Research Article
Viral Hepatitis

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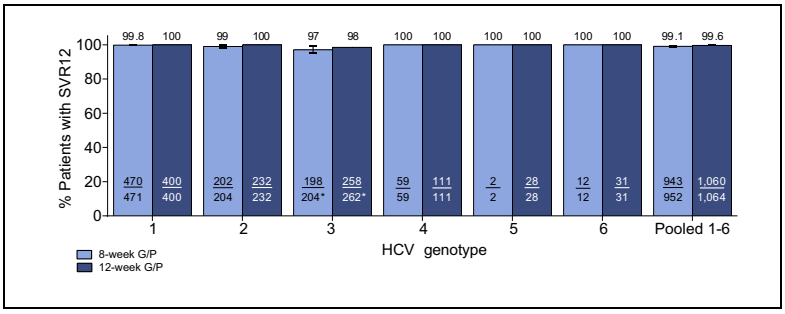
# High SVR12 with 8-week and 12-week glecaprevir/pibrentasvir therapy: An integrated analysis of HCV genotype 1–6 patients without cirrhosis

## Graphical abstract




## Highlights

- A short-duration, pangenotypic cure for HCV infection may help treat more patients.
- Glecaprevir plus pibrentasvir (G/P) therapy for 8 weeks had an overall cure rate of 98%.
- The efficacy of 12-week G/P therapy (99%) was not significantly higher than that of 8-week G/P therapy ($p = 0.2$).
- Treatment responses were high irrespective of any baseline patient or viral trait.
- G/P demonstrated a favourable safety profile regardless of treatment duration.

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## Lay summary

In this integrated analysis of nine clinical trials, patients with chronic HCV genotype 1–6 infection without cirrhosis were treated for either 8 or 12 weeks with the direct-acting antiviral regimen glecaprevir/pibrentasvir (G/P). The cure rate was 98% and 99% following 8 and 12 weeks of treatment, respectively; the difference in rates was not significant ($p = 0.2$), nor was there a significant difference in the cure rates across the two treatment durations on the basis of baseline patient or viral characteristics. These results, along with a favourable safety profile, indicate that G/P is a highly efficacious and well-tolerated pangenotypic eight-week therapy for most patients with chronic HCV infection.



http://dx.doi.org/10.1016/j.jhep.2018.03.007
 J. Hepatol. 2018, 69, 293–300

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# High SVR12 with 8-week and 12-week glecaprevir/pibrentasvir therapy: An integrated analysis of HCV genotype 1–6 patients without cirrhosis

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**Background & Aims**: Glecaprevir plus pibrentasvir (G/P) is a pangenotypic, once-daily, ribavirin-free direct-acting antiviral (DAA) treatment for hepatitis C virus (HCV) infection. In nine phase II or III clinical trials, G/P therapy achieved rates of sustained virologic response 12 weeks after treatment (SVR12) of 93–100% across all six major HCV genotypes (GTs). An integrated efficacy analysis of 8- and 12-week G/P therapy in patients without cirrhosis with HCV GT 1–6 infection was performed.

**Methods**: Data were pooled from nine phase II and III trials including patients with chronic HCV GT 1–6 infection without cirrhosis who received G/P (300 mg/120 mg) for either 8 or 12 weeks. Patients were treatment naïve or treatment experienced with peginterferon, ribavirin, and/or sofosbuvir; all patients infected with HCV GT 3 were treatment naïve. Efficacy was evaluated as the SVR12 rate.

**Results**: The analysis included 2,041 patients without cirrhosis. In the intent-to-treat population, 943/965 patients (98%) achieved SVR12 when treated for eight weeks, and 1,060/1,076 patients (99%) achieved SVR12 when treated for 12 weeks; the difference in rates was not significant ($p = 0.2$). A subgroup analysis demonstrated SVR12 rates > 95% across baseline factors traditionally associated with lower efficacy. G/P was well tolerated, with one DAA-related serious adverse event (<0.1%); grade 3 laboratory abnormalities were rare.

**Conclusions**: G/P therapy for eight weeks in patients with chronic HCV GT 1–6 infection without cirrhosis achieved an overall SVR12 rate of 98% irrespective of baseline patient or viral characteristics; four additional weeks of treatment did not significantly increase the SVR12 rate, demonstrating that the optimal treatment duration in this population is eight weeks.

**Lay summary**: In this integrated analysis of nine clinical trials, patients with chronic HCV genotype 1–6 infection without cirrhosis were treated for either 8 or 12 weeks with the direct-acting antiviral regimen glecaprevir/pibrentasvir (G/P). The cure rate was 98% and 99% following 8 and 12 weeks of treatment, respectively; the difference in rates was not significant ($p = 0.2$), nor was there a significant difference in the cure rates across the two treatment durations on the basis of baseline patient or viral characteristics. These results, along with a favourable safety profile, indicate that G/P is a highly efficacious and well-tolerated pangenotypic eight-week therapy for most patients with chronic HCV infection.



## Introduction

Hepatitis C virus (HCV) infects an estimated 71–80 million individuals worldwide, and is a leading cause of cirrhosis, hepatocellular carcinoma, and liver-related deaths.[1] The era of direct-acting antiviral (DAA) agents for the treatment of HCV infection has resulted in a rapid and steady decline in the number of infected patients and an improvement in disease outcomes. As more patients with chronic HCV infection are being treated, it is projected that up to 75% of new patients will be HCV treatment naïve and without cirrhosis.[2]

According to recent US and European guidelines, most approved regimens for patients with HCV infection without cirrhosis have treatment durations of 12 weeks or more.[3,4] Shorter treatment durations have been associated with improved adherence, which may benefit difficult-to-treat populations, such as prisoners, psychiatric patients, and injection drug users.[5–8] Until recently, there were only two options for a shorter, eight-week duration for patients with HCV genotype 1

Keywords: Hepatitis C; Short duration; Direct-acting antiviral; Pangenotypic.
*Received 31 October 2017; received in revised form 29 January 2018; accepted 5 March 2018; available online 16 March 2018*

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infection without cirrhosis: sofosbuvir plus ledipasvir, and ombitasvir/paritaprevir/ritonavir plus dasabuvir. However, each regimen has restrictions: treatment with sofosbuvir plus ledipasvir for eight weeks is restricted by baseline HCV RNA level ($<6 \times 10^6$ IU/ml), prior HCV treatment experience (treatment naïve), HIV-1 coinfection status (negative), and race (non-black);[9] patients treated with ombitasvir/paritaprevir/ritonavir plus dasabuvir are eligible only for eight-week treatment in Europe, and treatment is restricted by viral subtype (genotype 1b), prior HCV treatment experience (treatment naïve), and fibrosis stage (F0–F2).[10] An eight-week, pangenotypic treatment option for treatment-naïve patients without cirrhosis that provides high response rates regardless of baseline patient or viral characteristics could simplify treatment decisions and potentially allow the treatment of more patients.

