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Efficacy and safety profile of boceprevir- or telaprevir-based triple therapy or dual peginterferon alfa-2a or alfa-2b plus ribavirin therapy in chronic hepatitis C: the real-world PegBase observational study

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Abstract

Background The aim of the study was to determine the efficacy and safety of triple therapy with a first-generation protease inhibitor (PI; boceprevir, telaprevir) plus peginterferon alfa-2a or -2b plus ribavirin, and dual therapy (peginterferon alfa-2a or -2b plus ribavirin) in patients with chronic hepatitis C (CHC) in routine clinical practice.

Methods PegBase was an international, prospective, observational study in which 4441 patients with CHC were enrolled in 27 countries. This analysis focuses on results in 4100 treatment-naïve and previously treated patients treated with PI-based triple therapy or dual therapy, according to the discretion of the investigator and local standards of practice. The primary efficacy outcome was sustained virological response after 12-week follow up (SVR12).

Results SVR12 rates in treatment-naïve genotype (G) 1 patients were 56.6% and 62.9% for recipients of boceprevir plus peginterferon alfa-2a/ribavirin and boceprevir plus peginterferon alfa-2b/ribavirin, respectively, and 65.3% and 58.6% for recipients of telaprevir plus peginterferon alfa-2a/ribavirin and telaprevir plus peginterferon alfa-2b/ribavirin, respectively. In previously treated patients assigned to these four regimens, SVR12 rates were 43.6%, 48.3%, 60.3% and 56.1%, respectively. Among treatment-naïve patients assigned to peginterferon alfa-2a/ribavirin and peginterferon alfa-2b/ribavirin, respectively, SVR12 rates were 49.2% and 41.9% in G1 patients, 75.7% and 83.3% in G2 patients, 65.9% and 65.9% in G3 patients, and 49.7%, and 51.1% in G4 patients. The safety and tolerability of dual and triple therapy were consistent with previous reports.

Conclusion The efficacy and safety of first-generation PI-based triple-therapy and dual-therapy regimens in this real-world cohort were broadly comparable to those of previous studies.

Keywords Boceprevir, peginterferon, ribavirin, telaprevir, virological response

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Introduction

Hepatitis C virus (HCV) is the most common infectious cause of chronic liver disease. More than 185 million people worldwide are infected with HCV, of whom 350,000 die each year [1]. The highest prevalence of chronic hepatitis C (CHC) is in Asia, the Middle East and North Africa. Untreated CHC can result in cirrhosis, liver failure and hepatocellular carcinoma [1]. HCV genotype (G) 1 is the most prevalent among HCV genotypes, comprising almost half of all HCV infections [2]. Patients with CHC have a 15-30% risk of cirrhosis within 20 years [3], while the risk of hepatocellular carcinoma for people with cirrhosis is approximately 2-4% per year [4]. It has been estimated that HCV infection accounts for the loss of over 12,000 disability-adjusted life years worldwide [5].

The primary objective of CHC treatment is eradication of the virus from the host, usually characterized as a sustained virological response (SVR), defined by the absence of detectable HCV RNA in the serum 3-6 months after the end of treatment (EoT) [1]. Until 2011, the combination of peginterferon alfa and ribavirin for 24 or 48 weeks (dual therapy) was the standard of care for patients with CHC, and produced an overall SVR rate of approximately 40%. SVR rates with interferon-based therapy vary according to host and viral factors, such as HCV genotype, HCV RNA level, host *IL28B* genotype and the extent of hepatic fibrosis. Since 2011, direct-acting antivirals (DAAs) have been available for the treatment of CHC. The first DAAs, boceprevir and telaprevir, were inhibitors (PI) of the HCV protease NS 3/4A and, when added to peginterferon alfa/ribavirin as triple therapy, improved SVR rates to approximately 60-70% in G1 patients [6,7]. First-generation PI-based triple therapy is associated with a higher rate of hematological adverse events (AEs), in particular anemia, and potentially severe hypersensitivity reactions are common with telaprevir [6-9]. While tolerability was an issue, and the costs of treatment made DAAs unavailable for many patients, triple therapy became the standard of care for patients with G1 infection. Boceprevir and telaprevir have since been superseded by next-generation DAAs with improved efficacy and tolerability, and with the availability of interferon-free combinations of DAAs with higher efficacy and broader genotype coverage, these two drugs have been withdrawn from the US market [10-12]. However, availability and cost considerations mean that many patients still do not have access to newer DAAs, so that peginterferon-based regimens may still be relevant in some countries [11,12].

The PegBase study is an international, prospective, observational study that was initiated after the first PIs became available in 2011 with the objective of characterizing the efficacy and safety of boceprevir- and telaprevir-based triple therapy, as well as dual therapy, in patients with CHC in routine clinical practice.

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Patients and methods

The PegBase study was a prospective, international cohort study in patients with CHC conducted in 27 countries (Belgium, Egypt, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Kuwait, Lebanon, Former Yugoslav Republic of Macedonia, Morocco, Oman, Pakistan, Portugal, Qatar, Romania, Saudi Arabia, Serbia, Sweden, Switzerland, Syrian Arab Republic, Taiwan, Turkey, United Arab Emirates and the United Kingdom).

Adult patients with untreated or previously treated CHC were eligible if they had quantifiable HCV RNA at the start of treatment and were prescribed, as part of standard care according to local labeling, either dual combination therapy with peginterferon alfa-2a or -2b plus ribavirin, or boceprevir- or telaprevir-based triple therapy incorporating peginterferon alfa 2a or 2b plus ribavirin. Patients with hepatitis B virus coinfection were excluded. Drug dosages and treatment durations were left to the discretion of the investigator and were to be determined according to the local label and standards of practice. Patients were followed up for 24 weeks after completion of treatment.

The current analysis includes results from HCV mono-infected patients who received dual peginterferon alfa/ribavirin therapy, and patients with HCV G1 infection who received boceprevir- or telaprevir-based triple therapy, and comprised the core population. A comprehensive list of exclusion criteria used to define the core population for this analysis is shown in Supplemental Table 1. The protocol was approved by the Independent Ethics Committee or Institutional Review Board at each center, and each patient provided written informed consent. The trial is registered with clinicaltrials.gov: NCT01447446.

Study endpoints

Virological response (VR) was defined as HCV RNA <50 IU/mL (dual therapy) or undetectable HCV RNA (triple therapy), using a test with a lower limit of detection ≤50 IU/mL. The primary endpoint of the study was SVR. When the trial was designed, SVR was defined as VR at 24 weeks post-treatment (SVR24); however, after the study was initiated, determination of SVR at 12 weeks post-treatment (SVR12) became an accepted definition for treatment success [13]. Both SVR12 and SVR24 were obtained and are presented. However, in this real-world study, patients who achieved an SVR12 may have been less likely to return for an assessment at 24-week follow up. SVR12 and SVR24 were defined as achievement of a VR ≥70 and ≥140 days after the day of last treatment. Scheduling of HCV

RNA assessments was at the discretion of the local investigator. HCV RNA was measured using polymerase chain reaction according to standard methods. Secondary endpoints included on-treatment VR rates, relapse rates (defined as detectable HCV RNA during follow up in recipients of triple therapy or HCV RNA ≥50 IU/mL during follow up in recipients of dual therapy in patients with an EoT VR) and rates of breakthrough (HCV RNA detectable/≥50 IU/mL while still on treatment after an initial response), or rebound (≥1-$\log_{10}$ increase in HCV RNA over nadir during treatment). Extended rapid VR (eRVR) was defined as a VR at weeks 4 and 12 of treatment in patients treated with telaprevir and a VR at weeks 8 and 24 in patients treated with boceprevir.

VR rates were also presented by fibrosis status. Investigators reported the method of assessment (biopsy, noninvasive or best guess) and the result of assessment (cirrhosis, transition to cirrhosis, no cirrhosis) on the electronic case report form (eCRF). For patients with a biopsy result, transition to cirrhosis was prespecified in the eCRF as ISHAK stage 5 or 4 (with nodules or >3 bridges), METAVIR stage 3, Batts and Ludwig stage 3, Knodell stage 3 and Scheuer stage 3. Cirrhosis was defined as ISHAK stage 6, METAVIR stage 4, Batts and Ludwig stage 4, Knodell stage 4 and Scheuer stage 4. In the present analysis, cirrhosis and transition to cirrhosis were combined into one category. For patients with no documented biopsy result, the determination was based either on a noninvasive assessment (if documented in the patient record) or a "best guess" assessment. In such cases, one of the three categories (cirrhosis, transition to cirrhosis and no cirrhosis) was reported in the eCRF, based on the investigator's judgment without prespecified definitions.

Safety endpoints included AEs, serious AEs (SAEs), laboratory abnormalities and dose modifications of peginterferon alfa and ribavirin. AEs were recorded continuously. Laboratory (hematological) parameters were measured at the discretion of the investigator according to local guidelines.

Statistical analysis

For statistical analysis, no hypothesis testing was performed and the endpoints were analyzed by descriptive and exploratory methods. The planned sample size of 4000 patients included in the overall study was based on feasibility considerations and no formal sample size calculations were performed. All analyses reported here were conducted in the core study population.

