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PANCREAS, BILIARY TRACT, AND LIVER

Eight Weeks of Treatment With Glecaprevir/Pibrentasvir Is Safe and Efficacious in an Integrated Analysis of Treatment-Naïve Patients With Hepatitis C Virus Infection

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BACKGROUND & AIMS: **The direct-acting antiviral combination glecaprevir/pibrentasvir has been approved by the Food and Drug Administration for 8 weeks of treatment in treatment-naïve patients with hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis. We performed an integrated analysis of data from trials to evaluate the overall efficacy and safety of 8 weeks of glecaprevir/pibrentasvir in treatment-naïve patients without cirrhosis or with compensated cirrhosis.**

METHODS: **We pooled data from 8 phase 2 or phase 3 trials of treatment-naïve patients with HCV genotype 1 to 6 infections, without cirrhosis or with compensated cirrhosis, who received 8 weeks of glecaprevir/pibrentasvir.**

RESULTS: **Of 1248 patients, 343 (27%) had cirrhosis. Most patients were white (80%) and had HCV genotype 1 infection (47%) or genotype 3 infection (22%); the median age was 54 years. Overall rates of sustained virologic response at post-treatment week 12 were 97.6% (1218 of 1248) in the intention to treat (ITT) and 99.3% (1218 of 1226) in the modified ITT populations. When we excluded patients with genotype 3 infections with compensated cirrhosis (consistent with the European label), rates of sustained virologic response at post-treatment week 12 were 97.6% in the ITT and 99.4% in the modified ITT populations. Eight virologic failures (7 in patients without cirrhosis and 1 in a patient with cirrhosis) occurred in the ITT population. Virologic failure was not associated with markers of advanced liver disease or populations of interest (current alcohol use, opioid substitution therapy, history of injection-drug use, and severe renal impairment). Treatment-emergent adverse events (AEs) occurred in 58% of patients. The most frequent AEs (>10%) were headache (12%) and fatigue (12%). Serious AEs and AEs that led to glecaprevir/pibrentasvir discontinuation were reported in 2% and less than 1% of patients, respectively.**

Abbreviations used in this paper: AE, adverse event; APRI, aspartate aminotransferase to platelet ratio index; DAA, direct-acting antiviral; G/P, glecaprevir/pibrentasvir; GT, genotype; GTΔ3CC, population excluding genotype 3–infected patients with compensated cirrhosis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ITT, intention-to-treat; mITT, modified intention-to-treat; OST, opioid substitution therapy; SVR12, sustained virologic response at post-treatment week 12.

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CONCLUSIONS: **In a pooled analysis of data from 8 trials, we found that 8 weeks of treatment with glecaprevir/pibrentasvir is efficacious and well tolerated in treatment-naïve patients with HCV genotype 1 to 6 infections, with or without cirrhosis.**

Keywords: DAA; Liver; Pangenotypic; Fibrosis; Panfibrotic.

Hepatitis C virus (HCV) infection, one of the leading causes of chronic liver disease worldwide, can lead to extensive fibrosis and cirrhosis and an increased risk for developing hepatocellular carcinoma.[1] In 2016, the World Health Organization (WHO) established targets to eliminate HCV as a global health threat, including reductions in HCV-related mortality by 65%, incidence by 80%, increase in diagnosis to 90% of all HCV infections, and treatment of 80% of eligible persons by 2030.[2]

With the approval of direct-acting antivirals (DAAs) beginning in 2014, the HCV population has evolved. DAA treatment initially was prioritized for patients with more advanced liver disease or those who had failed interferon-based treatments previously.[3,4] As a result of this prioritization and increasing incidence among young people who use drugs, the remaining HCV patient population has shifted rapidly to be younger and more often treatment-naïve without cirrhosis.[5,6] Based on a retrospective analysis from US academic and community centers, 45% of treated patients had cirrhosis in 2014. This percentage steadily decreased to 21% by the end of 2017.[6] Because this represents only patients receiving treatment, this percentage may be an overestimation of the actual proportion of patients with cirrhosis because many US publicly funded payers required that patients have F3 or F4 fibrosis to be approved for treatment in 2017. This same analysis also saw the percentage of patients with no prior treatment experience increase from 56% in 2014 to 86% in 2017.

The DAA era also has facilitated the evolution of HCV patient care, leading to increased awareness to improve access to treatment to achieve elimination. A key factor in the HCV elimination effort is expanding treatment to primary care settings. As such, simplification of pretreatment evaluations and patient monitoring aim to reduce new provider barriers to HCV management.[7] In the latter half of 2019, The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America released guidelines with a simplified treatment algorithm for treatment-naïve HCV patients without cirrhosis or with compensated cirrhosis.[8] Two highly effective pangenotypic DAA regimens are recommended in each simplified algorithm, sofosbuvir/velpatasvir[9] and glecaprevir/pibrentasvir (G/P). These guideline updates highlight a treatment paradigm shift away from individualized treatment by HCV specialists to broad dissemination of HCV care by nonspecialists who may facilitate expansion of the HCV treater pool and HCV elimination.[10,11]

The clinical trial program for the once-daily, all-oral, fixed-dose DAA combination of glecaprevir, an NS3/4A protease inhibitor, and pibrentasvir, an NS5A inhibitor (collectively G/P), compared an 8-week regimen with a 12-week regimen in patients chronically infected with HCV genotypes (GT)1 to 6.[12,13] An 8-week duration initially was approved by the US Food and Drug Administration and the European Medicines Agency in 2017 for treatment-naïve patients without cirrhosis, and a 12-week duration was approved in treatment-naïve patients with compensated cirrhosis.[12] In recent real-world studies, G/P achieved high sustained virologic response at post-treatment week 12 (SVR12) rates consistent with those observed in clinical trials.[14–16]

A recent phase 3b study (EXPEDITION-8) that evaluated G/P administered for 8 weeks in HCV treatment-naïve patients with HCV GT1 to 6 infection and compensated cirrhosis showed a high modified intention-to-treat (mITT) SVR12 rate of 99.7%.[17] This finding led to a US label update in September 2019 and an EU label update in March 2020 to shorten the treatment duration from 12 to 8 weeks in treatment-naïve patients with HCV and compensated cirrhosis across all HCV genotypes (GT1–6).[18,19] Currently, G/P is the only 8-week pangenotypic treatment available for treatment-naïve patients with chronic HCV irrespective of cirrhosis status,[10,18,20] meeting the needs of a changing HCV patient population.[5,6]

The objective of this analysis was to assess the pooled efficacy and safety of 8-week G/P treatment in HCV treatment-naïve patients with chronic HCV GT1 to 6 infection without cirrhosis or with compensated cirrhosis. Pre-approval and postapproval studies included in this analysis enrolled diverse HCV patient populations, including patients with HCV/human immunodeficiency virus (HIV)-1 co-infection, all stages of chronic kidney disease, or a history of injection-drug use.