The DAAs glecaprevir (GLE; an inhibitor of the NS3/4A protease, identified by AbbVie and Enanta) and pibrentasvir (PIB; an NS5A inhibitor) were coformulated for phase III studies to comprise the once-daily, pangenotypic regimen GLE/PIB (G/P), approved for the treatment of HCV genotype 1–6 infection.[11,12] Both DAAs demonstrate a high barrier to resistance and potent pangenotypic anti-HCV activity *in vitro*, with the half-maximal effective concentration of GLE and PIB ranging from 0.85 to 4.6 nM and from 1.4 to 5.0 pM, respectively, across HCV genotypes 1–6.[13,14] GLE and PIB are minimally metabolized in the liver, have negligible renal excretion, and exhibit a favourable drug–drug interaction profile with most commonly administered concomitant medications.[15] In phase II and III clinical trials, treatment of patients without cirrhosis and with compensated cirrhosis, including those with severe renal impairment, with the all-oral, interferon-, and ribavirin-free GLE and PIB combination regimen achieved rates of sustained virologic response (SVR; HCV RNA level below the lower limit of quantification) at post-treatment week 12 (SVR12) of 93–100% across all six major HCV genotypes.[16–19]

Herein, data from nine trials were pooled to conduct an integrated efficacy analysis of 2,041 patients with HCV genotype 1–6 infection without cirrhosis treated with the GLE and PIB combination regimen for either 8 or 12 weeks, and to determine whether any baseline factors impacted achievement of SVR12.

## Patients and methods

### Patients

Eligibility criteria are described herein for phase III studies; any discrepancies in the criteria between phase II and III studies are noted (Table S1). Adults aged 18 years or older with chronic HCV genotype 1–6 infection (HCV RNA level >1,000 IU/ml) were eligible for enrolment. Patients were either HCV treatment naïve or HCV treatment experienced with interferon or pegylated interferon with or without ribavirin, or sofosbuvir plus ribavirin with or without pegylated interferon. An eight-week duration of G/P therapy was not evaluated in treatment-experienced patients with HCV genotype 3 infection; therefore, in this analysis comparing 8- and 12-week treatment durations, all patients with HCV genotype 3 infection were treatment naïve. In two studies (ENDURANCE-1 and EXPEDITION-2), patients with HCV/HIV-1 coinfection were allowed to enroll. Prior HCV treatment experience with a DAA other than sofosbuvir was exclusionary, as was coinfection with hepatitis B virus. Active injection drug use was not exclusionary unless it could preclude adherence to the protocol, per investigator assessment. Absence of cirrhosis was documented by liver biopsy, transient elastography, or serum biomarkers; cut-offs and indeterminate ranges (for FibroScan® and FibroTest®) are listed in the supplementary material. All patients provided written informed consent. Studies were designed according to good clinical practice guidelines, the Declaration of Helsinki, and applicable local regulations, with independent ethics committee or institutional review board approval for all study sites.

### Study design

Data were pooled from arms of nine phase II or III clinical trials (EXPEDITION-2, -4, ENDURANCE-1, -2, -3, -4, SURVEYOR-I Part 2, SURVEYOR–II Parts 1 and 2, and SURVEYOR-II Part 4). Patients received GLE at 300 mg and PIB at 120 mg (phase II formulation, dosed as separate tablets) or coformulated G/P (300 mg/120 m g; phase III formulation) without ribavirin orally dosed as three pills once daily for either 8 or 12 weeks (Fig. 1). All authors had access to the study data, and reviewed and approved the final manuscript for submission.

### Assessments

HCV genotype and subtype were determined at screening with use of the Versant® HCV genotype Inno LiPA assay, version 2.0 (Siemens Healthcare Diagnostics, Tarrytown, NY, USA), and confirmed by phylogenetic analysis of viral sequences. Plasma HCV

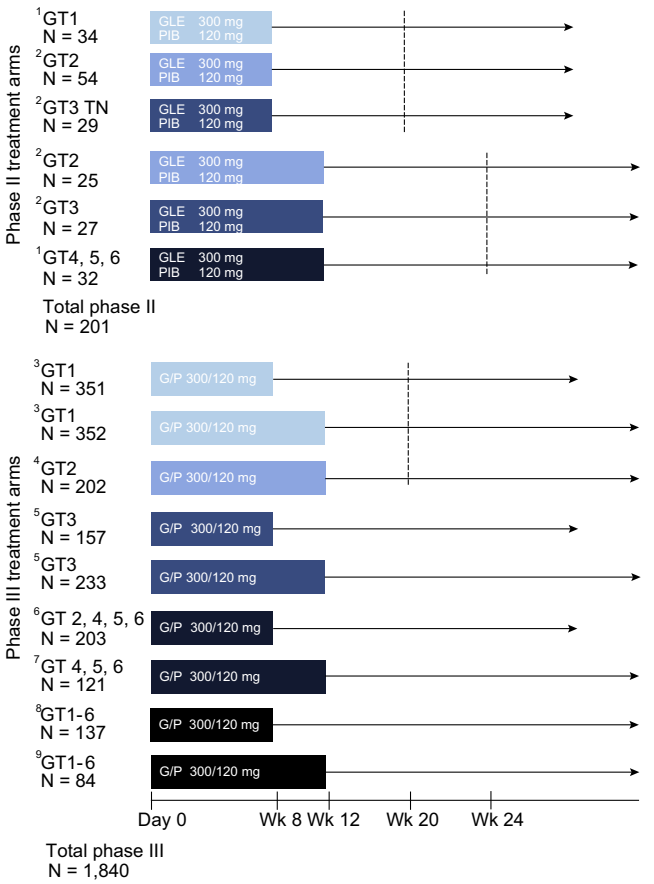


**Fig. 1. Study design.** The arms of the nine clinical trials from which patients were pooled, including the number of patients enrolled by genotype (GT) in either phase II or III studies. 1, SURVEYOR-I Part 2; 2, SURVEYOR-II Parts 1 and 2; 3, ENDURANCE-1; 4, ENDURANCE-2; 5, ENDURANCE-3; 6, SURVEYOR-II Part 4; 7, ENDURANCE-4; 8, EXPEDITION-2; 9, EXPEDITION-4; GLE, glecaprevir; G/P, glecaprevir/pibrentasvir; PIB, pibrentasvir; TN, treatment naive.