VR rates were calculated with 95% confidence intervals, based on the normal approximation to the binomial distribution. Subgroup analyses were performed by HCV genotype (dual therapy only), presence or absence of transition to cirrhosis or cirrhosis, host rs12979860 *IL28B* gene polymorphism, and baseline HCV RNA level (≤400,000 or >400,000 IU/mL). For patients with missing virological data during the treatment period, if the HCV measurements before and after the missing measurement both showed VR, the missing measurement was assumed to also show VR. Similarly, for patients with a missing EoT measurement, if the next available measurement post-treatment showed VR, VR was assumed for EoT. In all other cases, missing measurements were considered as non-response.

AEs were categorized according to the Medical Dictionary for Drug Regulatory Affairs version 18.1 and expressed as the proportion of patients with an AE. Laboratory safety variables were converted to SI units if required, with the results transformed to a standard reference range to allow comparison of results from different laboratories.

Results

A total of 4441 patients were enrolled and followed up between 1 September 2011 and 24 July 2015. Of these, 4352 individuals received at least one dose of study medication and were included in the safety population. A total of 252 patients in the safety population were excluded from the core population (Supplemental Table 2). The core population for analysis comprised 4100 patients, of whom 1292 were assigned to boceprevir- or telaprevir-based triple therapy (all infected with HCV G1). Baseline characteristics are shown by treatment regimen and treatment history for patients receiving triple therapy in Table 1 and for treatment-naïve patients receiving dual therapy in Table 2.

Among patients assigned to triple-therapy, 70.2% received telaprevir and 29.8% boceprevir (Fig. 1). Patient disposition is shown in Table 3 and reasons for premature withdrawal from treatment are shown in Table 4.

VR in treatment-naïve patients receiving triple therapy

Among treatment-naïve patients assigned to triple therapy, SVR12 rates were 56.6% and 62.9% for patients who received boceprevir in combination with peginterferon alfa-2a/ribavirin and peginterferon alfa-2b/ribavirin, respectively, and 65.3% and 58.6% for patients who received telaprevir in combination with peginterferon alfa-2a/ribavirin and peginterferon alfa-2b/ribavirin, respectively (Fig. 2A). Corresponding relapse rates in patients evaluable for relapse in these four treatment groups were 14.1%, 18.5%, 15.7% and 5.6%, respectively (Fig. 2B), whilst breakthrough or rebound occurred in 8.2%, 14.3%, 8.1% and 23.1%, respectively, of patients evaluable for breakthrough or rebound (Table 5).

An eRVR was achieved by 46.9% and 42.9% of patients receiving boceprevir with peginterferon alfa-2a/ribavirin and peginterferon alfa-2b/ribavirin, respectively, and 42.8% and 37.9% of patients receiving telaprevir with peginterferon alfa-2a/ribavirin and peginterferon alfa-2b/ribavirin, respectively.

SVR12 rates were consistently higher in non-cirrhotic than in cirrhotic patients and in patients with *IL28B* CC genotypes than in those with non-CC genotypes across the four treatment groups (Table 6). SVR12 rates also tended to be higher among

Table 1 Baseline patient and disease characteristics – triple therapy

Characteristic	Boceprevir plus PegIFN alfa-2a/RBV	Boceprevir plus PegIFN alfa-2b/RBV	Telaprevir PegIFN alfa-2a/RBV	Telaprevir PegIFN alfa-2b/RBV
Treatment-naïve	**N=143**	**N=35**	**N=285**	**N=29**
Female, n (%)	49 (34)	12 (34)	118 (41)	8 (28)
Race, n (%)				
Caucasian/white	130 (91)	33 (94)	256 (90)	29 (100)
Black	5 (3)	1 (3)	11 (4)	–
Asian/Oriental	8 (6)	1 (3)	17 (6)	–
Other	–	–	1 (<1)	–
Mean age, years (SD)	47.8 (11.0)	48.8 (12.5)	49.4 (11.7)	52.8 (9.7)
Mean body mass index, kg/m^2 (SD)	26.3 (4.9)	25.6 (4.9)	25.9 (4.2)	27.2 (4.9)
Mean HCV RNA, $\log_{10}$ IU/mL (SD)	6.1 (0.7)	6.0 (0.8)	6.0 (0.7)	5.8 (0.7)
HCV RNA >400,000 IU/mL, n (%)	111 (78)	27 (79)	212 (74)	20 (69)
Method of assessing liver fibrosis, n (%)				
Biopsy	49 (34)	18 (51)	87 (31)	6 (21)
Noninvasive	83 (58)	15 (43)	174 (61)	21 (72)
Not assessed or best guess	11 (8)	2 (6)	24 (8)	2 (7)
Liver fibrosis status, n (%)				
Cirrhosis	32 (22)	8 (23)	61 (21)	12 (41)
Transition to cirrhosis	23 (16)	4 (11)	37 (13)	6 (21)
No cirrhosis	88 (62)	23 (66)	187 (66)	11 (38)
IL28B rs12979860 host genotype, n (%)				
CC	25/80 (31)	5/15 (33)	29/143 (20)	3/19 (16)
TC	39/80 (49)	8/15 (53)	82/143 (57)	12/19 (63)
TT	16/80 (20)	2/15 (13)	32/143 (22)	4/19 (21)
Median duration of infection, years	20.0	23.0	18.0	12.5
Patients with type 2 diabetes, n (%)	11 (7.7)	2 (5.7)	20 (7.0)	1 (3.4)
Previously treated	**N=149**	**N=58**	**N=536**	**N=57**
Female, n (%)	59 (40)	25 (43)	213 (40)	35 (61)
Race, n (%)				
Caucasian/white	143 (96)	55 (95)	515 (96)	57 (100)
Black	2 (1)	–	7 (1)	–
Asian/Oriental	3 (2)	3 (5)	13 (2)	–
Other	1 (<1)	–	1 (<1)	–
Mean age, years (SD)	54.3 (8.1)	56.9 (9.6)	54.0 (9.5)	57.1 (9.3)
Mean body mass index, kg/m^2 (SD)	27.2 (5.0)	26.0 (4.0)	26.7 (4.5)	28.6 (6.4)
Mean HCV RNA, $\log_{10}$ IU/mL (SD)	6.1 (0.7)	6.1 (0.6)	6.1 (0.7)	5.8 (0.8)
HCV RNA >400,000 IU/mL, n (%)	113 (76)	44 (76)	417 (78)	41 (72)
Method of assessing liver fibrosis, n (%)				
Biopsy	35 (23)	7 (12)	66 (12)	8 (14)
Noninvasive	91 (61)	42 (72)	367 (68)	42 (74)
Not assessed or best guess	23 (15)	9 (16)	103 (19)	7 (12)

(*Contd...*)

Table 1 (*Continued*)

Characteristic	Boceprevir plus PegIFN alfa-2a/RBV	Boceprevir plus PegIFN alfa-2b/RBV	Telaprevir PegIFN alfa-2a/RBV	Telaprevir PegIFN alfa-2b/RBV
Previously treated	N=149	N=58	N=536	N=57
Liver fibrosis status, n (%)				
Cirrhosis	56 (38)	18 (31)	156 (29)	14 (25)
Transition to cirrhosis	27 (18)	11 (19)	87 (16)	11 (19)
No cirrhosis	66 (44)	29 (50)	293 (55)	32 (56)
IL28B rs12979860 host genotype, n/N (%)				
CC	10/82 (12)	5/37 (14)	43/288 (15)	5/42 (12)
TC	51/82 (62)	25/37 (68)	179/288 (62)	27/42 (64)
TT	21/82 (26)	7/37 (19)	65/288 (23)	10/42 (24)
Negative	–	–	1/288 (<1)	–
Median duration of infection, years	21.0	17.0	21.0	8.0
Patients with type 2 diabetes, n (%)	24 (16.1)	10 (17.2)	68 (12.7)	1 (1.8
Response to prior treatment, n (%)				
Relapse	44 (30)	19 (33)	177 (33)	27 (48)
Breakthrough	5 (3)	3 (5)	37 (7)	2 (4)
Non-response	82 (55)	28 (48)	248 (47)	17 (30)
Other	17 (11)	7 (12)	68 (13)	10 (18)
Missing	1 (1)	1 (2)	6 (1)	1 (2)

IL28B rs12979860 genotype was known for 257 treatment-naïve patients and 449 treatment-experienced patients; percentages are calculated from those with available data. One treatment-experienced patient was negative for rs12979860
HCV, hepatitis C virus; PegIFN, peginterferon; RBV, ribavirin; SD, standard deviation

patients with low baseline HCV RNA levels (≤400,000 IU/mL), although this was not the case in the small number of patients with low HCV RNA levels assigned to boceprevir plus peginterferon alfa-2a/ribavirin (n=32; Table 6).

