV RNA ≤4,000,000 IU/mL, two of 48 patients (4%) had viral relapse. Both patients were Black/African American, treatment-naive, with *IL28B* TT GT and GT1a infection (one with and one without baseline NS3 Q80K polymorphism) (Supporting Information).

AEs occurred in a similar proportion of patients in both treatment arms (Table 5). Two of the grade 3 AEs reported were considered possibly related to study treatment: pyelonephritis in a patient with a predisposing condition of dysfunctional kidney (12-week arm) and increased amylase (8-week arm). Serious AEs occurred in one of 155 (1%; *Clostridium difficile* colitis) and three of 155 (2%; gastroesophageal reflux disease, mania, and whiplash) patients in the 12-week and 8-week arms, respectively; none were considered related to study treatment. The most frequently reported AEs (≥10% of patients in either arm) were nausea, headache, and fatigue (Table 5); all of these were grade 1 or 2, were transient, and did not lead to permanent treatment discontinuation. Laboratory parameter abnormalities are reported in Supporting Table S2 (see also Supporting Information).

There were no important differences between treatment groups in mean PRO scores at baseline (Table 1; Supporting Information). Overall, PRO scores improved from baseline to the week 12 follow-up, but most changes were not clinically important (Supporting Information and Supporting Fig. S3). The mean change from baseline for all four PRO endpoints showed greater improvements in patients who achieved SVR12 versus those who did not (Supporting Information and Supporting Table S3).

Discussion

In OPTIMIST-1, 12 weeks of simeprevir +sofosbuvir in HCV GT1-infected treatment-naive and treatment-experienced patients without cirrhosis led to SVR12 rates of 97% overall and demonstrated superiority over the historical control rate (87%), confirming the high SVR rates achieved in the phase 2 COSMOS

TABLE 4. NS3 and NS5B Emerging Mutations in Patients Not Achieving SVR12

	Simeprevir 150 mg QD+ Sofosbuvir 400 mg QD	
	12 Weeks	8 Weeks
Patients with failure*	5/155 (3%)	27/155 (17%)
NS3 sequencing data available†	3/5 (60%)	25/27 (93%)
No emerging NS3 mutations	1/3 (33.3%)	23 (92.0%)
Emerging NS3 mutations‡	2/3 (66.7%)	2 (8.0%)
I170T	0	1 (4.0%)
R155K+D168E+I170T	1/3 (33.3%)	0
S122G	0	1 (4.0%)
V55A+N174S	1/3 (33.3%)	0
NS5B sequencing data available†	3/5 (3%)	25/27 (17%)
No emerging NS5B mutations	3/3 (100%)	24/25 (96%)
Emerging NS5B mutations§	0	1/25 (4%)
S282T	0	1/25 (4%)

*All patients not achieving SVR12.
†Only patients with baseline and post-baseline sequencing data are considered.
‡Amino acid substitutions at NS3 positions 36, 41, 43, 54, 55, 80, 107, 122, 132, 138, 155, 156, 158, 168, 169, 170, 174, and 175 are considered.
§Amino acid substitutions at NS5B positions 96, 142, 159, 282, 316, 320, 321, 390, and 415 are considered.

study.[7] The SVR12 rate in the OPTIMIST-1 12-week arm was similar to those reported in other large trials with DAA regimens.[6,8,13-17] The SVR12 rate achieved with 8 weeks of simeprevir+sofosbuvir (83%) was lower than that observed following 8 weeks of treatment with sofosbuvir+ledipasvir (94%) in HCV GT1-infected patients without cirrhosis.[8] However, this was not a head-to-head comparison, and the patient populations were different as OPTIMIST-1 included treatment-experienced patients.

Consistently high SVR12 rates (≥92%) were observed in all patients treated with 12 weeks of simeprevir+sofosbuvir, including treatment-experienced patients and those with baseline characteristics historically associated with a poor response to HCV treatment (*IL28B* non-CC GT, high baseline HCV RNA levels, and historical HCV GT1a infection). Previous studies demonstrated that the presence of the NS3 Q80K polymorphism at baseline reduced SVR rates when simeprevir was administered in combination with pegIFN/RBV.[18,19] The presence of baseline Q80K polymorphism did not adversely affect SVR12 rates in patients treated with 12 weeks of simeprevir+sofosbuvir. In the 8-week arm, lower SVR12 rates were observed among patients with baseline NS3 Q80K polymorphism compared with those without Q80K at baseline. In the OPTIMIST-2 study, in which patients with cirrhosis were treated with a 12-week regimen of simeprevir+sofosbuvir, SVR12 rates were also numerically higher for HCV GT1a-infected patients without Q80K (92%) versus those with Q80K (74%).[20] As expected, the presence of NS5A polymorphisms did not have an impact on the efficacy of a regimen containing simeprevir and sofosbuvir (Supporting Information).

