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

Alessandra Mangia¹, Graham R. Foster³, Christoph P. Berg¹, Manuela Curescu⁴, Victor De Ledinghen⁵, François Habersetzer³, Spilios Manolakopoulos⁹, Elisa Negri³, George Papatheodoridis⁷, Silke Ahlers⁸, Marco Castillo, Georgios Bakalos¹, Stefan Mauss on behalf of the PegBase Group Investigators

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 38.6% 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 NS3/4A 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.

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, Batte and Ludwig stage 3, Knodell stage 3 and Scheuer stage 3. Cirrhosis was defined as ISHAK stage 6, METAVIR stage 4, Batte 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/m² (SD)      | 26.3 (4.9)                          | 25.6 (4.9)                          | 25.9 (4.2)                     | 27.2 (4.9)                     |
| Mean HCV RNA, log<sub>10</sub> 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/m² (SD)      | 27.2 (5.0)                          | 26.0 (4.0)                          | 26.7 (4.5)                     | 28.6 (6.4)                     |
| Mean HCV RNA, log<sub>10</sub> 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...)
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 (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/m² (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 | 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 (%)* | | |
| 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) |

*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...
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 × 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            |                                     |                                     |                                     |                                     |                    |                    |
| Completed 12-week treatment| N=143                               | N=35                                | N=285                               | N=29                                | N=815              | N=198              |
|                          | 130 (90.9)                          | 34 (97.1)                           | 259 (90.9)                          | 26 (89.7)                           | 776 (95.2)         | 178 (89.9)         |
| Completed 24-week follow up|                                     |                                     |                                     |                                     |                    |                    |
| HCV genotype non-1        |                                     |                                     |                                     |                                     |                    |                    |
| Completed 12-week treatment|                                     |                                     |                                     |                                     |                    |                    |
| Completed 24-week follow up|                                     |                                     |                                     |                                     |                    |                    |
| **Previously treated**    |                                     |                                     |                                     |                                     |                    |                    |
| Completed 12-week treatment| N=149                               | N=58                                | N=536                               | N=57                                | N=348              | N=82               |
|                          | 135 (90.6)                          | 50 (86.2)                           | 481 (89.7)                          | 50 (87.7)                           | 315 (90.5)         | 75 (91.5)          |
| Completed 24-week follow up|                                     |                                     |                                     |                                     |                    |                    |

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**          |                                     |                                     |                                     |                                     |                    |                    |
| Adverse event                | N=143                               | N=35                                | N=285                               | N=29                                | N=1964             | N=414              |
|                            | 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**      |                                     |                                     |                                     |                                     |                    |                    |
| Adverse event               | N=149                               | N=58                                | N=536                               | N=57                                | N=348              | N=82               |
|                            | 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
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/
riparivirin 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 trials (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 5** Virological response (VR), relapse and breakthrough rates – triple therapy

| Event                        | PegIFN alfa-2a/RBV  | PegIFN alfa-2b/RBV  | PegIFN alfa-2a/RBV  | PegIFN alfa-2b/RBV  |
|------------------------------|---------------------|---------------------|---------------------|---------------------|
| Treatment-naïve              | N=143               | N=33                | 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; 33.6-65.1) | 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                      | 38/89 (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; 5.1-12.0) |
| 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; SVR, sustained virological response at least 12 weeks after end of treatment (at least 70 days after day of last dose); SVR24, sustained virological response at least 24 weeks after end of treatment (at least 140 days after day of last dose).
### Table 6: Subgroup analysis by baseline characteristics of SVR12 in HCV G1 patients receiving triple therapy

| Baseline characteristic | 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 (%)

| 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 |
|-------|-------------------------------------|-------------------------------------|------------------------------------|------------------------------------|
| 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 (%)

| 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 |
|-------|-------------------------------------|-------------------------------------|------------------------------------|------------------------------------|
| 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 (%)

| 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 |
|-------|-------------------------------------|-------------------------------------|------------------------------------|------------------------------------|
| 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 (%)