VR in previously treated patients receiving triple therapy

SVR12 rates were generally lower in previously treated patients than in treatment-naïve patients assigned to the same treatment group (Tables 5, 6). Among previously treated patients assigned to triple therapy, SVR12 rates were 43.6% and 48.3% for patients who received boceprevir plus peginterferon alfa-2a/ribavirin and peginterferon alfa-2b/ribavirin, respectively and 60.3% and 56.1% for patients who received telaprevir plus peginterferon alfa-2a/ribavirin and peginterferon alfa-2b/ribavirin, respectively (Fig. 2C). Corresponding relapse rates in these four treatment groups were 28.1%, 22.2%, 12.6% and 8.6%, respectively, among patients evaluable for relapse (Fig. 2D), whilst breakthrough or rebound occurred in 9.2%, 17.0%, 18.7% and 20.8%, respectively, of patients evaluable for breakthrough or rebound (Table 5).

Consistently with trends observed in treatment-naïve patients, SVR12 rates were generally higher among previously treated patients who were non-cirrhotic compared to those who were cirrhotic, and among those with low baseline HCV RNA levels (Table 6). SVR12 rates tended to be higher in patients with CC than in those with non-CC genotypes, although the number of patients with CC genotypes was very small among previously treated patients (i.e., 3 of 4 groups had ≤10 patients) and the trend was not observed consistently in all treatment groups.

SVR12 rates were generally, but not exclusively, higher in patients with a prior relapse than among those with a prior breakthrough or non-response (Table 6). When all four triple therapy groups were combined, the overall response rates in patients with a prior relapse, breakthrough or non-response were 73.8% (197/267), 55.3% (26/47) and 44.3% (166/375), respectively.

Safety in patients receiving triple therapy

Across the four triple-therapy treatment groups, the overall incidence of AEs ranged from 76.7% to 90.7% and the overall incidence of SAEs ranged from 4.7% to 19.9% (Table 7). The spectrum and frequency of individual AEs was similar to that reported previously, with anemia being the most frequently reported AE. Safety-related dose modifications were required

Table 2 Baseline patient and disease characteristics of patients assigned to dual therapy

Characteristic	PegIFN alfa-2a/RBV	PegIFN alfa-2b/RBV
Treatment-naïve	N=1964	N=414
Female, n (%)	773 (39)	210 (51)
Race, n (%)		
Caucasian/white	1709 (87)	370 (89)
Black	29 (1)	2 (<1)
Asian/Oriental	222 (11)	42 (10)
Other	4 (<1)	–
Mean age, years (SD)	46.7 (13.0)	49.1 (12.8)
Genotype, n (%)		
1	815 (41.5)	198 (47.8)
2	268 (13.6)	78 (18.8)
3	528 (26.9)	91 (22.0)
4	340 (17.3)	45 (10.9)
5	5 (0.3)	1 (0.2)
6	8 (0.4)	1 (0.2)
Mean body mass index, kg/m^2 (SD)	26.4 (4.5)	25.6 (4.7)
Mean HCV RNA, log_{10} IU/mL (SD)	5.8 (0.9)	5.8 (0.9)
HCV RNA >400,000 IU/mL, n (%)	1305 (66.5)	275 (66.4)
Method of assessing liver fibrosis, n/N (%)		
Biopsy	442/1963 (23)	84/414 (20)
Noninvasive	1152/1963 (59)	250/414 (60)
Not assessed or best guess	369/1963 (19)	80/414 (19)
Liver fibrosis status, n/N (%)		
Cirrhosis	234/1963 (12)	47/414 (11)
Transition to cirrhosis	265/1963 (13)	55/414 (13)
No cirrhosis	1464/1963 (75)	312/414 (75)
IL28B rs12979860 host genotype, n/N (%)[a]		
CC	468/1243 (38)	81/246 (33)
TC	617/1243 (50)	126/246 (51)
TT	157/1243 (13)	39/246 (16)
Median duration of infection, years	12.0	13.0
Patients with type 2 diabetes, n (%)	179 (9.1)	43 (10.4)

(*Contd...*)

Table 2 (*Continued*)

Treatment-naïve	PegIFN alfa-2a/RBV	PegIFN alfa-2b/RBV
Previously treated	N=348	N=82
Female, n (%)	137 (39)	40 (49)
Race, n (%)		
Caucasian/white	313 (90)	73 (89)
Black	4 (1)	2 (2)
Asian/Oriental	30 (9)	7 (9)
Other	1 (<1)	–
Mean age, years (SD)	51.6 (11.0)	54.6 (10.6)
Genotype, n (%)		
1	173 (49.7)	46 (56.1)
Non-1	175 (50.3)	36 (43.9)
Mean body mass index, kg/m^2 (SD)	26.5 (4.6)	27.0 (4.5)
Mean HCV RNA, log_{10} IU/mL (SD)	5.9 (0.8)	5.9 (0.7)
HCV RNA >400,000 IU/mL, n (%)	251 (72.1)	60 (73.2)
Method of assessing liver fibrosis, n (%)		
Biopsy	34 (10)	6 (7)
Noninvasive	221 (64)	60 (73)
Not assessed or best guess	93 (27)	16 (20)
Liver fibrosis status, n (%)		
Cirrhosis	76 (22)	15 (18)
Transition to cirrhosis	64 (18)	15 (18)
No cirrhosis	208 (60)	52 (63)
IL28B rs12979860 host genotype, n (%)*		
CC	69/219 (32)	16/51 (31)
TC	117/219 (53)	25/51 (49)
TT	33/219 (15)	10/51 (20)
Median duration of infection, years	17.0	15.0
Patients with type 2 diabetes, n (%)	41 (11.8)	13 (15.9)

*One patient assigned to peginterferon alfa-2a plus ribavirin was negative for rs12979860

HCV, hepatitis C virus; PegIFN, peginterferon; RBV, ribavirin; SD, standard deviation

more frequently for ribavirin (range 36.0% to 46.4%) than for peginterferon alfa (range 10.5% to 19.4%) across the four treatment groups. Anemia was the most frequently cited reason for ribavirin dose modifications, whilst neutropenia

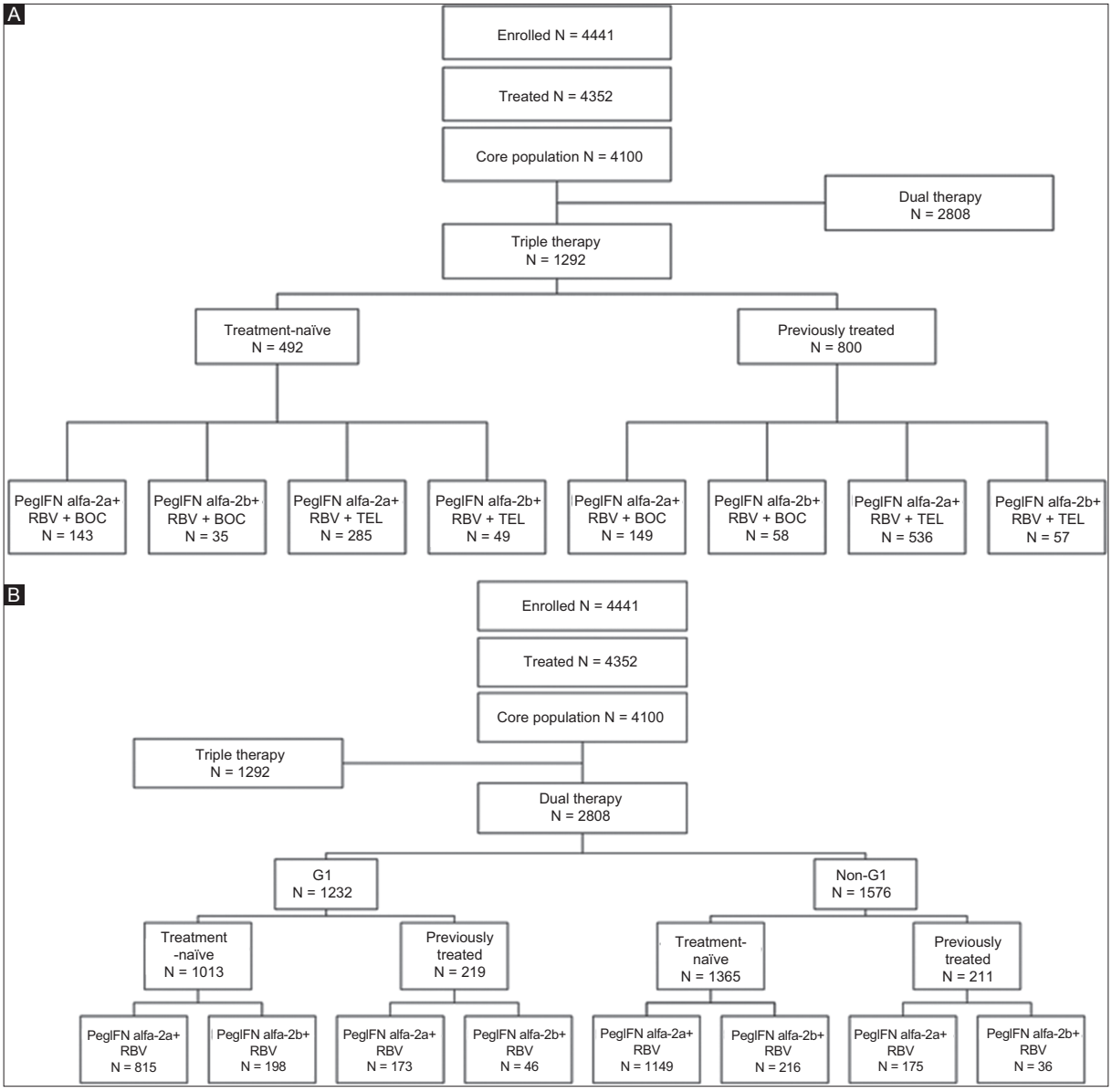

Figure 1 Disposition of treatment-naïve and previously treated patients with chronic hepatitis C who were enrolled and treated with boceprevir (BOC)- or telaprevir (TEL)-based triple therapy or dual peginterferon (PegIFN) alfa-2a or alfa-2b plus ribavirin (RBV). (A) Patients assigned to BOC- or TEL-based triple therapy. (B) Patients assigned to dual PegIFN alfa-2a or alfa-2b plus ribavirin therapy