Methods

Patients and Study Design

This post hoc analysis was performed using pooled data from 8 phase 2b, 3a, and 3b clinical trials of G/P, as follows: SURVEYOR-1[21] (part 2; NCT02243280), SURVEYOR-2[21,22] (parts 2 and 4; NCT02243293), ENDURANCE-1[23] (NCT02604017), ENDURANCE-3[23] (NCT02640157), EXPEDITION-2[24] (NCT02738138), ENDURANCE-5,6[25] (NCT02966795), EXPEDITION-5[26] (NCT03069365), and EXPEDITION-8[17] (NCT03089944). Patients were randomized or assigned to receive 8 weeks of oral, once-daily G/P 300/120 mg.

Details of the study design, patient population, and outcomes of these trials have been published previously.[17,21–26] In brief, patients were ages 18 years and older, were diagnosed with chronic HCV GT1 to 6 infection, and were HCV treatment-naïve. Patients without cirrhosis or with compensated cirrhosis were included in this analysis. Cirrhosis assessment was based on a liver biopsy, FibroScan (Echosens, Waltham, MA), or a combination of FibroTest (BioPredictive, Paris, France) and the aspartate aminotransferase to platelet ratio index (APRI). Cirrhosis status was determined within each study protocol, and was not re-assessed for this analysis. Cirrhosis was defined as a liver biopsy with a METAVIR fibrosis score of 4 (or equivalent), a FibroScan result of 14.6 kPa or greater, or a FibroTest result of 0.75 or higher with an APRI score greater than 2. Absence of cirrhosis was defined by a liver biopsy with a METAVIR fibrosis score of 3 or less (or equivalent), a FibroScan result less than 12.5 kPa, or a FibroTest result less than 0.72 with an APRI score of 2 or less or a FibroTest result of 0.48 or less with an APRI score of less than 1.

What You Need to Know

Background

An analysis of data from multiple trials is needed evaluate the overall efficacy and safety of 8 weeks of glecaprevir/pibrentasvir in treatment-naïve patients without cirrhosis or with compensated cirrhosis.

Findings

A pooled analysis of data from 8 trials found that 8 weeks of treatment with glecaprevir/pibrentasvir is efficacious and well tolerated in treatment-naïve patients with HCV genotype 1 to 6 infections, with or without cirrhosis.

Implications for patient care

Patients with chronic HCV genotype 1 to 6 infections, with or without cirrhosis, can be treated safely and effectively with glecaprevir/pibrentasvir for 8 weeks.

Analysis Populations

The intention-to-treat (ITT) population included all patients who received 1 or more doses of G/P. The mITT population excluded patients with nonvirologic failure (ie, patients who discontinued treatment without experiencing virologic failure or who were lost to follow-up evaluation).

Two data sets were used for this analysis: the GT1 to 6 data set included all patients without cirrhosis and those with compensated cirrhosis, and the population excluding genotype 3–infected patients with compensated cirrhosis (GTΔ3CC) data set (representative of the European Union label at the time of analysis).

Efficacy Analysis

Efficacy, assessed as the percentage of patients with SVR12, was determined in the ITT and the mITT patient populations. SVR12 rates were calculated along with 2-sided 95% CIs based on the Wilson score method. SVR12 rates were evaluated in patient subgroups stratified by clinical markers of advanced liver disease including platelet count, albumin, fibrosis-4, and APRI.

SVR12 rates also were assessed in various prespecified patient subgroups categorized according to baseline characteristics as follows: age, race, ethnicity, body mass index, genotype, fibrosis stage, HCV RNA level, recent injection-drug use ($\leq$12 months prior), former injection-drug use (>12 months prior), alcohol use, concomitant proton pump inhibitor use, stable opioid substitution therapy (OST), HIV co-infection, history of diabetes, history of depression/bipolar disorder, and severe renal impairment. Injection-drug use included all illicit drugs, and recent injection-drug use was patient-reported and/or confirmed by positive urine drug screen.

Safety Analysis

Treatment-emergent adverse events (AEs) were analyzed in the ITT population and defined as AEs with an onset after the start of G/P and no more than 30 days after treatment. Clinical laboratory abnormalities in alanine aminotransferase, aspartate aminotransferase, and total bilirubin levels during the treatment period were evaluated in the ITT population with available data.

Results

Patients and Demographics

The post hoc analysis of the GT1 to 6 data set (US label–consistent data) included 1248 patients in the ITT population, of whom 905 (73%) were noncirrhotic and 343 (27%) had compensated cirrhosis. Approximately 85% of patients were younger than age 65 years (median age, 54 y), and 80% were white. Most of the patients had HCV GT1 (47%) or GT3 (22%). The demographics and clinical characteristics of these patients at baseline are summarized in Table 1. The post hoc analysis of the GTΔ3CC data set (European Union label–consistent data) included 1185 patients in the ITT population. Demographic characteristics of patients in the GTΔ3CC data set were consistent with those in the GT1 to 6 data set (Supplementary Table 1).

Nonvirologic failure was reported in 22 and 21 patients in the GT1 to 6 and GTΔ3CC data sets, respectively (Table 2). Therefore, the mITT population included 1226 and 1164 patients, respectively.

Table 1. Demographics and Clinical Characteristics at Baseline: ITT Population, GT1 to 6 Data Set