RNA was quantified by PCR; assay details are described in the supplementary material. Next-generation sequencing was conducted on samples from all patients at the baseline; the presence of baseline polymorphisms at amino acid positions in NS3 and NS5A relative to the HCV subtype-specific reference sequence was evaluated with a 15% detection threshold in samples that had sequences available for both targets. The included amino acid positions are those associated with resistance for currently approved DAAs, and are listed in the supplementary material and relevant table legend. Treatment-emergent amino acid substitutions in NS3 and NS5A were analysed for patients who experienced virologic failure. Treatment adherence was determined by pill count. Safety was evaluated by monitoring of adverse events, physical examinations, and laboratory test assessments. Adverse events and their relatedness to the study drugs were assessed by the study investigator.

### Endpoints

The primary efficacy endpoints were the number and percentage of patients who achieved SVR12; the analysis was conducted in the intent-to-treat (ITT) population, which included all patients who received at least one dose of the study drug. The secondary efficacy endpoints were the number and percentage of patients in the ITT population with on-treatment virologic failure and post-treatment relapse.

### Statistical analysis

Statistical tests and CIs were two-sided with a significance level of 0.05. CIs were determined by Wilson's score method; overall comparisons between treatment durations were evaluated by Fisher's exact test. Subgroup analyses were conducted in the modified ITT (mITT) population, which excluded patients with non-virologic failure (*e.g.* SVR12 non-response due to early discontinuation and/or lost to follow-up). A total of 19 variables were included in the analysis to compare the SVR12 rates in each subgroup following 8- *vs.* 12-week treatment. An additional subgroup analysis was performed on the treatment-naïve and treatment-experienced patient cohorts. Lastly, the potential interaction between treatment duration and 17 independent variables (listed in Table S2) was examined separately for each of those 17 variables in the mITT population with use of a logistic regression model that includes the interaction effect between treatment duration and the variable; Firth's penalized maximum likelihood estimation was used in all logistic regression analyses to handle quasi-complete separation due to sparse SVR12 failures.

For further details regarding the methods used, please refer to the CTAT table and supplementary information.

## Results

This analysis included 2,041 patients infected with HCV genotype 1–6 without cirrhosis enrolled in phase II (N = 201) and phase III (N = 1,840) studies between 8 September 2014 and 10 October 2016. For the remainder of the article, we refer to the study drug as G/P, regardless of whether the phase II GLE plus PIB regimen or the phase III coformulated G/P regimen was administered. In total, 965 and 1,076 patients received G/P for 8 and 12 weeks, respectively (Fig. 1). Baseline demographics and disease characteristics were generally similar between the 8- and 12-week treatment groups (Table 1). Most patients were white, male, and HCV treatment naïve. For the 8- and 12-week treatment durations, 16% and 2%, respectively, were coinfected with HIV-1, 11% had F3 fibrosis, and 59% had plasma HCV RNA $>1 \times 10^6$ IU/ml at the baseline visit. Most patients (80–83%) had no baseline drug class-specific amino acid polymorphisms in either NS3 or NS5A; polymorphisms in NS5A (15–18%) were more common than those in NS3 (<1–1%), and <1% of patients had baseline polymorphisms in both targets.

The SVR12 rate for patients with HCV genotype 1–6 infection treated for eight weeks was 98% (943/965; 95% CI 96.6–98.5%), and the SVR12 rate for patients treated for 12 weeks was 99% (1,060/1,076; 95% CI 97.6–99.1%) (Fig. 2A). The difference in SVR12 rates between the two treatment durations was not significant ($p = 0.2$). The rate of post-treatment relapse was 0.7% (7/951; 95% CI 0.4–1.5%) and 0.3% (3/1,057; 95% CI 0.1–0.8%) in patients treated for 8 and 12 weeks, respectively. The on-treatment virologic failure rate was less than 1% regardless of treatment duration: two of the 965 patients (0.2%) treated for eight weeks and one of the 1,076 patients (<0.1%) treated for 12 weeks had on-treatment virologic failure (Table 2). Information on patients with virologic failure, including baseline and treatment-emergent resistance-associated substitutions, is included (Table S3). Excluding patients with non-virologic failure, the mITT rate of SVR12 for the 8- and 12-week treatment durations across all genotypes was 99.1% (943/952; 95% CI 98.2–99.5%) and 99.6% (1,060/1,064; 95% CI 99.0–99.9%) respectively (Fig. 2B).

A subgroup analysis in the mITT population of 19 variables showed that the SVR12 rates for patients treated for 8 *vs.* 12 weeks were similarly high (≥95%), regardless of variables such as race, prior treatment experience, HCV/HIV-1 coinfection, fibrosis stage, viral load, proton pump inhibitor use, history of injection drug use, and presence of baseline polymorphisms in NS3 or NS5A (Fig. 3). The logistic regression analysis confirmed that SVR12 was not impacted by treatment duration, and that there was no significant difference in the rates of SVR12 in the 8- *vs.* 12-week arms for any of the baseline factors analysed, including HCV genotype and presence of baseline polymorphisms.

An additional subgroup analysis conducted in patients receiving eight-week G/P therapy demonstrated high rates of SVR12 (>95%; mITT) in HCV treatment-naïve patients across subgroups traditionally associated with lower rates of response; there were no virologic failures in patients older than 65 years, with body mass index of ≥30 kg/m$^2$, of black race, using concomitant PPIs, or with HIV-1 coinfection (Table S4). Importantly, for all patient subgroups treated for eight weeks, there was no clinically significant difference in SVR12 rates between treatment-naïve patients and those with HCV treatment experience.