was the most frequently cited reason for peginterferon alfa dose modifications (Table 7). Approximately 40% of patients in each treatment group experienced a hemoglobin level <100 g/dL during therapy and approximately 40% to 50% of patients experienced a platelet level $<100 \times 10^9$/L at some point during treatment (Table 7). Hepatic failure was rare, being reported as an SAE in two patients assigned to telaprevir plus peginterferon alfa-2a/ribavirin and as a non-serious AE in two additional patients (one assigned to boceprevir plus peginterferon alfa-2a/ribavirin, and one assigned to telaprevir plus peginterferon alfa-2a/ribavirin). Infections were reported as SAEs in 11 of 385 (2.9%) patients assigned to boceprevir-based triple therapy and in 34 of 907 (3.7%) patients assigned to telaprevir-based triple therapy. A total of 11 patients assigned to boceprevir- or telaprevir-based triple therapy died during the study; seven of the deaths were unrelated to CHC or treatment. Two deaths were considered to be related to CHC and to the study drug in the opinion of the investigator; both patients had been assigned to telaprevir plus peginterferon alfa-2a (one death was attributed to esophageal variceal hemorrhage and the other to hepatic failure). Two additional deaths from liver cancer, both in patients assigned to telaprevir plus peginterferon alfa-2a, were considered to be related to CHC, but not to the study drug.

Table 3 Patient disposition

Patient disposition, n (%)	Boceprevir plus PegIFN alfa-2a/RBV	Boceprevir plus PegIFN alfa-2b/RBV	Telaprevir plus PegIFN alfa-2a/RBV	Telaprevir plus PegIFN alfa-2b/RBV	PegIFN alfa-2a/RBV	PegIFN alfa-2b/RBV
Treatment-naïve						
HCV genotype 1	**N=143**	**N=35**	**N=285**	**N=29**	**N=815**	**N=198**
Completed 12-week treatment	130 (90.9)	34 (97.1)	259 (90.9)	26 (89.7)	776 (95.2)	178 (89.9)
Completed 24-week follow up	97 (67.8)	24 (68.6)	215 (75.4)	19 (65.5)	556 (68.2)	121 (61.1)
HCV genotype non-1	–	–	–	–	**N=1149**	**N=216**
Completed 12-week treatment					1089 (94.8)	202 (93.5)
Completed 24-week follow up					834 (72.6)	173 (80.1)
Previously treated	**N=149**	**N=58**	**N=536**	**N=57**	**N=348**	**N=82**
Completed 12-week treatment	135 (90.6)	50 (86.2)	481 (89.7)	50 (87.7)	315 (90.5)	75 (91.5)
Completed 24-week follow up	95 (63.8)	36 (62.1)	395 (73.7)	35 (61.4)	200 (57.5)	37 (45.1)

PegIFN, peginterferon; RBV, ribavirin

Table 4 Reasons for withdrawal from treatment with peginterferon

Reason for withdrawal, n (%)	Boceprevir plus PegIFN alfa-2a/RBV	Boceprevir plus PegIFN alfa-2b/RBV	Telaprevir plus PegIFN alfa-2a/RBV	Telaprevir plus PegIFN alfa-2b/RBV	PegIFN alfa-2a/RBV	PegIFN alfa-2b/RBV
Treatment-naïve	**N=143**	**N=35**	**N=285**	**N=29**	**N=1964**	**N=414**
Adverse event	20 (14.0)	1 (2.9)	40 (14.0)	3 (10.3)	111 (5.7)	37 (8.9)
Insufficient response	14 (9.8)	4 (11.4)	10 (3.5)	4 (13.8)	196 (10.0)	53 (12.8)
Good response	5 (3.5)	1 (2.9)	12 (4.2)	1 (3.4)	59 (3.0)	14 (3.4)
Refused treatment, withdrew consent, or did not cooperate	5 (3.5)	2 (5.7)	17 (6.0)	4 (13.8)	102 (5.2)	20 (4.8)
Failure to return	7 (4.9)	0 (0)	6 (2.1)	1 (3.4)	92 (4.7)	16 (3.9)
Administrative or other reason	1 (0.7)	0 (0)	2 (0.7)	0 (0)	11 (0.6)	4 (1.0)
Death	0 (0)	0 (0)	0 (0)	0 (0)	1 (<0.1)	1 (0.2)
Previously treated	**N=149**	**N=58**	**N=536**	**N=57**	**N=348**	**N=82**
Adverse event	17 (11.4)	8 (13.8)	48 (9.0)	5 (8.8)	34 (9.8)	6 (7.3)
Insufficient response	36 (24.2)	12 (20.7)	85 (15.9)	6 (10.5)	76 (21.8)	23 (28.0)
Good response	1 (0.7)	1 (1.7)	24 (4.5)	4 (7.0)	4 (1.1)	0 (0)
Refused treatment, withdrew consent, or did not cooperate	2 (1.3)	3 (5.2)	21 (3.9)	2 (3.5)	22 (6.3)	3 (3.7)
Failure to return	4 (2.7)	1 (1.7)	13 (2.4)	5 (8.8)	15 (4.3)	3 (3.7)
Administrative or other reason	1 (0.7)	1 (1.7)	11 (2.1)	0 (0)	2 (0.6)	2 (2.4)
Death	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)

PegIFN, peginterferon; RBV, ribavirin

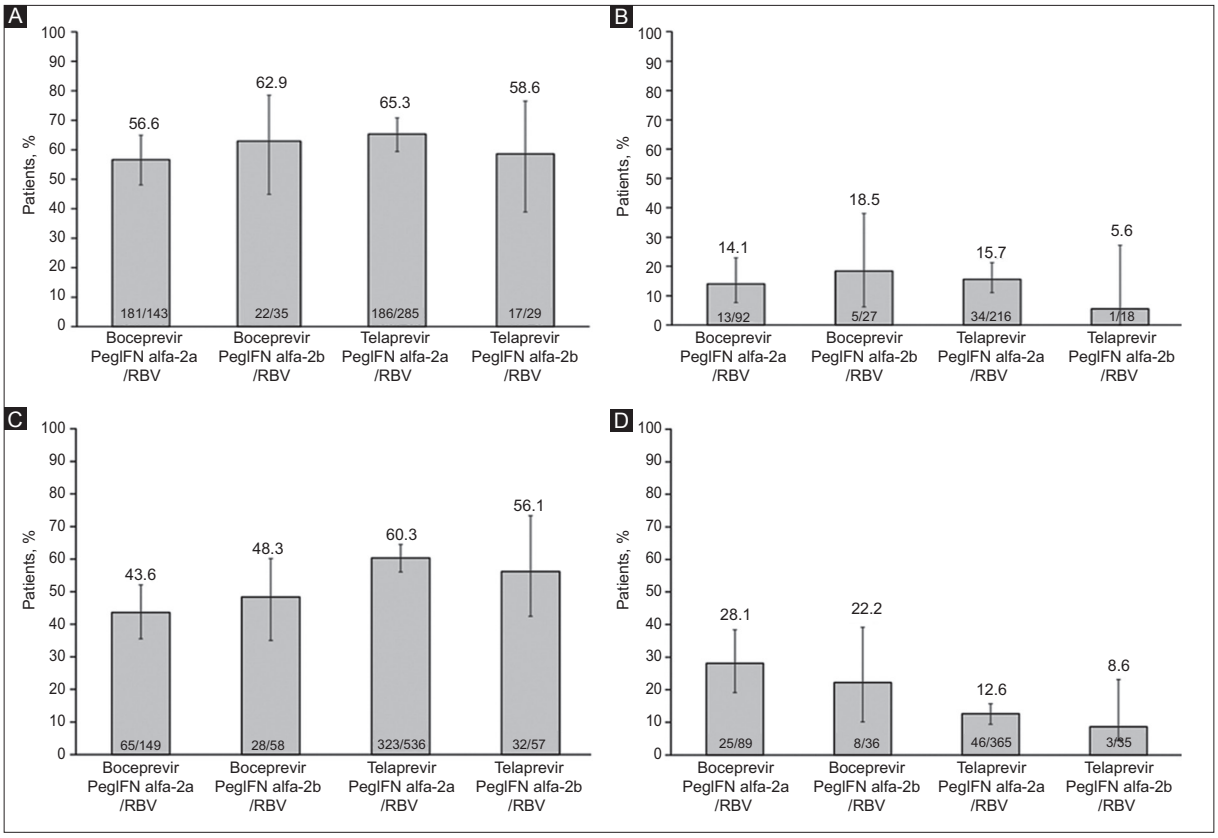

Figure 2 SVR12 and relapse rates for patients receiving boceprevir- and telaprevir-based triple therapy. (A) SVR12 rates in treatment- naïve patients including 95% confidence intervals. (B) Relapse rates in treatment-naïve patients including 95% confidence intervals. (C) SVR12 rates in previously treated patients including 95% confidence intervals. (D) Relapse rates in previously treated patients including 95% confidence intervals
PegIFN, peginterferon; RBV, ribavirin; SVR12, sustained virological response 12 weeks after the end of treatment