	GT1 to 6 treatment-naïve		
	Noncirrhotic (n = 905)	Cirrhotic (n = 343)	Overall (N = 1248)
Male	492 (54.4)	217 (63.3)	709 (56.8)
Age, median, *y*	52.0	58.0	54.0
<65 *y*	800 (88.4)	257 (74.9)	1057 (84.7)
Race			
White	708 (78.2)	285 (83.1)	993 (79.6)
Black	67 (7.4)	28 (8.2)	95 (7.6)
Asian	112 (12.4)	28 (8.2)	140 (11.2)
Other[a]	18 (2.0)	2 (0.6)	20 (1.6)
Ethnicity			
Hispanic or Latino	92 (10.2)	43 (12.5)	135 (10.8)
Not Hispanic or Latino	813 (89.8)	300 (87.5)	1113 (89.2)
Mean BMI, kg/m^2	26.3	28.3	26.8
≥30 kg/m^2	160 (17.7)	101 (29.4)	261 (20.9)
HCV GT			
1	352 (38.9)	231 (67.3)	583 (46.7)
2	202 (22.3)	26 (7.6)	228 (18.3)
3	217 (24.0)	63 (18.4)	280 (22.4)
4	53 (5.9)	13 (3.8)	66 (5.3)
5	19 (2.1)	1 (0.3)	20 (1.6)
6	62 (6.9)	9 (2.6)	71 (5.7)
Fibrosis stage			
F0–F1	741/902 (82.2)	0	741/1245 (59.5)
F2	53/902 (5.9)	0	53/1245 (4.3)
F3	107/902 (11.9)	0	107/1245 (8.6)
F4	1/902 (0.1)	343 (100)	344/1245 (27.6)
HCV RNA, ≥1,000,000 *IU/mL*	547 (60.4)	231 (67.3)	778 (62.3)
Platelet count, $<100 \times 10^9$/L	6 (0.7)	63 (18.4)	69 (5.5)
APRI ≥2	34/901 (3.8)	113/331 (34.1)	147/1232 (11.9)
FIB-4 ≥3.25	46/901 (5.1)	168/331 (50.8)	214/1232 (17.4)
History of injection-drug use[b]			
Recent (≤12 months prior)	22/624 (3.5)	4 (1.2)	26/967 (2.7)
>12 months prior	226/624 (36.2)	88 (25.7)	314/967 (32.5)
No history	376/624 (60.3)	251 (73.2)	627/967 (64.8)
Stable OST	69 (7.6)	27 (7.9)	96 (7.7)
HIV co-infection	121 (13.4)	0	121 (9.7)
History of diabetes	60 (6.6)	68 (19.8)	128 (10.3)
History of depression or bipolar disorder	206 (22.8)	11 (3.2)	217 (17.4)
Severe renal impairment	67 (7.4)	0	67 (5.4)
Concomitant PPI use	101 (11.2)	39 (11.4)	140 (11.2)
Alcohol use			
Drinker	349 (38.6)	70 (20.4)	419 (33.6)
Ex-drinker	284 (31.4)	126 (36.7)	410 (32.9)
Nondrinker	267 (29.5)	144 (42.0)	411 (32.9)
Unknown	5 (0.6)	3 (0.9)	8 (0.6)

NOTE. Data are n (%) or n/N (%) unless otherwise stated; percentages are calculated from nonmissing values.
APRI, aspartate aminotransferase to platelet ratio index; BMI, body mass index; FIB-4, fibrosis-4; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ITT, intention-to-treat; OST, opioid substitution therapy; PPI, proton pump inhibitor.
[a]Other races include American Indian, Alaska native, multiple, native Hawaiian, and other Pacific Islander categories.
[b]SURVEYOR-1 and -2 trials did not capture this information and are excluded from this assessment.

Efficacy

In the GT1 to 6 data set, the ITT SVR12 rate was 97.6% (95% CI, 96.6–98.3) and did not differ by cirrhosis status: 97.6% (95% CI, 96.3–98.4) in patients without cirrhosis and 97.7% (95% CI, 95.5–98.8) in patients with compensated cirrhosis. In the mITT population, the SVR12 rates were 99.2% (95% CI, 98.4–99.6) in the noncirrhotic group, 99.7% (95% CI, 98.3–99.9) in the compensated cirrhosis group, and 99.3% (95% CI, 98.7–99.7) overall (Figure 1). Similar results were observed in the GTΔ3CC data set, with SVR12 rates greater than 97% and greater than 99% for the ITT and mITT populations, respectively (Supplementary Figure 1).

In an examination of clinical markers of advanced liver disease, SVR12 rates were greater than 95%. In the ITT population, SVR12 rates were 95.7% and 96.6%

Table 2. Reasons for SVR12 Nonresponse: ITT Population, GT1 to 6 Data Set

Reasons for nonresponse, n (%)	GT1 to 6 treatment-naïve		
	Noncirrhotic (n = 905)	Cirrhotic (n = 343)	Overall (N = 1248)
On-treatment virologic failure	1 (0.1)	0	1 (<0.1)
Relapse[a]	6/890 (0.7)	1/336 (0.3)	7/1226 (0.6)
Nonvirologic failure	15 (1.7)	7 (2.0)	22 (1.8)
Study-drug discontinuation	6 (0.7)	1 (0.3)	7 (0.6)
Lost to follow-up evaluation	9 (1.0)	6 (1.7)	15 (1.2)

GT, genotype; ITT, intention-to-treat; SVR12, sustained virologic response at post-treatment week 12.
[a]Denominator includes patients who completed treatment with hepatitis C virus RNA less than the lower limit of quantification at the end of treatment and had post-treatment hepatitis C virus RNA data.

among patients with platelet counts less than 100×10^9/L and albumin levels less than 3.5 g/dL, respectively; the mITT SVR12 rates were 98.5% and 100%, respectively (Figure 2). SVR12 rates in subgroups defined by clinical markers of advanced liver disease in the GTΔ3CC data set were similar to those observed in the GT1 to 6 data set (Supplementary Figure 2).

In the GT1 to 6 data set, virologic failure was observed in 1 of 343 patients (0.3%) with compensated cirrhosis (GT3) and in 7 of 905 patients (0.8%) without cirrhosis (6 GT3 and 1 GT5) in the ITT population; of these 8 cases of virologic failure, 7 were relapses and 1 was on-treatment virologic failure (Table 2). For GT3 patients in the mITT population with available resistance data (using a 15% threshold), 23 of 270 (8.5%) had A30K substitutions at baseline, 4 of whom experienced virologic failure; additional resistance details of these virologic failures have been reported previously.[19] In addition, 14 of 270 (5.2%) GT3 patients had Y93H substitutions at baseline; none of these patients experienced virologic failure. In the GTΔ3CC data set, there were 6 relapses and 1 on-treatment virologic failure (Supplementary Table 2). The rate of nonvirologic failure was less than 2% in both the GT1 to 6 data set (Table 2) and the GTΔ3CC data set (Supplementary Table 2). In both data sets, roughly one third of the patients with nonvirologic failure discontinued G/P prematurely; the rest were lost to follow-up evaluation.

Efficacy by Baseline Characteristics

ITT SVR12 rates were greater than 95% across assessed baseline characteristics, with the exception of recent injection-drug use (88.5%; 23 of 26) and F3 fibrosis (93.5%; 100 of 107) (Table 3); however, the majority of these non-SVRs were owing to missing SVR12 data rather than virologic failure. As such, SVR12 rates were very high in the mITT population (≥95%) (Table 3), irrespective of baseline characteristics, including history of injection-drug use, fibrosis score, alcohol use, OST, and HIV co-infection. In the GTΔ3CC data set, mITT SVR12 rates across all subgroups also were high. Supplementary Table 3 shows SVR12 rates for the GTΔ3CC mITT and ITT populations. SVR12 rates by genotype in treatment-naïve, noncirrhotic patients are shown for the ITT and mITT populations in Supplementary Table 4.