Safety was similar in patients treated for either 8 or 12 weeks with G/P (Table 3). The most common adverse events were headache (17%) and fatigue (14%). Serious adverse events occurred in 2% and 3% of patients treated for 8 and 12 weeks, respectively. Adverse events leading to premature study drug use discontinuation occurred in <1% of patients across both treatment durations. Less than 1% of overall patients (and none of those treated for eight weeks) had DAA-related serious adverse events or discontinued use of the drug. Of the 2,041 total patients who received G/P, one (<0.1%) had a grade 3 elevation in alanine aminotransferase level; the elevation was in the context of cholelithiasis, and the patient achieved SVR12.

**Table 1. Baseline demographics and disease characteristics.**

| Characteristic | 8-week G/P therapy (n = 965) | 12-week G/P therapy (n = 1,076) |
|---|---|---|
| Male, n (%) | 537 (56) | 584 (54) |
| Race, n (%) | | |
| White | 794 (82) | 825 (77) |
| Asian | 87 (9) | 163 (15) |
| Black | 65 (7) | 61 (6) |
| Age, median (range), years | 52 (19–84) | 53 (20–83) |
| BMI, median (range), $kg/m^2$ | 25.5 (17.3–65.7) | 25.3 (17.4–54.1) |
| Genotype, n (%) | | |
| 1 | 474 (49) | 401 (37) |
| Subtype 1a | 244 (25) | 168 (16) |
| Subtype 1b | 229 (24) | 230 (21) |
| Other | 1 (0.1) | 3 (0.3) |
| 2 | 206 (21) | 234 (22) |
| 3 | 208 (22) | 270 (25) |
| 4 | 62 (6) | 112 (10) |
| 5 | 2 (0.2) | 28 (3) |
| 6 | 13 (1) | 31 (3) |
| *IL28B* non-CC genotype, n (%) | 627 (65) | 723 (67) |
| HCV treatment naïve, n (%) | 768 (80) | 801 (74) |
| HCV treatment experienced, n (%)[†] | 197 (20) | 275 (26) |
| IFN-based | 187 (19) | 266 (97) |
| SOF-based | 10 (1) | 9 (3) |
| HCV RNA level, median (range), $log_{10}IU/ml$ | 6.2 (0.7–7.6) | 6.2 (2.5–7.8) |
| Baseline HCV RNA level, IU/ml, n (%) | | |
| $<1 \times 10^6$ | 392 (41) | 446 (41) |
| $\geq 1 \times 10^6$ | 573 (59) | 630 (59) |
| $<6 \times 10^6$ | 734 (76) | 850 (79) |
| $\geq 6 \times 10^6$ | 231 (24) | 226 (21) |
| Fibrosis stage, n (%)[‡] | | |
| F0–F1 | 798 (83) | 870 (81) |
| F2 | 58 (6) | 87 (8) |
| F3 | 106 (11) | 118 (11) |
| Presence of baseline polymorphisms, n (%)[δ] | | |
| NS3 only | 8 (<1) | 14 (1) |
| NS5A only | 141 (15) | 184 (18) |
| Both NS3 and NS5A | 3 (<1) | 6 (<1) |
| None | 765 (83) | 809 (80) |
| HIV-1 coinfected, n (%) | 152 (16) | 18 (2) |
| Chronic kidney disease stage, n (%)[‖] | | |
| Stage 4 | n.a. | 13 (1) |
| Stage 5 | n.a. | 70 (7) |
| Concomitant PPI use, n (%) | 72 (7) | 125 (12) |
| History of injection drug use, n (%) | | |
| Yes | 427 (44) | 371 (34) |
| Within the past 12 months[¶] | 23 (4) | 15 (1) |
| >12 months ago[¶] | 253 (39) | 316 (32) |
| Receiving stable opiate substitution, n (%) | 73 (8) | 63 (6) |
| >80% treatment adherent, n (%) | 848 (88) | 979 (91) |
| APRI, n (%) | | |
| <1 | 793 (82) | 881 (82) |
| ≥1 | 172 (18) | 195 (18) |
| FibroScan®, n (%)[**] | | |
| <9.6 kPa (F2 cut-off) | 596 (87) | 703 (88) |
| ≥9.6 kPa | 92 (13) | 98 (12) |
| FibroTest®, n (%)[**] | | |
| <0.59 | 322 (80) | 292 (80) |
| ≥0.59 | 81 (20) | 75 (20) |

APRI, aspartate aminotransferase to platelet ratio; BMI, body mass index; G/P, glecaprevir/pibrentasvir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; PPI, proton pump inhibitor; ribavirin; SOF, sofosbuvir.

[†]IFN-based, IFN or pegylated IFN with or without ribavirin; SOF-based, SOF plus ribavirin plus pegylated IFN.

[‡]N adjusted to exclude three patients with missing data.

[δ]Baseline polymorphisms relative to subtype-specific reference sequence detected at 15% next-generation sequencing threshold in samples that had sequences available for both targets at a drug class-specific subset of amino acid positions. NS3: 155, 156, 168; NS5A: 28, 30, 31, 93, or H58D, E62A in genotype 1a; 31 or 93 in genotype 1b; 24, 28, 30, 92, 93 in genotype 2; 24, 28, 30, 31, 58, 93 in genotype 3; 24, 28, 30, 31, 93 in genotype 4; 24, 28, 30, 31, 58, 92, 93 in genotypes 5 and 6.

[‖]Includes patients from the EXPEDITION-4 study only.

[¶]Excludes patients from phase II studies and the phase III study SURVEYOR-2 Part 4 (data not collected).

[**]N adjusted to exclude missing values; cut-offs per statistical analysis plan are described in the supplementary material.