VR and safety in patients receiving dual therapy

Among treatment-naïve patients assigned to dual therapy with peginterferon alfa-2a/ribavirin and peginterferon alfa-2b/ribavirin, SVR12 rates were 49.2% and 41.9%, respectively, in patients with G1 infection, 75.7% and 83.3% in patients with G2 infection, 65.9% and 65.9% in patients with G3 infection, and 49.7% and 51.1% in patients with G4 infection (Table 8). SVR12 rates are shown by HCV genotype and baseline characteristic in Table 9.

Among previously treated patients assigned to dual therapy with peginterferon alfa-2a/ribavirin and peginterferon alfa-2b/ribavirin, overall SVR12 rates were 35.6% (124/348) and 25.6% (21/82), respectively.

The overall safety profile of dual therapy is presented in Table 10. Among patients assigned to peginterferon alfa-2a/ribavirin and peginterferon alfa-2b/ribavirin, the incidence of AEs was 60.3% and 65.7% respectively, and the incidence of SAEs was 6.4% and 6.7%, respectively. The most commonly reported AE was anemia (in 19.7% and 28.6% of patients, respectively). Safety-related dosage modifications were required more frequently for ribavirin than for the peginterferon alfa component of the respective regimens and the most frequently cited reason for ribavirin dose reductions was anemia (in 13.6% and 20.4% of patients assigned to peginterferon alfa-2a/ribavirin and peginterferon alfa-2b/ribavirin, respectively) (Table 10).

Hepatic failure was reported as an SAE in three patients (two recipients of peginterferon alfa-2a and 1 recipient of peginterferon alfa-2b). Infections were reported as SAEs in 35 of 2312 (1.5%) patients assigned peginterferon alfa-2a plus ribavirin and in 8 of 496 (1.6%) patients assigned to peginterferon alfa-2b plus ribavirin. A total of nine patients assigned to dual therapy died, including 6 deaths in patients treated with peginterferon alfa-2a/ribavirin and 3 deaths in patients treated with peginterferon alfa-2b/ribavirin. All were unrelated to treatment in the opinion of the investigator, two were considered to be related to CHC (septic shock in a patient treated with peginterferon alfa-2a/ribavirin, and gastrointestinal hemorrhage in a patient treated with peginterferon alfa-2b/ribavirin), and for two patients no assessment of the relationship to CHC was provided.

Discussion

With the advent of second-generation DAAs, telaprevir and boceprevir have been withdrawn from the US market and PI-based triple therapy and dual peginterferon alfa/

Table 5 Virological response (VR), relapse and breakthrough rates – triple therapy

Event	Response rate N, (%; 95% CI)			
	Boceprevir plus PegIFN alfa-2a/RBV	Boceprevir plus PegIFN alfa-2b/RBV	Telaprevir plus PegIFN alfa-2a/RBV	Telaprevir plus PegIFN alfa-2b/RBV
Treatment-naïve	**N=143**	**N=35**	**N=285**	**N=29**
eRVR	67 (46.9; 38.5-55.4)	15 (42.9; 26.3-60.6)	122 (42.8; 37.0-48.8)	11 (37.9; 20.7-57.7)
EoT VR	103 (72.0; 63.9-79.2)	29 (82.9; 66.4-93.4)	228 (80.0; 74.9-840.5)	19 (65.5; 45.7-82.1)
SVR12	81 (56.6; 48.1-64.9)	22 (62.9; 44.9-78.5)	186 (65.3; 59.4-70.8)	17 (58.6; 38.9-76.5)
SVR24	75 (52.4; 43.9-60.9)	20 (57.1; 39.4-73.7)	169 (59.3; 53.3-65.1)	15 (51.7; 32.5-70.6)
Relapse	13/92 (14.1; 7.7-23.0)	5/27 (18.5; 6.3-38.1)	34/216 (15.7; 11.2-21.3)	1/18 (5.6; 0.1-27.3)
Breakthrough/rebound	11/134 (8.2; 4.2-14.2)	5/35 (14.3; 4.8-30.3)	22/272 (8.1; 5.1-12.0)	6/26 (23.1; 9.0-43.6)
Previously treated	**N=149**	**N=58**	**N=536**	**N=57**
eRVR*	43 (28.9; 21.7-36.8)	15 (25.9; 15.3-39.0)	252 (47.0; 42.7-51.3)	30 (52.6; 39.0-66.0)
EoT VR	93 (62.4; 54.1-70.2)	38 (65.5; 51.9-77.5)	387 (72.2; 68.2-76.0)	38 (66.7; 52.9-78.6)
SVR12	65 (43.6; 35.5-52.0)	28 (48.3; 35.0-61.8)	323 (60.3; 56.0-64.4)	32 (56.1; 42.4-69.3)
SVR24	61 (40.9; 33.0-49.3)	27 (46.6; 33.3-60.1)	305 (56.9; 52.6-61.1)	26 (45.6; 32.4-59.3)
Relapse	25/89 (28.1; 19.1-38.6)	8/36 (22.2; 10.1-39.2)	46/365 (12.6; 9.4-16.5)	3/35 (8.6; 1.8-23.1)
Breakthrough/rebound	13/141 (9.2; 5.0-15.3)	9/53 (17.0; 8.1-29.8)	96/513 (18.7; 15.4-22.4)	10/48 (20.8; 10.5-35.0)

VR was defined as undetectable HCV RNA as assessed by a test with lower limit of detection ≤50 IU/mL, *eRVR was defined differently for patients receiving telaprevir (VR at weeks 4 and 12) and boceprevir (VR at weeks 8 and 24), Relapse was defined as non-response at the last HCV RNA assessment during the treatment-free follow-up period in patients with an EoT response. Patients were included in the calculation of relapse if they had an EoT response and an available HCV RNA measurement for SVR12 or an earlier follow-up assessment showing non-response during the treatment-free follow-up period (i.e., patients lost to follow up after EoT were not included in the calculation of relapse), Breakthrough/rebound was defined as non-response during the treatment period in patients with a previous response or increase in HCV RNA by ≥1 log10 during the treatment period versus the lowest value previously recorded during the treatment period. Patients were included in the calculation of breakthrough/rebound if they had ≥2 HCV RNA measurements during treatment (which could include imputation of EoT response)

CI, confidence interval; EoT, end of treatment; eRVR, extended rapid virological response; PegIFN, peginterferon; RBV, ribavirin; SVR12, sustained virological response at least 12 weeks after the end of treatment (≥70 days after day of last dose); SVR24, sustained virological response at least 24 weeks after end of treatment (≥140 days after day of last dose)

ribavirin therapy are no longer recommended in treatment guidelines as a preferred treatment for patients infected with HCV G1 [10-12]. However, availability and cost restrictions mean that peginterferon-based regimens may continue in some countries, as is explicitly recognized by the European and Asian guidelines [11,12]. It therefore remains important to understand the efficacy and safety of peginterferon-based regimens in real-world settings, and the PegBase observational study provides data to this end.

The efficacy of first-generation PI-based triple therapy in PegBase was somewhat lower than that reported in phase III studies. The range of SVR12 rates achieved in treatment-naïve patients with boceprevir-based triple therapy in the PegBase study (57-63%) overlaps with that obtained in the phase III trial (SPRINT-2, 63-66%) [7]. SVR12 rates achieved with telaprevir-based triple therapy in PegBase (59-65%) are below those observed with the approved regimen in ADVANCE (75%) [6] and ILLUMINATE (72%) [14]. These results are likely to be a reflection of differences between the highly restrictive criteria used to select patients for registration studies, the heterogeneous characteristics of patients encountered in routine clinical practice, and differences in the extent of monitoring and follow up between registration trials and real-world studies. For example, a higher proportion of patients with fibrosis assessments had transition to cirrhosis or had cirrhosis in PegBase (>30%) than in phase III trials of boceprevir (7-9%) or telaprevir (20%).