Safety

In the GT1 to 6 data set, the rate of any AEs was 58%, with the most common AEs (≥10%) being headache (12%) and fatigue (12%). The rate of serious AEs was 2%. None of the serious AEs were considered related to G/P treatment. AEs leading to premature G/P discontinuation occurred in 2 (<1%) patients (all noncirrhotic); both were serious AEs with no reasonable possibility of being related to G/P treatment (adenocarcinoma and ileus). One patient with a history of diabetic nephropathy and moderate ascites at screening enrolled as a protocol violation and experienced a nonserious event of worsening ascites (grade 1) on day 8, which was ongoing at the end of the study. Six patients (<1%) experienced hepatic laboratory abnormalities of grade 3 severity or higher in levels of alanine aminotransferase (n = 1), aspartate aminotransferase increase (n = 1), or total bilirubin (n = 4). None of the cases were consistent with drug-induced liver injury (Table 4). Two patients without cirrhosis died; 1 death was the result of adenocarcinoma and the other was owing to an accidental overdose on post-treatment day 77; both were considered not related to study-drug treatment.

Safety results in the GTΔ3CC data set were similar to those in the GT1 to 6 data set: AEs were reported in 59% of patients, and the rates of AEs leading to discontinuation (<1%), serious AEs (3%), and serious AEs leading to discontinuation (<1%) were low (Supplementary Table 5). There were no serious AEs related to G/P treatment. The 2 deaths observed in the GT1 to 6 data set were captured in this data set as well.

Discussion

This post hoc analysis shows that treatment with G/P for 8 weeks is highly efficacious (GT1–6 data set: mITT SVR12 >99%; ITT SVR12, >97%) in HCV treatment-naïve patients with chronic HCV GT1 to 6 infection regardless of cirrhosis status, with a virologic failure rate of less than 0.8%. The analysis in the GTΔ3CC data set showed similar results: SVR12 rates were high (>99% in the mITT population and >97% in the ITT population) regardless of cirrhosis status. Similarly, effectiveness data from real-world studies of 8-week treatment with G/P in treatment-naïve populations are consistent with

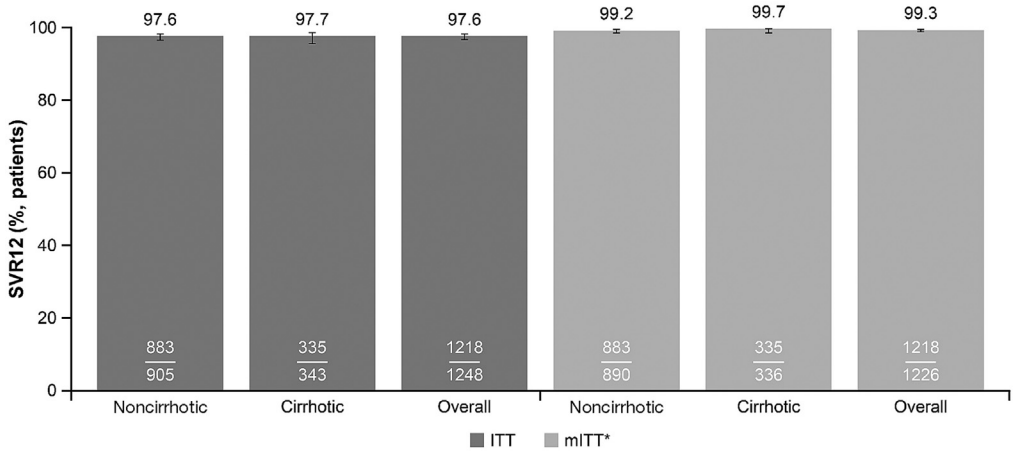

Figure 1. SVR12 rates after glecaprevir/pibrentasvir treatment for 8 weeks by cirrhosis status (GT1–6 data set). Numbers represent the number of patients with SVR12/total number of patients in each group. Error bars represent 95% CIs. *The mITT population excluded patients with nonvirologic failure. GT, genotype; ITT, intention-to-treat; mITT, modified intention-to-treat; SVR12, sustained virologic response at post-treatment week 12.

the rates of SVR12 observed in this analysis.[15,27–31] These high SVR12 rates support the product labeling that recommends the use of G/P for 8 weeks in treatment-naïve HCV patients without cirrhosis or with compensated cirrhosis, regardless of genotype.

The subgroup analysis conducted in the present study confirmed that G/P treatment resulted in high mITT SVR12 (≥95%) rates across all patient subgroups categorized by clinical markers of advanced liver disease and baseline characteristics, including concomitant proton pump inhibitor, OST, and history of injection-drug use. However, in both the GT1 to 6 and GTΔ3CC data sets, patients with a recent history of injection-drug use had slightly lower ITT SVR12 rates, although there were no