Simeprevir+sofosbuvir for 8 weeks led to SVR12 rates of 83% overall but did not achieve superiority versus the historical control. The main driver for these lower SVR12 rates was the high proportion of patients experiencing viral relapse (17% versus 3% in the 12-week arm). Treatment for 12 weeks appeared to reduce the relapse rate versus the 8-week treatment group, indicating that treatment duration in the latter arm was too short. The majority of patients not achieving SVR12 following 8 weeks of simeprevir+sofosbuvir had no emerging NS3 mutations at the time of failure. This suggests that there was insufficient clearance of intrahepatic wild-type virus in these patients, further indicating that 8 weeks of treatment was too short. With the exception of one patient in the 8-week arm, no emerging NS5B mutations were observed in OPTIMIST-1, similar to results obtained for the COSMOS study.[7]

TABLE 5. Summary of AEs During the Simeprevir+Sofosbuvir Treatment Phase (Intent-to-Treat Population)

AE	Simeprevir 150 mg QD+ Sofosbuvir 400 mg QD	
	12 Weeks (n = 155)	8 Weeks (n = 155)
Any AE	103 (66%)	97 (63%)
Worst grade AE		
Grade 1/2	99 (64%)	94 (61%)
Grade 3	3 (2%)	3 (2%)
Grade 4	1 (1%)*	0
Serious AE	1 (1%)	3 (2%)
AE with fatal outcome	0	0
AE leading to permanent discontinuation†	0	0
Most common AEs‡		
Nausea	23 (15%)	14 (9%)
Headache	22 (14%)	26 (17%)
Fatigue	19 (12%)	23 (15%)
AEs of interest		
Increased bilirubin	1 (1%)	1 (1%)
Rash (any type)	10 (6%)	12 (8%)
Pruritus (any type)	7 (5%)	9 (6%)
Photosensitivity	2 (1%)	5 (3%)
Dyspnea	3 (2%)	1 (1%)

Data are n (%).
*Elevated gamma-glutamyl transpeptidase levels not related to simeprevir+sofosbuvir treatment.
†Permanent discontinuation of at least one drug.
‡In ≥10% of patients in at least one of the two arms.

Similar to the COSMOS safety results,[7] 12 or 8 weeks of simeprevir+sofosbuvir in OPTIMIST-1 was generally well tolerated, with the majority of AEs being clinically manageable. There were no discontinuations due to AEs and no grade 3 or 4 increases in bilirubin laboratory parameters. No new safety issues were identified.

PROs were assessed to understand the impact of simeprevir+sofosbuvir on outcomes that are important from the patients' perspective. Patient-reported symptoms and health-related quality of life improved from baseline to the week 12 follow-up in both treatment arms. Clinically important differences were observed between patients who achieved SVR12 and those who did not in terms of greater improvement in fatigue scores in both treatment arms, and in symptoms and health-related quality of life scores in the 12-week arm. In a pooled analysis based on pivotal phase 3 simeprevir study results, in which pegIFN/RBV was used, better PROs were also observed in patients who achieved SVR12.[21]

In OPTIMIST-1, SVR12 rates were compared against a composite historical control calculated based on the highest SVR12 rates obtained with approved DAA-based regimens available at the time of study design (all with pegIFN/RBV). This approach is well established and in accordance with Food and Drug Administration guidance.[22]

Limitations of the study include the small patient numbers in certain subgroups, which limited the conclusions that could be drawn. The open-label nature of the study and lack of a comparator arm could also be viewed as potential limitations.

A strength of the study was that both treatment-naive and treatment-experienced patients (including prior relapser, prior partial responder, and null responder patients) were enrolled. In addition, IFN-intolerant patients were included (12 of 13 [92%] of whom achieved SVR12 overall; Supporting Information), and 16% and 18% of patients were Hispanic and Black/African American, respectively, two populations that have not been well represented in HCV clinical trials.

In conclusion, the combination of simeprevir and sofosbuvir for 12 weeks was efficacious and well tolerated by treatment-naive and treatment-experienced patients with chronic HCV GT1 infection without cirrhosis, and these findings further confirm the use of this regimen in this patient population.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.28467/suppinfo.