Likewise, in previously treated patients, overall SVR12 rates in PegBase were 44-48% in patients assigned to boceprevir-based triple therapy, compared with 59-66% in RESPOND-2 [8], 56-60% in patients assigned to telaprevir-based triple therapy and 64% with the approved regimen in REALIZE [9]. Responses in previously treated patients are largely a reflection of the type of prior therapy, for example, interferon monotherapy or combination therapy with ribavirin, and the nature of the prior response to interferon-based therapy, with generally higher SVR rates in relapsers than in non-responders [15-17]. In RESPOND-2, approximately two-thirds of patients had a prior relapse and approximately one-third of patients had a prior non-response to peginterferon-based therapy [8]. Likewise, more than half of the patients in REALIZE (53%) had a previous relapse and 28% had a previous non-response to peginterferon-based therapy [9]. In contrast, almost half of the previously treated patients enrolled in the present study were prior non-responders, while only one-third of them had experienced a prior relapse. In addition, some previously treated patients had received conventional interferon monotherapy or peginterferon monotherapy. Thus, differences in response rates between

Table 6 Subgroup analysis by baseline characteristics of SVR12 in HCV G1 patients receiving triple therapy

Baseline characteristic	Patients with SVR12, N (%)			
	Boceprevir plus PegIFN alfa-2a/RBV	Boceprevir plus PegIFN alfa-2b/RBV	Telaprevir plus PegIFN alfa-2a/RBV	Telaprevir plus PegIFN alfa-2b/RBV
Treatment-naïve	**N=143**	**N=35**	**N=285**	**N=29**
Overall	81 (56.6)	22 (62.9)	186 (65.3)	17 (58.6)
Fibrosis status				
Cirrhosis	24/55 (43.6)	6/12 (50.0)	53/98 (54.1)	10/18 (55.6)
No cirrhosis	57/88 (64.8)	16/23 (69.6)	133/187 (71.1)	7/11 (63.6)
IL28B rs12979860 host genotype*				
CC	18/25 (72.0)	4/5 (80.0)	26/29 (89.7)	2/3 (66.7)
CT	22/39 (56.4)	6/8 (75.0)	51/82 (62.2)	7/12 (58.3)
TT	10/16 (62.5)	0/2 (0.0)	22/32 (68.8)	1/4 (25.0)
Unknown	31/63 (49.2)	12/20 (60.0)	87/142 (61.3)	7/10 (70.0)
HCV RNA, IU/mL				
≤400,000	15/32 (46.9)	6/7 (85.7)	51/73 (69.9)	6/9 (66.7)
>400,000	66/111 (59.5)	15/27 (55.6)	135/212 (63.7)	11/20 (55.0)
Missing	–	1/1 (100)	–	–
Previously treated	**N=149**	**N=58**	**N=536**	**N=57**
Overall	65 (43.6)	28 (48.3)	323 (60.3)	32 (56.1)
Fibrosis status				
Cirrhosis	27/83 (32.5)	12/29 (41.4)	124/243 (51.0)	14/25 (56.0)
No cirrhosis	38/66 (57.6)	16/29 (55.2)	199/293 (67.9)	18/32 (56.3)
IL28B rs12979860 host genotype*				
CC	4/10 (40.0)	4/5 (80.0)	33/43 (76.7)	3/5 (60.0)
CT	24/51 (47.1)	11/25 (44.0)	102/179 (57.0)	15/27 (55.6)
TT	7/21 (33.3)	4/7 (57.1)	36/65 (55.4)	4/10 (40.0)
Unknown	30/67 (44.8)	9/21 (42.9)	151/248 (60.9)	10/15 (66.7)
HCV RNA, IU/mL				
≤400,000	19/36 (52.8)	8/14 (57.1)	85/117 (72.6)	12/16 (75.0)
>400,000	46/113 (40.7)	20/44 (45.5)	236/417 (56.6)	20/41 (48.8)
Missing	–	–	2/2 (100.0)	–
Prior response, n (%)				
Relapse	30/44 (68.2)	13/19 (68.4)	140/177 (79.1)	14/27 (51.9)
Breakthrough	1/5 (20.0)	2/3 (66.7)	22/37 (59.5)	1/2 (50.0)
Non-response	29/82 (35.4)	9/28 (32.1)	117/248 (47.2)	11/17 (64.7)
Other	4/17 (23.5)	3/7 (42.9)	39/68 (57.4)	6/10 (60.0)
Prior response unknown	1/1 (100)	1/1 (100)	5/6 (83.3)	0/1 (0)

SVR12 = percentage of patients with undetectable HCV RNA (to a test with lower limit of detection ≤50 IU/mL) at 12 weeks after completion of the treatment period (at least 70 days after day of last treatment), *Host genotype was unknown in 235 treatment-naïve patients and 351 Previously treated patients. One previously treated patient was negative for rs12979860

HCV, hepatitis C virus; PegIFN, peginterferon; RBV, ribavirin; SVR, sustained virological response

PegBase and phase III studies reflect not only differences in baseline characteristics, but also differences in the proportion of patients with prior relapse or non-response and in the intensity of the previous treatment regimen.

Predictors of good VR include absence of cirrhosis, homozygosity for the *IL28B* rs12979860 C allele and low viral load [18]. In the PegBase study, patients without transition to cirrhosis or cirrhosis had better virological outcomes than

Table 7 Safety outcomes in patients with HCV genotype 1 mono-infection receiving triple therapy (includes treatment-naïve and-previously treated patients)

Event	Boceprevir plus PegIFN alfa-2a/RBV	Boceprevir plus PegIFN alfa-2b/RBV	Telaprevir plus PegIFN alfa-2a/RBV	Telaprevir plus PegIFN alfa-2b/RBV
	N=292	N=93	N=821	N=86
Patients with ≥1 AE, n (%)	224 (76.7)	82 (88.2)	745 (90.7)	75 (87.2)
Patients with ≥1 SAE, n (%)	43 (14.7)	9 (9.7)	163 (19.9)	4 (4.7)
Death	2 (0.7)	1 (1.1)	8 (1.0)	0
Incidence of individual AEs*, n (%)				
Anemia, n (%)	120 (41.1)	45 (48.4)	398 (48.5)	44 (51.2)
Neutropenia	39 (13.4)	25 (26.9)	86 (10.5)	24 (27.9)
Asthenia	53 (18.2)	23 (24.7)	246 (30.0)	9 (10.5)
Pruritus	37 (12.7)	16 (17.2)	240 (29.2)	10 (11.6)
Thrombocytopenia	33 (11.3)	6 (6.5)	98 (11.9)	23 (26.7)
Leukopenia	10 (3.4)	6 (6.5)	60 (7.3)	31 (36.0)
Nausea	36 (12.3)	24 (25.8)	135 (16.4)	11 (12.8)
Fatigue	68 (23.3)	23 (24.7)	172 (21.0)	13 (15.1)
Rash	26 (8.9)	9 (9.7)	161 (19.6)	10 (11.6)
Influenza-like illness	31 (10.6)	17 (18.3)	97 (11.8)	7 (8.1)
Decreased appetite	25 (8.6)	16 (17.2)	118 (14.4)	8 (9.3)
Headache	33 (11.3)	15 (16.1)	94 (11.4)	5 (5.8)
Dysgeusia	33 (11.3)	14 (15.1)	40 (4.9)	1 (1.2)
Hemoglobin increased	1 (0.3)	0	16 (1.9)	13 (15.1)
Insomnia	18 (6.2)	7 (7.5)	100 (12.2)	4 (4.7)
Diarrhea	17 (5.8)	11 (11.8)	79 (9.6)	5 (5.8)
Pyrexia	14 (4.8)	11 (11.8)	36 (4.4)	4 (4.7)
Alopecia	14 (4.8)	10 (10.8)	51 (6.2)	2 (2.3)
Cough	23 (7.9)	10 (10.8)	72 (8.8)	1 (1.2)
Dry skin	22 (7.5)	10 (10.8)	66 (8.0)	3 (3.5)
Peginterferon dose modification‡, n (%)	49 (16.8)	18 (19.4)	104 (12.7)	9 (10.5)
Neutropenia	31 (10.6)	10 (10.8)	24 (2.9)	5 (5.8)
Thrombocytopenia	9 (3.1)	1 (1.1)	37 (4.5)	3 (3.5)
Anemia	3 (1.0)	2 (2.2)	14 (1.7)	0
Other	8 (2.7)	7 (7.5)	36 (4.4)	1 (1.2)
Ribavirin dose modification‡, n (%)	125 (42.8)	40 (43.0)	381 (46.4)	31 (36.0)
Anemia	115 (39.4)	37 (39.8)	336 (40.9)	29 (33.7)
Other	14 (4.8)	8 (8.6)	75 (9.1)	2 (2.3)
Laboratory abnormalities, lowest value after BL, n (%)				
Hemoglobin <100 g/L	121 (41.6)	36 (39.1)	357 (43.8)	36 (43.4)
Platelets <100 × 10^9/L	145 (50.0)	42 (45.7)	400 (49.1)	31 (37.3)
Neutrophils <2.0 × 10^9/L	262 (90.7)	85 (92.4)	707 (87.4)	60 (73.2)