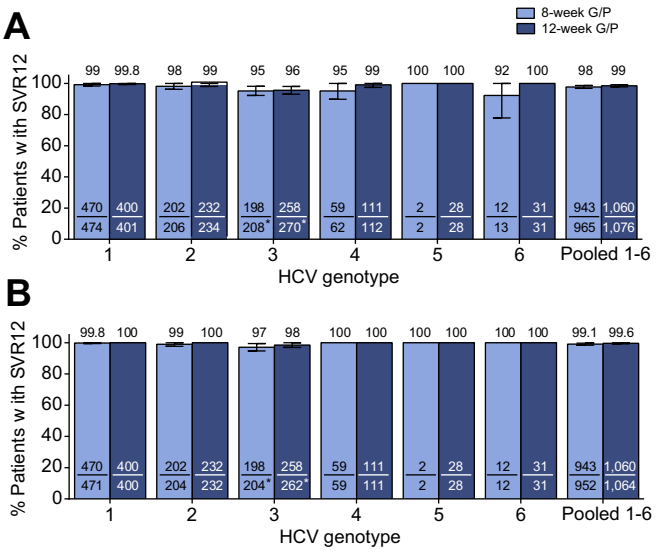


**Fig. 2. Integrated efficacy of glecaprevir/pibrentasvir (G/P).** Rates of sustained virologic response 12 weeks after treatment (SVR12) by genotype and overall in patients treated for eight weeks (light blue) or 12 weeks (dark blue) weeks in the (A) intent-to-treat (ITT) and (B) modified intent-to-treat (mITT) populations. The modified intent-to-treat population excludes patients with non-virologic failure). *Includes only genotype 3 patients who were treatment naïve. HCV, hepatitis C virus.

**Table 2. Reasons for non-response, pooled.**

| Reasons for non-response | 8-week G/P therapy (n = 965) | 12-week G/P therapy (n = 1,076) |
|---|---|---|
| Breakthrough, n (%) | 2 (0.2)[†] | 1 (<0.1)[‡] |
| Relapse, n (%) | 7 (0.7)[δ] | 3 (0.3)[‖,¶] |
| Non-virologic failure | | |
| Discontinuation, n (%) | 5 (0.5) | 6 (0.6) |
| Missing SVR12 data, n (%) | 8 (0.8) | 6 (0.6) |

*G/P, glecaprevir/pibrentasvir; SVR12, sustained virologic response 12 weeks after treatment.
[†]One genotype 1, one genotype 3.
[‡]One genotype 3.
[δ]Two genotype 2, five genotype 3.
[‖]Three genotype 3.
[¶]One patient with a history of injection drug use was later determined by phylogenetic analysis to have a reinfection; no other reinfections were observed in this analysis.

## Discussion

Treatment with all-oral, once daily G/P therapy for 8 or 12 weeks demonstrated high SVR12 rates (≥97%, mITT) across all six major HCV genotypes, with <1% rate of relapse regardless of treatment duration. There were no virologic failures in patients with HCV genotype 4–6 infection, and treatment-naïve patients with genotype 3 infection achieved SVR12 rates of ≥95% regardless of 8- or 12-week treatment duration. These high SVR rates were also achieved irrespective of key patient or viral characteristics, and were consistent in patients with HIV-1 coinfection (SVR12 rate of 99%) and severe renal impairment (SVR12 rate of 98%[20]), with no virologic failures in either subgroup.

For patients without cirrhosis, eight-week, pangenotypic DAA regimens were not available until recently. G/P is now approved in both the USA and Europe as an eight-week treatment regimen for patients without cirrhosis across all genotypes.[11,12] In Europe, eight-week sofosbuvir/velpatasvir/voxilaprevir therapy is approved for DAA-naïve patients without cirrhosis with HCV genotype 1–6 infection; however, that indication and duration are not approved in the USA, where sofosbuvir/velpatasvir/voxilaprevir is indicated only as a 12-week regimen for DAA-experienced patients.[21,22] Treatment of patients without cirrhosis with eight weeks of sofosbuvir/velpa tasvir/voxilaprevir therapy resulted in an 8% relapse rate among patients with the genotype 1a subtype compared with 0% in those treated with 12 weeks of sofosbuvir/velpatasvir therapy.[23] In contrast, in patients without cirrhosis infected with genotype 1a treated with G/P for eight weeks, the relapse rate was 0%.

The extensive subgroup analysis conducted in patients infected with genotype 1–6 without cirrhosis treated for 8 and 12 weeks with G/P confirmed high rates of SVR12 regardless of baseline characteristics traditionally associated with lower efficacy for other HCV regimens, such as treatment experience, baseline NS3 or NS5A polymorphisms, race, HCV genotype/subtype, F3 fibrosis, and high baseline viral load.[17] Among patients with F3 fibrosis, the SVR12 rate (mITT) in patients treated for eight weeks was 96.1% (99/103; 95% CI 90.4–98.5%) *vs.* 100% (117/117; 95% CI 96.8–100%) in patients treated for 12 weeks; the difference in SVR12 rates was not significant. Of note, one of the four F3 patients with virologic failure following eight weeks of treatment had poor adherence and a low study drug plasma concentration, which could account for the failure (an on-treatment breakthrough). Among the nine patients (0.4%) with baseline polymorphisms in both NS3 (position 155, 156, or 168) and NS5A, there were two virologic failures, one for each treatment duration; one of these failures was in a patient treated for eight weeks with low study drug exposures due to poor adherence (mentioned earlier). Importantly, the lower SVR12 rates were in the context of small sample sizes consistent with an NS5A and protease inhibitor-naïve population, and there is no evidence indicating an efficacy benefit from using the 12-week over the eight-week duration in this population. Finally, a logistic regression analysis confirmed that there was no statistically significant difference in SVR12 rates across the two treatment durations for any of the subgroups analysed.

G/P demonstrated a favourable safety and tolerability profile regardless of treatment duration in the 2,041 patients included in this analysis. Regimens containing HCV protease inhibitors have historically been associated with marked hyperbilirubinemia, elevated ALT, and gastrointestinal adverse events.[24–26] However, in this integrated analysis, treatment with G/P demonstrated a lower frequency of isolated grade 3 increases in total bilirubin level (0.3%; 7/2,041) than other HCV protease inhibitors,[23–25] and there were no incidences of drug-induced liver injury. In addition, the frequency of diarrhoea following treatment with G/P was 6% in this pooled analysis *vs.* 15–19% for the sofosbuvir/velpatasvir/voxilaprevir regimen.[23,27]

Limitations of this integrated analysis include the low number of patients in some subgroups (specifically, the number of patients with prior sofosbuvir experience, and those with genotype 5 or 6 infection), and the inclusion of patients from both phase II and III clinical trials, which had marginally different eligibility criteria.