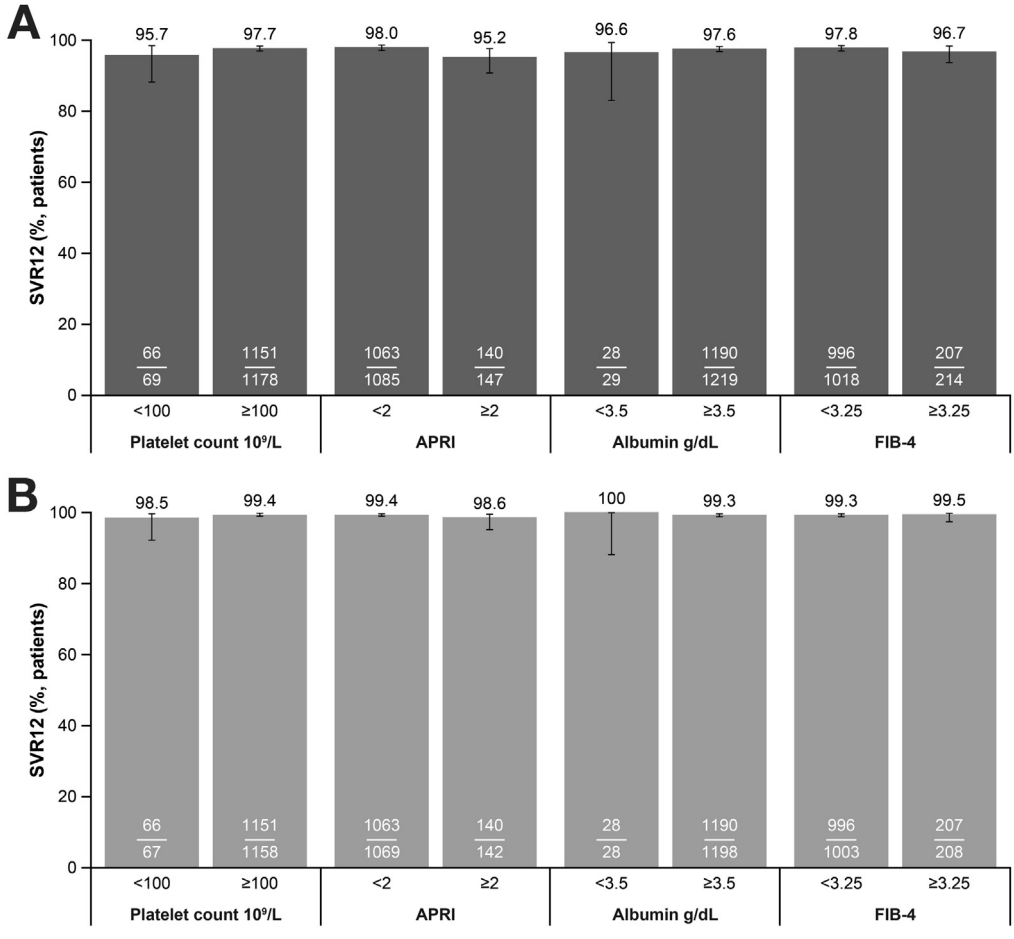

Figure 2. SVR12 rates after glecaprevir/pibrentasvir treatment for 8 weeks by clinical markers of advanced liver disease (GT1–6 data set): (*A*) ITT and (*B*) mITT population*. Numbers represent the number of patients with SVR12/total number of patients in each group. Error bars represent 95% CIs. *The mITT population excluded patients with nonvirologic failure. APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4; GT, genotype; ITT, intention-to-treat; mITT, modified intention-to-treat; SVR12, sustained virologic response at post-treatment week 12.

Table 3. SVR12 Rates After G/P Treatment for 8 Weeks by Subgroups of Interest: GT1 to 6 Data Set

	GT1 to 6 treatment-naive			
	ITT		mITT[a]	
	n/N (%)	95% CI	n/N (%)	95% CI
<65 *y*	1033/1057 (97.7)	96.6–98.5	1033/1041 (99.2)	98.5–99.6
≥65 *y*	185/191 (96.9)	93.3–98.6	185/185 (100)	98.0–100
Black	92/95 (96.8)	91.1–98.9	92/92 (100)	96.0–100
Non-black	1126/1153 (97.7)	96.6–98.4	1126/1134 (99.3)	98.6–99.6
Hispanic or Latino	133/135 (98.5)	94.8–99.6	133/134 (99.3)	95.9–99.9
Not Hispanic or Latino	1085/1113 (97.5)	96.4–98.3	1085/1092 (99.4)	98.7–99.7
BMI <30 *kg/m²*	962/987 (97.5)	96.3–98.3	962/970 (99.2)	98.4–99.6
BMI ≥30 *kg/m²*	256/261 (98.1)	95.6–99.2	256/256 (100)	98.5–100
HCV GT1	573/583 (98.3)	96.9–99.1	573/573 (100)	99.3–100
HCV GT2	226/228 (99.1)	96.9–99.8	226/226 (100)	98.3–100
HCV GT3	267/280 (95.4)	92.2–97.3	267/274 (97.4)	94.8–98.8
HCV GT4	63/66 (95.5)	87.5–98.4	63/63 (100)	94.3–100
HCV GT5	19/20 (95.0)	76.4–99.1	19/20 (95.0)	76.4–99.1
HCV GT6	70/71 (98.6)	92.4–99.8	70/70 (100)	94.8–100
Fibrosis stage F0–1	728/741 (98.2)	97.0–99.0	728/730 (99.7)	99.0–99.9
Fibrosis stage F2	51/53 (96.2)	87.2–99.0	51/53 (96.2)	87.2–99.0
Fibrosis stage F3	100/107 (93.5)	87.1–96.8	100/103 (97.1)	91.8–99.0
Fibrosis stage F4	336/344 (97.7)	95.5–98.8	336/337 (99.7)	98.3–99.9
HCV RNA, <1,000,000 *IU/mL*	460/470 (97.9)	96.1–98.8	460/461 (99.8)	98.8–100
HCV RNA, ≥1,000,000 *IU/mL*	758/778 (97.4)	96.1–98.3	758/765 (99.1)	98.1–99.6
Recent injection-drug use (≤12 months prior)[b]	23/26 (88.5)	71.0–96.0	23/23 (100)	85.7–100
Injection-drug use >12 months prior[b]	304/314 (96.8)	94.2–98.3	304/308 (98.7)	96.7–99.5
No history of injection-drug prior[b]	618/627 (98.6)	97.3–99.2	618/622 (99.4)	98.4–99.7
On stable OST	93/96 (96.9)	91.2–98.9	93/93 (100)	96.0–100
Not on stable OST	1125/1152 (97.7)	96.6–98.4	1125/1133 (99.3)	98.6–99.6
HIV co-infection	120/121 (99.2)	95.5–99.9	120/120 (100)	96.9–100
No HIV co-infection	1098/1127 (97.4)	96.3–98.2	1098/1106 (99.3)	98.6–99.6
History of diabetes	125/128 (97.7)	93.3–99.2	125/126 (99.2)	95.6–99.9
No history of diabetes	1093/1120 (97.6)	96.5–98.3	1093/1100 (99.4)	98.7–99.7
History of depression/bipolar disorder	212/217 (97.7)	94.7–99.0	212/212 (100)	98.2–100
No history of depression/bipolar disorder	1006/1031 (97.6)	96.4–98.4	1006/1014 (99.2)	98.5–99.6
Concomitant PPI	136/140 (97.1)	92.9–98.9	136/136 (100)	97.3–100
No concomitant PPI	1082/1108 (97.7)	96.6–98.4	1082/1090 (99.3)	98.6–99.6
Severe renal impairment	65/67 (97.0)	89.8–99.2	65/65 (100)	94.4–100
No severe renal impairment	1153/1181 (97.6)	96.6–98.4	1153/1161 (99.3)	98.6–99.7
Drinker	409/419 (97.6)	95.7–98.7	409/412 (99.3)	97.9–99.8
Ex-drinker	395/410 (96.3)	94.1–97.8	395/400 (98.8)	97.1–99.5
Nondrinker	406/411 (98.8)	97.2–99.5	406/406 (100)	99.1–100

NOTE. n/N, number of patients with SVR12/ total number of patients in each subgroup.
BMI, body mass index; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ITT, intention-to-treat; mITT, modified intention-to-treat; OST, opioid substitution therapy; PPI, proton-pump inhibitor; SVR12, sustained virologic response at post-treatment week 12.
[a]mITT population excluded patients with nonvirologic failure.
[b]SURVEYOR-1 and SURVEYOR-2 trials did not capture this information, thus they were excluded from this assessment.