*Incidence ≥10% in at least one of the treatment groups, †Total number of deaths regardless of relation to treatment in the opinion of the investigator, ‡Because of adverse event or laboratory abnormality

AE, adverse event; BL, baseline; HCV, hepatitis C virus; PegIFN, peginterferon; RBV, ribavirin; SAE, serious adverse event

Table 8 Rates of virological response (VR) and relapse in treatment-naïve patients receiving dual therapy

Event	Response rate, n, (%; 95% CI)							
	Peginterferon alfa-2a plus ribavirin				Peginterferon alfa-2b plus ribavirin			
	G1 N=815	G2 N=268	G3 N=528	G4 N=340	G1 N=198	G2 N=78	G3 N=91	G4 N=45
VR by week 4	192 (23.6; 20.7-26.6)	210 (78.4; 72.9-83.1)	330 (62.5; 58.2-66.6)	93 (27.4; 22.7-32.4)	50 (25.3; 19.4-31.9)	59 (75.6; 64.6-84.7)	52 (57.1; 46.3-67.5)	12 (26.7; 14.6-41.9)
VR by week 12	495 (60.7; 57.3-64.1)	247 (92.2; 88.3-95.1)	463 (87.7; 84.6-90.4)	238 (70.0; 64.8-74.8)	110 (55.6; 48.3-62.6)	72 (92.3; 84.0-97.1)	72 (79.1; 69.3-86.9)	32 (71.1; 55.7-83.6)
EoT VR	551 (67.6; 64.3-70.8)	239 (89.2; 84.8-92.6)	461 (87.3; 84.2-90.0)	232 (68.2; 63.0-73.2)	122 (61.6; 54.5-68.4)	74 (94.9; 87.4-98.6)	76 (83.5; 74.3-90.5)	28 (62.2; 46.5-76.2)
SVR12	401 (49.2; 45.7-52.7)	203 (75.7; 70.2-80.8)	348 (65.9; 61.7-69.9)	169 (49.7; 44.3-55.2)	83 (41.9; 35.0-49.1)	65 (83.3; 73.2-90.8)	60 (65.9; 55.3-75.5)	23 (51.1; 35.8-66.3)
SVR24	386 (47.4; 43.9-50.9)	200 (74.6; 69.0-79.7)	335 (63.4; 59.2-67.6)	158 (46.5; 41.1-51.9)	78 (39.4; 32.5-46.6)	64 (82.1; 71.7-89.8)	58 (63.7; 53.0-73.6)	23 (51.1; 35.8-66.3)
Relapse	106/502 (21.1; 17.6-25.0)	25/227 (11.0; 7.3-15.8)	59/400 (14.8; 11.4-18.6)	25/193 (13.0; 8.6-18.5)	30/112 (26.8; 18.9-36.0)	8/73 (11.0; 4.9-20.5)	9/69 (13.0; 6.1-23.3)	2/25 (8.0; 1.0-26.0)

VR was defined as HCV RNA <50 IU/mL, Relapse was defined as last HCV RNA showing non-response during the treatment-free follow-up period in patients with an EoT response. Patients were included in the calculation of relapse if they had an EoT response and an available HCV RNA measurement for SVR12 or an earlier follow-up assessment showing non-response during the treatment-free follow-up period (i.e., patients lost to follow up after EoT were not included in the calculation of relapse)

CI, confidence interval; EoT, end of treatment; HCV, hepatitis C virus; SVR, sustained virological response; VR, virological response

patients with transition to cirrhosis or cirrhosis, and higher response rates were seen in patients homozygous for the *IL28B* rs12979860 C allele than in patients heterozygous for the C and T alleles or in patients homozygous for the T allele. There was little difference in treatment response between treatment-naïve patients with high or low viral loads; however, previously treated patients with low viral loads responded better than those with high viral loads.

The spectrum of AEs observed in PegBase is consistent with that reported in phase III studies of boceprevir- and telaprevir-based triple therapy [6-9]. The lower incidence of certain AEs, such as rash, in PegBase (approximately 16%) than in phase III trials (>30%) is possibly a reflection of closer patient monitoring in registration studies.

The efficacy of first-generation PI-based triple therapy in PegBase is consistent with other "real-world" studies in that they also report lower SVR rates than those in registration studies [19-22]. For example, in the German PAN cohort study [23], SVR12 rates of 55% (boceprevir) and 63% (telaprevir) were obtained in treatment-naïve patients and 51% (boceprevir) and 68% (telaprevir) in previously treated patients. The Kaiser Permanente Medical Care Program in Northern California reported SVR rates of 53% and 56% with boceprevir- and telaprevir-based triple therapy [21]. SVR rates were also lower in previously treated patients with cirrhosis who received first-generation triple therapy in the French CUPIC study [20]. The CUPIC study is noteworthy in that it reported comparatively high rates of SAEs (50%) and hepatic decompensation (8%), and deaths were associated with severe infections, perhaps as a result of the inclusion of patients with contraindications for the triple-therapy regimens. The lower rates of SAEs, hepatic failure and the absence of a link between serious infection and deaths in PegBase suggests that contraindications were observed when selecting patients for PegBase.

The efficacy and safety profile of dual peginterferon alfa/ribavirin therapy in PegBase is similar to that reported in previous randomized controlled studies and in other large real-world studies [24-27]. The place of dual therapy in the treatment of CHC has continued to diminish since the PegBase study was initiated. In particular, dual therapy is no longer suitable in patients with access to DAAs, because of the lower efficacy and longer duration of treatment [10-12].

No firm conclusions can be drawn regarding the comparative efficacy or safety of boceprevir and telaprevir or of peginterferon alfa-2a and peginterferon alfa-2b on the basis of this study, as patients were not randomized and between-group differences may be due to selection bias. Moreover, the dose and duration of treatment were left to the discretion of the investigators. Patient assessments were performed in local laboratories, which means that certain baseline characteristics, for example, *IL28B* genotype, were not known for all patients, and that the sensitivity of assays used to determine SVR varied between sites.

In conclusion, the overall efficacy of first-generation PI-based triple-therapy regimens in this real-world study was similar to that reported in other non-interventional studies and somewhat

Table 9 Sustained virological response at 12 weeks after the end of treatment in treatment-naïve patients with HCV mono-infection receiving dual therapy by baseline characteristics

Baseline characteristic	Percentage of patients with SVR12 n/N (%)							
	Genotype 1		Genotype 2		Genotype 3		Genotype 4	
	PegIFN alfa-2a/ RBV	PegIFN alfa-2b/RBV	PegIFN alfa-2a/ RBV	PegIFN alfa-2b/RBV	PegIFN alfa-2a/ RBV	PegIFN alfa-2b/ RBV	PegIFN alfa-2a/ RBV	PegIFN alfa-2b/ RBV
Fibrosis status								
Cirrhosis	76/219 (34.7)	20/52 (38.5)	30/47 (63.8)	14/19 (73.7)	77/146 (52.7)	8/20 (40.0)	33/83 (39.8)	4/11 (36.4)
No cirrhosis	325/595 (54.6)	63/146 (43.2)	173/221 (78.3)	51/59 (86.4)	271/382 (70.9)	52/71 (73.2)	136/257 (52.9)	19/34 (55.9)
IL28B rs12979860 host genotype								
CC	135/200 (67.5)	22/35 (62.9)	64/75 (85.3)	16/19 (84.2)	111/154 (72.1)	10/18 (55.6)	24/34 (70.6)	7/9 (77.8)
CT	145/327 (44.3)	16/52 (30.8)	59/84 (70.2)	23/29 (79.3)	103/158 (65.2)	22/31 (71.0)	15/44 (34.1)	7/14 (50.0)
TT	35/80 (43.8)	8/21 (38.1)	10/16 (62.5)	6/7 (85.7)	24/37 (64.9)	4/8 (50.0)	10/24 (41.7)	1/3 (33.3)
Unknown	85/207 (41.1)	37/90 (41.1)	70/93 (75.3)	20/23 (87.0)	110/179 (61.5)	24/34 (70.6)	120/238 (50.4)	8/19 (42.1)
HCV RNA (IU/mL)								
≤400,000	148/234 (63.2)	28/63 (44.4)	77/99 (77.8)	21/24 (87.5)	124/183 (67.8)	19/34 (55.9)	79/139 (56.8)	11/18 (61.1)
>400,000	253/581 (43.5)	55/135 (40.7)	126/169 (74.6)	44/54 (81.5)	223/342 (65.2)	41/57 (71.9)	90/201 (44.8)	12/27 (44.4)

SVR12 = percentage of patients with response at least 12 weeks after completion of the treatment period, i.e., HCV RNA <50 IU/mL at least 70 days after day of last dose. Response: HCV RNA <50 IU/mL

HCV, hepatitis C virus; PegIFN, peginterferon; RBV, ribavirin; SVR, sustained virological response

lower than that reported in registration trials, whilst the safety profile of triple therapy was broadly comparable to that in phase III clinical trials. Efficacy and safety with dual-therapy regimens were comparable to previous real-world studies.