Multiple DAA regimens are currently available for the treatment of HCV infection; most of these are recommended for 12 weeks of treatment.[3,4,9,28–30] Two pangenotypic, interferon- and ribavirin-free treatments are now available with eight-week treatment durations.[11,12,23] A pangenotypic regimen that combines the high efficacy expected from DAA-based

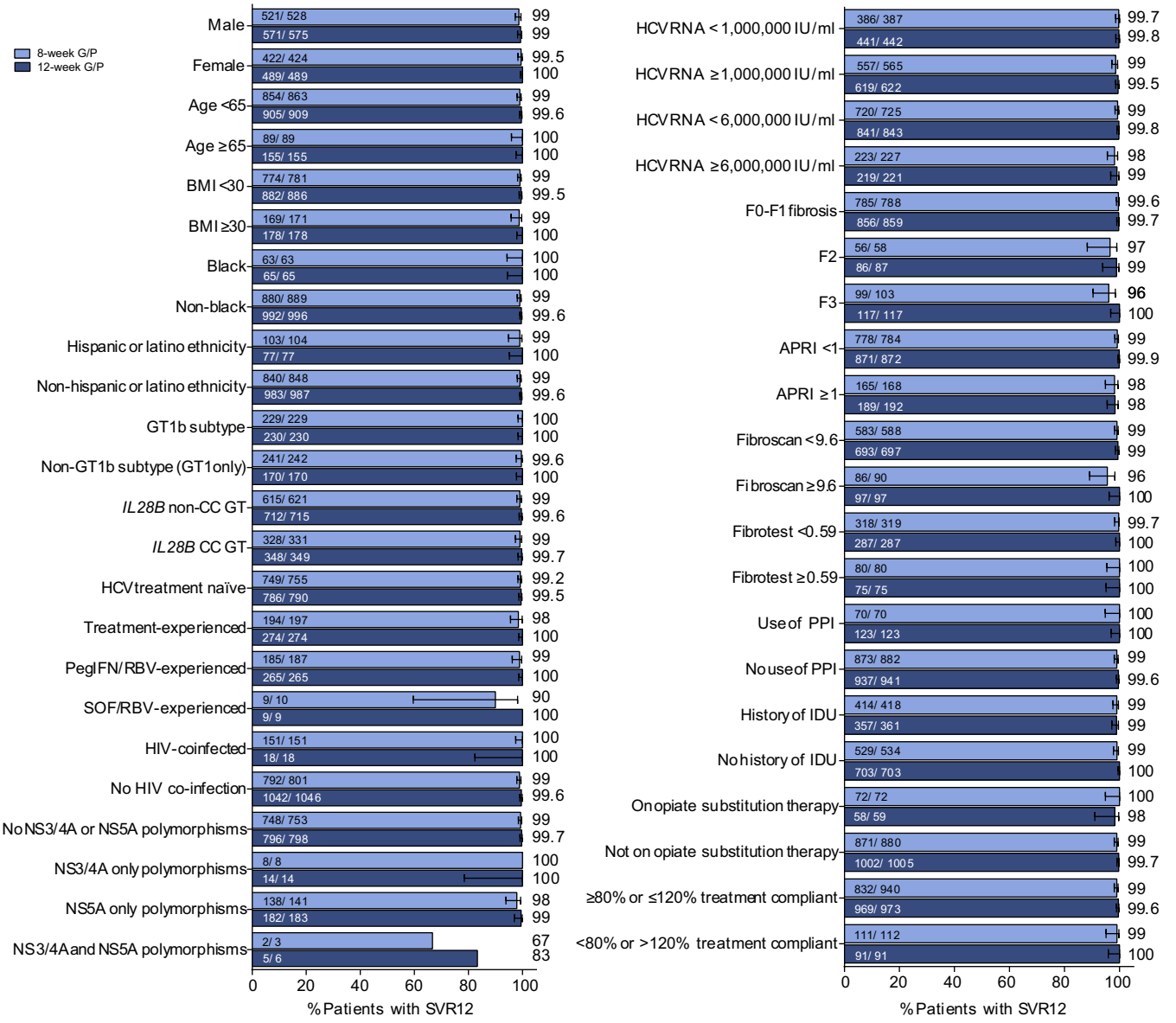


**Fig. 3. Sustained virologic response 12 weeks after treatment (SVR12) by subgroup.** Rates of modified intent-to-treat population SVR12 and two-sided 95% CIs for patients treated for eight weeks (light blue) or 12 weeks (dark blue) are shown. APRI, aspartate aminotransferase to platelet ratio; BMI, body mass index; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, intravenous drug use; pegIFN, pegylated interferon; PPI, proton pump inhibitor; RBV, ribavirin; SOF, sofosbuvir.

therapies with a treatment duration of eight weeks has the potential advantages of reducing treatment burden and simplifying treatment algorithms. Specifically, a pangenotypic option without restrictions may eliminate the need for genotyping and other baseline assessments (*e.g.* resistance-associated polymorphisms), which may not be available in resource-limited settings. The minimal/no on-treatment monitoring provided by a shorter treatment duration could increase treatment access in areas with fewer specialized physicians (as complex treatment algorithms typically require specialists). Taken together, this suggests that the costs associated with medical visits and diagnostic procedures will be reduced, and that the simplicity of the regimen will make it more accessible to a greater number of providers, potentially allowing the treatment of more patients. Currently, most of the estimated 70 million individuals with HCV infection are treatment naïve and do not have cirrhosis; cirrhosis is associated with an increased risk of hepatocellular carcinoma, and is the eighth leading cause of death in the USA.[31] Consequently, curative treatment of a larger number of patients without cirrhosis afforded by an eight-week treatment regimen could have a significant public health impact, as sustained virologic response has been associated with long-term improvements in fibrosis and other markers of liver disease, as well as reductions in HCV-associated comorbidities and extrahepatic manifestations.[32]