virologic failures (mITT SVR12, 100%); these data are limited because of small sample sizes, but remain consistent with previous results.[32] Historically, patients with certain baseline disease or viral characteristics were considered to be harder to cure.[33,34] In the present analysis, none of the evaluated baseline characteristics affected the rate of virologic failure. Achieving high SVR12 rates with the G/P 8-week regimen regardless of HCV genotype and patient baseline characteristics might eliminate the need for genotyping and other baseline assessments before therapy.[11] The updated American Association for the Study of Liver Diseases and the Infectious Diseases Society of America simplified treatment algorithm does not recommend any genotype-specific assessments in patients with HCV GT1 to 6 and compensated cirrhosis before the initiation of HCV treatment with G/P, which is not the case with sofosbuvir/velpatasvir.[10] High SVR12 rates observed in the present integrated analysis across all genotypes validate these recommendations with respect to G/P treatment.

Treatment with G/P was well tolerated; treatment-related serious AEs, discontinuations because of AEs, and laboratory abnormalities of grade 3 or higher severity were rare and not consistent with drug-induced

Table 4. Treatment-Emergent Adverse Events and Postbaseline Clinical Laboratory Abnormalities: ITT Population; GT1 to 6 Data Set

	GT1 to 6 treatment-naïve		
	Noncirrhotic (n = 905)	Cirrhotic (n = 343)	Overall (N = 1248)
AEs, n (%)			
Any AE	563 (62.2)	158 (46.1)	721 (57.8)
Any serious AE	24 (2.7)	6 (1.7)	30 (2.4)
Any serious AE possibly related to G/P	0	0	0
Any AE leading to G/P discontinuation	2 (0.2)	0	2 (0.2)
Any serious AE leading to G/P discontinuation	2 (0.2)	0	2 (0.2)
Deaths[a]	2 (0.2)	0	2 (0.2)
AEs in ≥10% in any group			
Headache	120 (13.3)	28 (8.2)	148 (11.9)
Fatigue	115 (12.7)	30 (8.7)	145 (11.6)
Laboratory abnormalities, n/N (%)			
Alanine aminotransferase Grade ≥3	0/903	1/342 (0.3)	1/1245 (<0.1)
Aspartate aminotransferase Grade ≥3	1/903 (0.1)	0/342	1/1245 (<0.1)
Total bilirubin Grade ≥3	4/903 (0.4)	0/342	4/1245 (0.3)

n/N, number of patients with respective parameter/number of patients with available data.
AE, treatment-emergent adverse event; G/P, glecaprevir/pibrentasvir; GT, genotype; ITT, intention-to-treat.
[a]Includes non–treatment-emergent deaths

liver injury. No new safety signals were observed in the current analysis.

There were limitations to this analysis that are inherent to its design. Because this is a post hoc analysis, it does not have the statistical power to compare patient groups. In addition, not all of the studies included in the analysis reported the same data, specifically SURVEYOR-1 and SURVEYOR-2 did not capture data on whether patients had a history of injection-drug use 12 months or fewer prior or more than 12 months prior. A further limitation was the low number of patients in some subgroups, for example, patients with recent injection-drug use and patients with HCV GT5.

In conclusion, the results of this analysis show that G/P for 8 weeks is efficacious in treating treatment-naïve patients, who comprise the current majority of infected patients with HCV. Considering the high overall mITT SVR12 rate and the very low number of virologic failures, there would be little benefit in trying to identify negative predictors or a subpopulation with low SVR, adding to the evidence that treatment with 8 weeks of G/P potentially simplifies pretreatment assessment. Furthermore, the short treatment duration may help the effort to improve patient adherence to treatment, reduce treatment burden, and support elimination efforts.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.06.044.

References

1. Pawlotsky J-M, Negro F, Aghemo A, et al. EASL recommendations on treatment of hepatitis C 2018. J Hepatol 2018; 69:461–511.
2. Viral hepatitis elimination: call to action. Available from: https://www.aasld.org/programs-initiatives/viral-hepatitis-elimination-call-action. Accessed January 22, 2020.
3. Franco RA, Galbraith JW, Overton ET. Direct-acting antivirals and chronic hepatitis C: towards elimination. Hepatoma Res 2018;4:74–92.
4. Smolić R, Jakab J, Kuna L, et al. Approaches and considerations for the successful treatment of HCV infection. Chapter 16. In: Smolić M, ed. Update on hepatitis C:205–216. Available from: https://www.intechopen.com/books/update-on-hepatitis-c/approaches-and-considerations-for-the-successful-treatment-of-hcv-infection. Accessed January 7, 2020.
5. Tsai N, Bacon B, Curry M, et al. Change in demographics of direct-acting antiviral (DAA)-prescribed HCV patients from 2013 to 2018: data from 19,994 patients in the TRIO network (abstract 613). Hepatology 2018;68:365A–366A.
6. Tsai N, Bacon B, Curry M, et al. Changing demographics among populations prescribed HCV treatment, 2013-2017. Am J Manag Care 2019;25:319–323.
7. Hagan LM, Schinazi RF. Best strategies for global HCV eradication. Liver Int 2013;33(Suppl 1):68–79.
8. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015; 62:932–954.
9. Jacobson IM, Lawitz E, Gane EJ, 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.
10. Simplified HCV treatment algorithm for treatment-naive adults with compensated cirrhosis. Available from: https://www.hcvguidelines.org/treatment-naive/simplified-treatment-compensated-cirrhosis. Accessed January 6, 2020.
11. Puoti M, Foster GR, Wang S, et al. High SVR12 with 8-week and 12-week glecaprevir/pibrentasvir therapy: an integrated analysis of HCV genotype 1-6 patients without cirrhosis. J Hepatol 2018; 69:293–300.
12. AbbVie. Mavyret (glecaprevir and pibrentasvir) US prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209394s008lbl.pdf. Accessed: August 12, 2020.
13. AbbVie. Maviret (glecaprevir and pibrentasvir) prescription drug note. Available from: https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/112130_6250113F1021_1_05. Accessed: August 12, 2020.