| 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 |
|-------|-------------------------------------|-------------------------------------|------------------------------------|------------------------------------|
| Hemoglobin <100 g/L | 121 (41.6)                           | 36 (39.1)                           | 357 (43.8)                         | 36 (43.4)                          |
| Platelets <100 × 10⁹/L | 145 (50.0)                           | 42 (45.7)                           | 400 (49.1)                         | 31 (37.3)                          |
| Neutrophils <2.0 × 10⁹/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
response rate, n, (\% ; 95\% CI)
23 (51.1 ; 35.8-66.3)
330 (62.5 ; 58.2-66.6)
59/400 (14.8 ; 11.4-18.6)
401 (49.2 ; 45.7-52.7)
247 (92.2 ; 88.3-95.1)
348 (65.9 ; 61.7-69.9)
9/69 (13.0 ; 6.1-23.3)
59 (75.6 ; 64.6-84.7)
78 (39.4 ; 32.5-46.6)
58 (63.7 ; 53.0-73.6)
110 (55.6 ; 48.3-62.6)
72 (79.1 ; 69.3-86.9)
238 (70.0 ; 64.8-74.8)
74 (94.9 ; 87.4-98.6)
64 (82.1 ; 71.7-89.8)
50 (25.3 ; 19.4-31.9)
239 (89.2 ; 84.8-92.6)
463 (87.7 ; 84.6-90.4)
23 (51.1 ; 35.8-66.3)
60 (65.9 ; 55.3-75.5)
210 (78.4 ; 72.9-83.1)
335 (63.4 ; 59.2-67.6)
386 (70.0 ; 64.8-74.8)
386 (47.4 ; 43.9-50.9)
200 (74.6 ; 69.0-79.7)
335 (63.4 ; 59.2-67.6)
158 (46.5 ; 39.6-53.4)
83 (41.9 ; 35.4-48.4)
72 (79.1 ; 69.3-86.9)
59 (75.6 ; 64.6-84.7)
72 (79.1 ; 69.3-86.9)
32 (75.6 ; 64.6-84.7)
12 (26.7 ; 14.6-41.9)

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

| Event                      | 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)              |
| VR by week 12              | 495 (60.7 ; 57.3-64.1)              | 247 (92.2 ; 88.3-95.1)              |
| EoT VR                    | 551 (67.6 ; 64.3-70.8)              | 239 (89.2 ; 84.8-92.6)              |
| SVR12                     | 401 (49.2 ; 45.7-52.7)              | 203 (75.7 ; 70.2-80.8)              |
| SVR24                     | 386 (47.4 ; 43.9-50.9)              | 200 (74.6 ; 69.0-79.7)              |
| Relapse                   | 106/502 (21.1 ; 17.6-25.0)          | 23/227 (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)              |
|                           | 59/348 (17.0 ; 13.7-20.7)           | 59 (75.6 ; 64.6-84.7)              |
|                           | 72 (79.1 ; 69.3-86.9)               | 52 (57.1 ; 46.3-67.5)              |
|                           | 32 (75.6 ; 64.6-84.7)               | 12 (26.7 ; 14.6-41.9)              |

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.

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 lower than that reported in previous randomized controlled studies and in other large real-world studies. The spectrum of AEs observed in PegBase is consistent with the spectrum of AEs observed in registration 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 registration studies is noteworthy. The efficacy and safety profile of dual peginterferon alfa/a2b and ribavirin is similar to that reported in previous randomized controlled studies and in other large real-world studies [10-12]. The efficacy and safety profile of dual peginterferon alfa/a2b and ribavirin is similar to that reported in previous randomized controlled studies and in other large real-world studies [10-12].
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 9  Sustained virological response at 12 weeks after the end of treatment in treatment-naive patients with HCV mono-infection receiving dual therapy by baseline characteristics

| Baseline characteristic | Genotype 1 (%) | Genotype 2 (%) | Genotype 3 (%) | Genotype 4 (%) |
|-------------------------|----------------|----------------|----------------|----------------|
|                         | 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)   | 14/19 (73.7)   | 77/146 (52.7)  |
| No cirrhosis            | 325/595 (54.6) | 63/146 (43.2)  | 173/221 (78.3) | 271/382 (70.9) |
| IL28B rs12979860 host genotype |                |                |                |                |
| CC                      | 135/200 (67.5) | 22/35 (62.9)   | 16/19 (84.2)   | 77/115 (71.2)  |
| CT                      | 145/327 (44.3) | 16/52 (30.8)   | 23/29 (79.3)   | 103/158 (65.2) |
| TT                      | 35/80 (43.8)   | 8/21 (38.1)    | 10/16 (62.5)   | 24/37 (64.9)   |
| Unknown                 | 85/207 (41.1)  | 37/90 (41.1)   | 70/93 (75.3)   | 110/179 (61.5) |
| HCV RNA (IU/mL)         |                |                |                |                |
| ≤400,000                | 148/234 (63.2) | 28/63 (44.4)   | 17/21 (82.9)   | 124/183 (67.8) |
| >400,000                | 253/581 (43.5) | 55/135 (40.7)  | 126/169 (74.6) | 223/342 (65.2) |

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.
Table 10 Safety outcomes in treatment-naive 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 x 10^9/L | 716 (31.6) | 110 (22.8) |
| Neutrophils <2.0 x 10^9/L | 1914 (86.1) | 420 (87.9) |

*Incidence ≥10% in one or both treatment groups, †Number of total 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

Dual or triple therapy for chronic hepatitis C

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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

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**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 |