In patients with HCV genotype 1–6 infection without cirrhosis, treatment with G/P achieved SVR12 rates of ≥98% with both 8 and 12 weeks of treatment, with similarly low rates of relapse (<1%). Treatment for eight weeks achieved high SVR12 rates regardless of HCV genotype/subtype, baseline viral load, fibrosis stage, NS3 or NS5A polymorphisms, or other baseline factors. Excluding non-virologic failures, the SVR12 rate was 99.1% with

**Table 3. Overview of adverse events and laboratory abnormalities.**

| Event | 8-week G/P therapy (n = 965) | 12-week G/P therapy (n = 1,076) |
|---|---|---|
| Any AE, n (%) | 610 (63) | 733 (68) |
| Serious AE, n (%) | 15 (2) | 27 (3) |
| DAA-related serious AE, n (%) | 0 | 1 (<0.1) |
| AE leading to discontinuation, n (%) | 1 (0.1) | 9 (0.8) |
| DAA-related AE leading to discontinuation, n (%) | 0 | 3 (0.3) |
| AEs occurring in ≥10% patients | | |
| Headache, n (%) | 152 (16) | 192 (18) |
| Fatigue, n (%) | 125 (13) | 156 (15) |
| Laboratory abnormalities, n/N (%) | | |
| ALT[†], grade ≥3 (>5 times ULN) | 0 | 1 (<0.1)[‡] |
| AST, grade ≥3 (>5 times ULN) | 3 (0.3) | 4 (0.4) |
| Total bilirubin, grade ≥3 (>3 times ULN) | 5 (0.5)[δ] | 2 (0.2)[δ] |

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase DAA, direct-acting antiviral; G/P, glecaprevir/pibrentasvir; ULN, upper level of normal.
[†]Postnadir increase (in grade).
[‡]Grade 3 ALT level elevation associated with grade 2 bilirubin and grade 3 AST and alkaline phosphatase level elevations at week 12 in the context of cholelithiasis (multiple gallstones); patient achieved sustained virologic response 12 weeks after treatment.
[δ]All patients had bilirubin level elevations at the baseline; the grade 3 elevations were primarily indirect, with no associated postnadir ALT level elevations by grade.

eight-week G/P therapy. These results indicate that eight-week G/P therapy is a highly efficacious and well-tolerated pangenotypic therapy for most patients with chronic HCV infection.

## Financial support

AbbVie sponsored the studies (NCT02604017, NCT02640482, NCT02636595, NCT02243293, NCT02640157, NCT02651194, NCT02738138, and NCT02243280), contributed to their design, and participated in the collection, analysis, and interpretation of the data, and in the writing, reviewing, and approval of this publication.

## Conflict of interest

M.P. is a temporary advisory board member and/or speaker at own events for AbbVie, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, Gilead, Merck Sharp & Dohme, and Roche, and has received research support from Gilead and Merck Sharp & Dohme. G.R.F. has received grant/research support from AbbVie, Bristol-Myers Squibb, Merck, Roche/Genentech, Gilead, Novartis, and Janssen, and is a consultant/advisor for AbbVie, Vertex, Bristol-Myers Squibb, Merck, Roche/Genentech, Gilead, GlaxoSmithKline, Janssen, Virco, and Novartis. D.M. is a consultant for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, and Merck. E.G. is an advisor for AbbVie, Gilead, Achillion, Idenix, Novartis, Roche, Merck, and Janssen. C.M. has received research grants from AbbVie, Bristol-Myers Squibb, Gilead Sciences, and Janssen, and is a consultant for AbbVie, Gilead Sciences, Janssen, Merck Sharp & Dohme, and Bristol-Myers Squibb. T.T.C is a clinical trial investigator for AbbVie. S.S.L. provides research support and is a consultant for AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Idenix Pharmaceuticals, Janssen Pharmaceuticals Inc., Merck, Roche, and Vertex Pharmaceuticals, and is a speaker for Bristol-Myers Squibb, Gilead Sciences, Merck, Roche, and Vertex Pharmaceuticals. R.M. is an advisory board member/speaker for AbbVie, Bayer, Gilead, Bristol-Myers Squibb, and Merck. J.F.D. is a member of advisory committees for AbbVie, Bayer, Bristol-Myers Squibb, Genfit, Gilead Sciences, Intercept, Merck, and Novartis, and has received an unrestricted research grant from Bayer. S.P. is a clinical investigator/speaker/consultant for AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, Sharp & Dohme, Novartis Pharmaceuticals, Roche, and Achillion. C.H. is a clinical investigator/speaker/consultant for AbbVie, Bristol-Myers Squibb, Gilead, Janssen Pharmaceuticals, Merck, Sharp & Dohme, and Roche. S.C.G. is a consultant for AbbVie, Bristol-Myers Squibb, CVS Caremark, Gilead, and Merck, and has received grant support from AbbVie, Bristol-Myers Squibb, Gilead, Intercept, and Merck. S.I.S. is an advisory board member/speaker for AbbVie, Gilead, Bristol-Myers Squibb, and Merck, Sharp & Dohme. P.J.T. has acted as a speaker for AbbVie and Gilead, and has received research grants from AbbVie, Gilead, and Bristol-Myers Squibb. S.W., Z.Z., S.L., T.P.-M., P.M., and F.J.M. are employees of AbbVie and may hold stock or stock options.

Please refer to the accompanying ICMJE disclosure forms for further details.

## Authors' contributions

F.J.M. and S.W. participated in the design of the study. S.L., Z.Z.Z., and T.P.-M. analysed the data. M.P., G.R.F., D.M., E.G., C.M., T.T.C., S.S.L., R.M., J.F.D., S.P., C.H., S.C.G., S.I.S., and P.J.T. conducted the studies and collected data. All authors participated in the interpretation of the data, preparation, review, and approval of the manuscript, and the decision to submit the manuscript for publication.

## Acknowledgements

The authors express their gratitude to the patients and their families, and the investigators and coordinators who made these studies possible. Medical writing support was provided by Zoë Hunter of AbbVie.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2018.03.007.

## References

*Author names in bold designate shared co-first authorship*

[1] Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017;2:161–176.