14. Berg T, Naumann U, Stoehr A, et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of chronic hepatitis C infection: data from the German Hepatitis C-Registry. Aliment Pharmacol Ther 2019; 49:1052–1059.
15. D'Ambrosio R, Pasulo L, Puoti M, et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir in 723 patients with chronic hepatitis C. J Hepatol 2019;70:379–387.
16. Wiegand J, Naumann U, Stoehr A, et al. Glecaprevir/pibrentasvir for the treatment of patients with chronic hepatitis C virus infection: updated real-world data from the German Hepatitis C-Registry (AASLD abstract 611). Hepatology 2018;68:364A.
17. Brown RS Jr, Buti M, Rodrigues L, et al. Glecaprevir/pibrentasvir for 8 weeks in treatment-naive patients with chronic HCV genotypes 1-6 and compensated cirrhosis: the EXPEDITION-8 trial. J Hepatol 2020;72:441–449.
18. AbbVie Receives FDA Approval of MAVYRET (glecaprevir/pibrentasvir) to Shorten Treatment Duration to Eight Weeks for Treatment-Naïve Patients with Chronic Hepatitis C and Compensated Cirrhosis Across All Genotypes. Available from: https://news.abbvie.com/news/press-releases/abbvie-receives-fda-approval-mavyret-glecaprevirpibrentasvir-to-shorten-treatment-duration-to-eight-weeks-for-treatment-nave-patients-with-chronic-hepatitis-c-and-compensated-cirrhosis-across-all-genotypes.htm. Accessed December 13, 2019.
19. Krishnan P, Pilot-Matias T, Schnell G, et al. Pooled resistance analysis in patients with hepatitis C virus genotype 1 to 6 infection treated with glecaprevir-pibrentasvir in phase 2 and 3 clinical trials. Antimicrob Agents Chemother 2018; 62:e01249–e01318.
20. AASLD-IDSA. Simplified HCV treatment algorithm for treatment-naive adults without cirrhosis. Available from: https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCV-Guidance_TxN-Simplified-Tx-No-Cirr_c.pdf. Accessed January 22, 2020.
21. Kwo PY, Poordad F, Asatryan A, et al. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis. J Hepatol 2017;67:263–271.
22. Asselah T, Kowdley KV, Zadeikis N, 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. Clin Gastroenterol Hepatol 2018;16:417–426.
23. Zeuzem S, Foster GR, Wang S, et al. Glecaprevir–pibrentasvir for 8 or 12 weeks in HCV genotype 1 or 3 infection. N Engl J Med 2018;378:354–369.
24. Rockstroh JK, Lacombe K, Viani RM, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients coinfected with hepatitis C virus and human immunodeficiency virus type 1: the EXPEDITION-2 study. Clin Infect Dis 2018;67:1010–1017.
25. Asselah T, Lee SS, Yao BB, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients with chronic hepatitis C virus genotype 5 or 6 infection (ENDURANCE-5,6): an open-label, multicentre, phase 3b trial. Lancet Gastroenterol Hepatol 2019;4:45–51.
26. Persico M, Flisiak R, Abunimeh M, et al. Efficacy and safety of glecaprevir/pibrentasvir in renally-impaired patients with chronic HCV genotype 1-6 infection (abstract THU-363). J Hepatol 2018;68:S292.
27. Lampertico P, Peck-Radosavljevic M, Bondin M, et al. Addressing barriers to hepatitis C virus (HCV) elimination: real-world outcomes in historically underserved patients with chronic HCV infection treated with glecaprevir/pibrentasvir (abstract 1583). Hepatology 2019;70:954A.
28. Marra F, Boyle A, McDonald N, et al. 8 Weeks of glecaprevir/pibrentasvir is effective and well tolerated in non-GT3 HCV patients with cirrhosis (abstract #1588). Hepatology 2019; 70:957A–958A.
29. Persico M, Aglitti A, Milella M, et al. Real-life glecaprevir/pibrentasvir in a large cohort of patients with hepatitis C virus infection: the MISTRAL study. Liver Int 2019;39:1852–1859.
30. Wedemeyer H, Erren P, Naumann U, et al. Glecaprevir/pibrentasvir is effective and well tolerated in hepatitis C patients with cirrhosis: real-world experience from the German Hepatitis C-Registry (abstract 1525). Hepatology 2019; 70:917A–918A.
31. Belperio PS, Shahoumian T, Loomis T, et al. Real-world effectiveness of glecaprevir/pibrentasvir in 1,941 patients with hepatitis C genotypes 1 through 4 (abstract 703). Hepatology 2018; 68:417A.
32. Hajarizadeh B, Cunningham EB, Reid H, et al. Direct-acting antiviral treatment for hepatitis C among people who use or inject drugs: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2018;3:754–767.
33. Terrault N. Difficult-to-cure populations with chronic hepatitis C: vanishing in the direct-acting antiviral era? Hepatology 2015;62:4–7.
34. Hilgenfeldt EG, Schlachterman A, Firpi RJ. Hepatitis C: treatment of difficult to treat patients. World J Hepatol 2015; 7:1953–1963.

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Conflicts of interest

The authors disclose the following: Eli Zuckerman has served as a speaker, consultant, and advisory board participant for AbbVie, Gilead, and Merck; Julio A. Gutierrez has served as a speaker and scientific advisor for AbbVie, Gilead, and Merck; Victor de Ledinghen has served as an advisory board participant and/or speaker for Gilead, AbbVie, Intercept, Medac, Supersonic Imagine, Promethera, Echosens, MYR-Pharma, Alfasigma, Bristol-Myers Squibb, Pfizer, Indivior, and Spimaco; Andrew J. Muir has served as an advisory board participant for AbbVie, Gilead, and MSD; Michael Gschwantler has served as a speaker/advisor for Janssen, MSD, Bristol-Myers Squibb, Gilead, and AbbVie, and has received research support for Gilead, AbbVie, and MSD; Massimo Puoti has served as a speaker/advisor for MSD, Gilead, and AbbVie; Florin Caruntu has served as a speaker and advisory board participant for AbbVie, Gilead, and Bayer; Jihad Slim has served as a speaker and advisory board participant for AbbVie, Gilead, MSD, and Jansen; Frederik Nevens has served as a consultant for AbbVie, Cook Medical, Genkyotex SA, Gilead, Gore, Intercept Pharmaceuticals, Ipsen, MSD, Promethera Biosciences, and Twin Pharma, and has received research grants from Astellas, Ipsen, and Gilead; Samuel Sigal has received research support from AbbVie, Gilead, Lilly, Genfit, Intercept, and Mallinckrodt; Stanley Cohen has served as a speaker, consultant, and received research support (for this study) from AbbVie, has served as a speaker and consultant for Gilead, as a speaker for Intercept, and has received research support from Viking; Douglas E. Dylla, Linda M. Fredrick, Ana Gabriela Pires dos Santos, and Lino Rodrigues Jr are employees of AbbVie and may hold stock/share options; and John F. Dillon has received research support and is a lecturer for AbbVie, Abbott, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharpe & Dohme, and Roche.