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Table 10 Safety outcomes in treatment-naïve and previously treated patients with HCV mono-infection (any genotype) receiving dual therapy

Adverse event	PegIFN alfa-2a/RBV (N=2312)	PegIFN alfa-2b/RBV (N=496)
Patients with ≥1 AE, n (%)	1393 (60.3)	326 (65.7)
Patients with ≥1 SAE, n (%)	148 (6.4)	33 (6.7)
Deaths†, n (%)	6 (0.3)	3 (0.6)
Incidence of individual AEs*, n (%)		
Anemia	456 (19.7)	142 (28.6)
Neutropenia	270 (11.7)	65 (13.1)
Asthenia	237 (10.3)	72 (14.5)
Fatigue	244 (10.6)	53 (10.7)
Pruritus	160 (6.9)	55 (11.1)
Peginterferon dose modification‡, n (%)	243 (10.5)	65 (13.1)
Neutropenia	138 (6.0)	22 (4.4)
Thrombocytopenia	46 (2.0)	9 (1.8)
Anemia	14 (0.6)	7 (1.4)
Other	71 (3.1)	34 (6.9)
Ribavirin dose modification‡, n (%)	384 (16.6)	120 (24.2)
Anemia	315 (13.6)	101 (20.4)
Other	95 (4.1)	22 (4.4)
Laboratory abnormalities, lowest values after BL, n (%)		
Hemoglobin <100 g/L	417 (18.4)	100 (20.7)
Platelets <100 × 10^9/L	716 (31.6)	110 (22.8)
Neutrophils <2.0 × 10^9/L	1914 (86.1)	420 (87.9)

*Incidence ≥10% in one or both treatment groups, †Total number of deaths regardless of relation to treatment in the opinion of the investigator, ‡Because of adverse event or laboratory abnormality

AE, adverse event; BL, baseline; HCV, hepatitis C virus; PegIFN, peginterferon; RBV, ribavirin; SAE, serious adverse event

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Summary Box

What is already known:

- When added to peginterferon alfa/ribavirin, the first direct-acting antiviral agents for chronic hepatitis C (boceprevir and telaprevir) increased sustained virological response (SVR) rates in genotype 1 patients and reduced the duration of treatment required to maximize SVR rates
- First-generation protease inhibitor (PI)-based triple therapy is associated with a higher adverse event burden than dual peginterferon alfa/ribavirin therapy
- SVR rates are higher in treatment-naïve patients than in previously treated patients
- Previous cohort studies of first-generation PI-based triple therapy reported lower SVR rates than those achieved in registration studies

What the new findings are:

- The results of this large real-world observational trial of boceprevir- and telaprevir-based triple therapy in a heterogeneous "real-world" population are consistent with previous, smaller cohort studies that have reported somewhat lower SVR rates than those obtained in phase III registration studies
- The tolerability profile of boceprevir- and telaprevir-based triple therapy in a real-world setting is similar to that reported in registration studies
- When triple therapy is prescribed in accordance with local standards of practice, as recommended in this trial, and the approved label, as in the present study, the incidence of hepatic decompensation and death is low

References

1. World Health Organization (WHO). Guidelines for the screening, care and treatment of persons with hepatitis C infection. April 2014. Available at: http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/. Last accessed: 3 March 2017.
2. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology* 2015;**61**:77-87.
3. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology* 2008;**48**:418-431.
4. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 2007;**132**:2557-2576.
5. Cooke GS, Lemoine M, Thursz M, et al. Viral hepatitis and the Global Burden of Disease: a need to regroup. *J Viral Hepat* 2013;**20**:600-601.
6. Jacobson IM, McHutchison JG, Dusheiko G, et al; ADVANCE Study Team. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011;**364**:2405-2416.
7. Poordad F, McCone J Jr, Bacon BR, et al; SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011;**364**:1195-1206.
8. Bacon BR, Gordon SC, Lawitz E, et al; HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011;**364**:1207-1217.
9. Zeuzem S, Andreone P, Pol S, et al; REALIZE Study Team. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011;**364**:2417-2428.
10. American Association for the Study of Liver Diseases (AASLD) & Infectious Diseases Society of America (IDSA). HCV Guidance: Recommendations for testing, managing, and treating hepatitis C. Updated 2016. Available at: http://www.hcvguidelines.org/fullreport. Accessed June 2016.
11. European Association for Study of Liver. EASL Recommendations on Treatment of Hepatitis C 2015. *J Hepatol* 2015;**63**:199-236.
12. Omata M, Kanda T, Wei L, et al. APASL consensus statements and recommendation on treatment of hepatitis C. *Hepatol Int* 2016;**10**:702-726.
13. European Association for Study of Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2014;**60**:392-420.
14. Sherman KE, Flamm SL, Afdhal NH, et al; ILLUMINATE Study Team. Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med* 2011;**365**:1014-1024.
15. Shiffman ML, Di Bisceglie AM, Lindsay KL, et al; Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis Trial Group. Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. *Gastroenterology* 2004;**126**:1015-1023; discussion 947.
16. Jacobson IM, Gonzalez SA, Ahmed F, et al. A randomized trial of pegylated interferon alpha-2b plus ribavirin in the retreatment of chronic hepatitis C. *Am J Gastroenterol* 2005;**100**:2453-2462.
17. Poynard T, Colombo M, Bruix J, et al; Epic Study Group. Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. *Gastroenterology* 2009;**136**:1618-1628.e2.
18. Poordad F, Bronowicki JP, Gordon SC, et al; SPRINT-2 and RESPOND-2 Investigators. Factors that predict response of patients with hepatitis C virus infection to boceprevir. *Gastroenterology* 2012;**143**:608-618.e1-e5.
19. Hézode C, Fontaine H, Dorival C, et al; CUPIC Study Group. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. *J Hepatol* 2013;**59**:434-441.
20. Hézode C, Fontaine H, Dorival C, et al; CUPIC Study Group. Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis. *Gastroenterology* 2014;**147**:132-142.e4.
21. Price JC, Murphy RC, Shvachko VA, Pauly MP, Manos MM. Effectiveness of telaprevir and boceprevir triple therapy for patients with hepatitis C virus infection in a large integrated care setting. *Dig Dis Sci* 2014;**59**:3043-3052.
22. Gordon SC, Muir AJ, Lim JK, et al; HCV-TARGET study group. Safety profile of boceprevir and telaprevir in chronic hepatitis C: real world experience from HCV-TARGET. *J Hepatol* 2015;**62**:286-293.
23. Mauss S, Böker K, Buggisch P, et al. Real-life experience with first generation HCV protease inhibitor therapy in Germany: The prospective, non-interventional PAN cohort. *Z Gastroenterol* 2015;**53**:644-654.
24. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;**358**:958-965.
25. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;**347**:975-982.
26. Hadziyannis SJ, Sette H Jr, Morgan TR, et al; PEGASYS International Study Group. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004;**140**:346-355.
27. Marcellin P, Cheinquer H, Curescu M, et al. High sustained virologic response rates in rapid virologic response patients in the large real-world PROPHESYS cohort confirm results from randomized clinical trials. *Hepatology* 2012;**56**:2039-2050.

Supplemental Tables

Supplemental Table 1 Definition of the core population

Adult male or female patients with chronic hepatitis C (CHC), hepatitis C virus (HCV) mono-infection with known HCV genotype and known pre-treatment status (naïve or previously treated) who gave informed consent and received one of the following treatment regimens exclusively: • Peginterferon alfa-2a + ribavirin • Peginterferon alfa-2b + ribavirin • Boceprevir + peginterferon alfa-2a + ribavirin • Boceprevir + peginterferon alfa-2b + ribavirin • Telaprevir + peginterferon alfa-2a + ribavirin • Telaprevir + peginterferon alfa-2b + ribavirin Excluded patients: CHC was not confirmed (i.e., no positive baseline HCV RNA record, or acute hepatitis C) Contraindications for any drug in the assigned regimen as per prescribing information (dual peginterferon plus ribavirin therapy or the direct-acting antiviral-containing regimen)
End-stage renal disease
Major organ transplantation
Hepatitis B virus coinfection
HIV coinfection or unknown HIV infection status
Infection with a non-1 HCV genotype and receipt of boceprevir- or telaprevir-based triple combination therapy Treatment with a combination other than the six described above Missing final confirmation of the data by the principal investigator

Supplemental Table 2 Reasons for exclusion of treated patients from the core population (safety population)

Reason for exclusion (more than one reason may apply)	N=252
HIV co-infection	131
No treatment or treatment other than Peg-IFN alfa-2a + RBV or Peg-IFN alfa-2b + RBV or one of these two regimens plus either boceprevir or telaprevir	23
Not HCV RNA-positive at baseline	14
Triple therapy administered to non-genotype 1 patient	29
No final confirmation by principal investigator	26
Non-adult CHC patient receiving dual or triple therapy	1
HCV genotype missing	9
Contraindication to one or more therapies in the assigned regimen	10
HBV co-infection	10
Response at baseline	6
End-stage renal disease	4
Major organ transplantation	3