[2] http://polarisobservatory.org/polaris/graphs.htm (accessed 10 July 2017).
[3] AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus, 2017.
[4] European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol 2018;69:461–511.
[5] Hatzakis A, Chulanov V, Gadano AC, Bergin C, Ben-Ari Z, Mossong J, et al. The present and future disease burden of hepatitis C virus (HCV) infections with today's treatment paradigm - volume 2. J Viral Hepat 2015;22:26–45.
[6] Razavi H, Waked I, Sarrazin C, Myers RP, Idilman R, Calinas F, et al. The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. J Viral Hepat 2014;21:34–59.
[7] Younossi ZM, Kanwal F, Saab S, Brown KA, El-Serag HB, Kim WR, et al. The impact of hepatitis C burden: an evidence-based approach. Aliment Pharmacol Ther 2014;39:518–531.
[8] Lafferty L, Treloar C, Guthrie J, Chambers GM, Butler T. Social capital strategies to enhance hepatitis C treatment awareness and uptake among men in prison. J Viral Hepat 2017;24:111–116.
[9] Gilead Sciences. HARVONI (ledipasvir and sofosbuvir). Prescribing information. Foster City: Gilead Sciences; 2015.
[10] AbbVie. VIEKIRAX + EXVIERA (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets). Summary of product characteristics. Maidenhead: AbbVie; 2016. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003839/WC500183997.pdf (accessed 1 October 2017).
[11] AbbVie. Mavyret (glecaprevir/pibrentasvir). Prescribing information. North Chicago: AbbVie; 2017.
[12] AbbVie. Maviret (glecaprevir/pibrentasvir). Summary of product characteristics. Maidenhead: AbbVie; 2017. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004430/WC500233677.pdf (accessed 1 October 2017).
[13] Ng T, Krishnan P, Pilot-Matias T, Kati W, Schnell G, Beyer J, et al. In vitro antiviral activity and resistance profile of the next generation hepatitis C virus NS5A inhibitor pibrentasvir. Antimicrob Agents Chemother 2017;61, pii: e02558-16.
[14] Ng TI, Tripathi R, Reisch T, Lu L, Middleton T, Hopkins TA, et al. In vitro antiviral activity and resistance profile of the next-generation hepatitis C virus NS3/4A protease inhibitor glecaprevir. Antimicrob Agents Chemother 2018;62, pii: e01620-17.
[15] Kosloski M, Zhao W, Asatryan A, Kort J, Geoffroy P, Liu W. No clinically relevant drug-drug interactions between methadone or buprenorphine/naloxone and anti-viral combination glecaprevir and pibrentasvir. Antimicrob Agents Chemother 2017;61 (10) pii: e00958–17.
[16] **Zeuzem S**, **Foster GR**, Wang S, Asatryan A, Gane E, Feld JJ, et al. Glecaprevir–pibrentasvir for 8 or 12 weeks in HCV genotype 1 or 3 infection. N Engl J Med 2018;378:354–369.
[17] Asselah T, Kowdley KV, Zadeikis N, Wang S, Hassanein T, Horsmans Y, et al. Efficacy of Glecaprevir/Pibrentasvir for 8 or 12 weeks in Patients with Hepatitis C Virus Genotype 2, 4, 5, or 6 Infection Without Cirrhosis. Clinical Gastroenterology and Hepatology 2018;16:417–426.
[18] Kwo PY, Poordad F, Asatryan A, Wang S, Wyles DL, Hassanein T, et al. High SVR rates upon 8- or 12-week treatment with glecaprevir and pibrentasvir in patients with chronic HCV genotype 1–6 infection without cirrhosis. J Hepatol 2017;67:263–271.
[19] Rockstroh J, Lacombe K, Viani RM, Orkin C, Wyles D, Luetkemeyer A, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients co-infected with hepatitis C virus and human immunodeficiency virus-1: the EXPEDITION-2 study, Abstract #522. J Hepatol 2017;66:S102.
[20] Gane E, Lawitz E, Pugatch D, Papatheodoridis G, Brau N, Brown A, et al. Glecaprevir and pibrentasvir in patients with HCV and severe renal impairment. N Engl J Med 2017;377:1448–1455.
[21] Gilead Sciences. VOSEVI (sofosbuvir/velpatasvir/voxilaprevir) prescribing information. Foster City: Gilead Sciences; 2017.
[22] VOSEVI (sofosbuvir/velpatasvir/voxilaprevir). Summary of product characteristics. Cambridge: Gilead Sciences International Ltd.; 2017. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004350/WC500235373.pdf (accessed 1 October 2017).
[23] Jacobson IM, Lawitz E, Gane EJ, Willems BE, Ruane PJ, Nahass RG, et al. Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials. Gastroenterology 2017;153:113–122.
[24] Kwo PY, Vinayek R. The therapeutic approaches for hepatitis C virus: protease inhibitors and polymerase inhibitors. Gut Liver 2011;5:406–417.
[25] Chae HB, Park SM, Youn SJ. Direct-acting antivirals for the treatment of chronic hepatitis C: open issues and future perspectives. Sci World J 2013;2013:704912.
[26] Banerjee D, Reddy KR. Review article: safety and tolerability of direct-acting anti-viral agents in the new era of hepatitis C therapy. Aliment Pharmacol Ther 2016;43:674–696.
[27] Bourlière M, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. N Engl J Med 2017;376:2134–2146.
[28] Gilead Sciences. EPCLUSA (sofosbuvir and velpatasvir) prescribing information. Foster City: Gilead Sciences; 2016.
[29] Merck, Sharp & Dohme. Zepatier (elbasvir/grazoprevir) prescribing information. Whitehouse Station: Merck, Sharp & Dohme; 2016.
[30] AbbVie. VIEKIRA PAK (ombitasvir, paritaprevir/ritonavir, dasabuvir). Prescribing information. North Chicago: AbbVie; 2015.
[31] Ge PS, Runyon BA. Treatment of patients with cirrhosis. N Engl J Med 2016;375:767–777.
[32] Negro F, Forton D, Craxi A, Sulkowski MS, Feld JJ, Manns MP, et al. Extrahepatic morbidity and mortality of chronic hepatitis C. Gastroenterology 2015;149:1345–1360.