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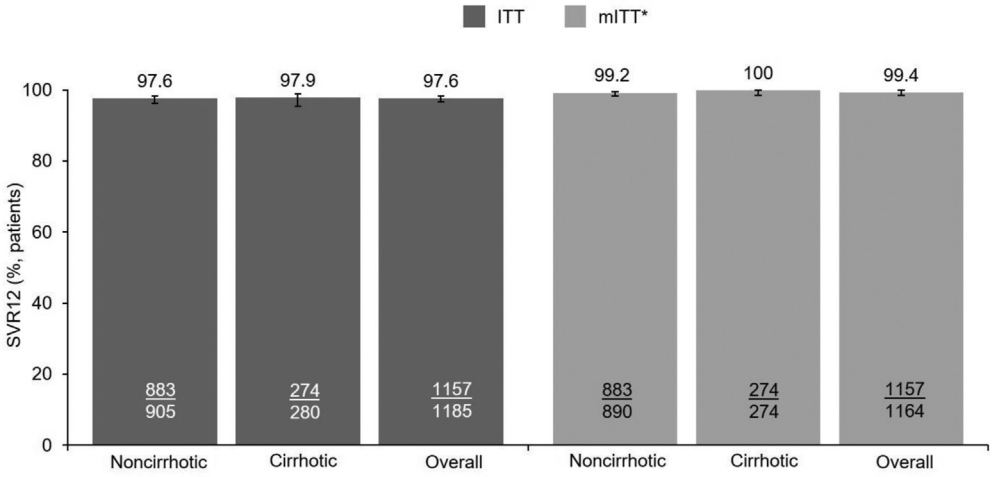
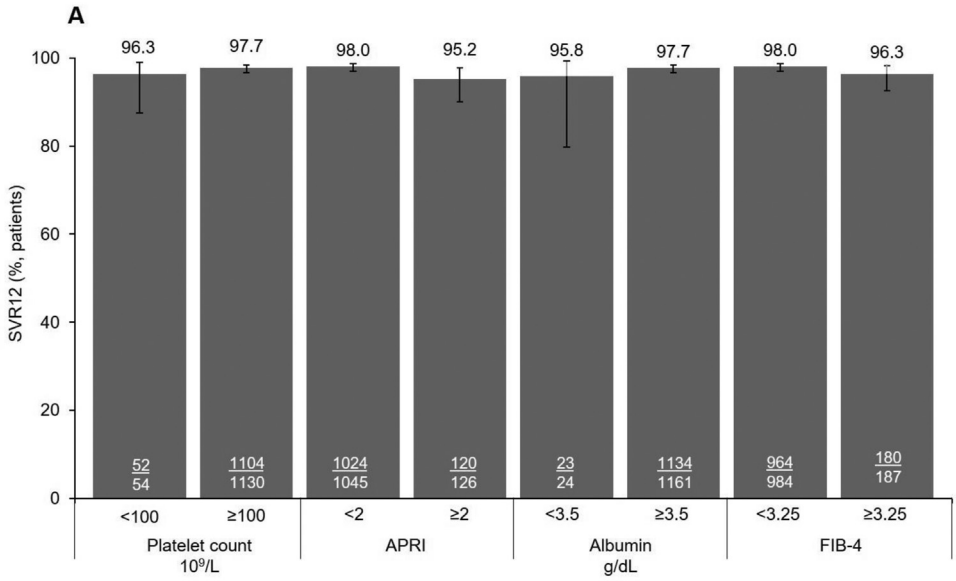
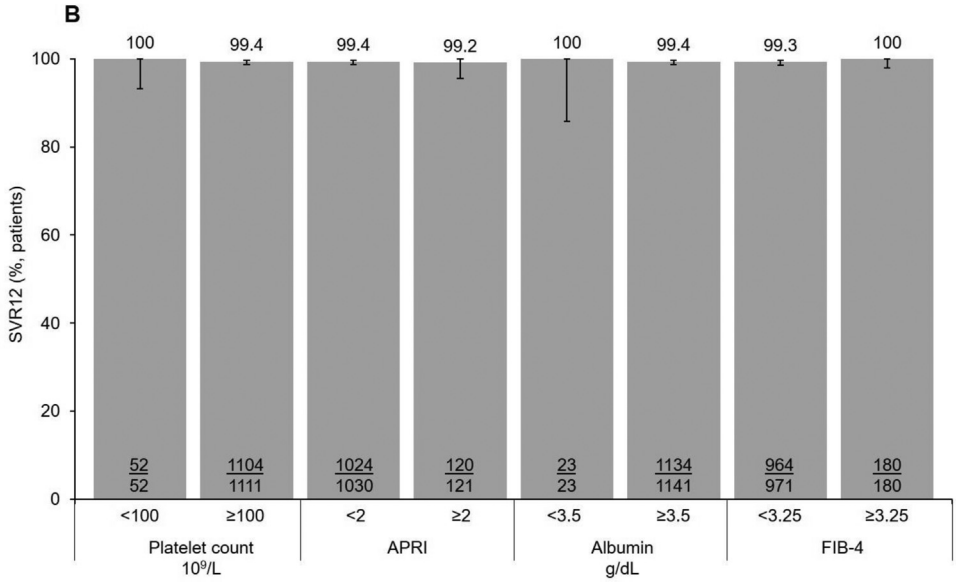


Supplementary Figure 1. SVR12 rates after G/P treatment for 8 weeks by cirrhosis status (GTΔ3CC data set). Numbers represent the number of patients with SVR12/total number of patients in each group. Error bars represent 95% CIs. *mITT population excluded patients with nonvirologic failure. G/P, glecaprevir/pibrentasvir; GTΔ3CC, population excluding genotype 3–infected patients with compensated cirrhosis; ITT, intention-to-treat; mITT, modified intention-to-treat; SVR12, sustained virologic response at post-treatment week 12.





Supplementary
Figure 2. SVR12 rates after G/P treatment for 8 weeks by clinical markers of advanced liver disease (GTΔ3CC data set): (*A*) ITT and (*B*) mITT population*. Numbers represent the number of patients with SVR12 and the total number of patients in each group. Error bars represent 95% CIs. *The mITT population excluded patients with nonvirologic failure. APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4; G/P, glecaprevir/pibrentasvir; GTΔ3CC, population excluding genotype 3–infected patients with compensated cirrhosis; ITT, intention-to-treat; mITT, modified intention-to-treat; SVR12, sustained virologic response at post-treatment week 12.

Supplementary Table 1. Demographics and Clinical Characteristics at Baseline: ITT Population, GTΔ3CC Data Set

	Treatment-naïve		
	GT1 to 6 Noncirrhotic (n = 905)	GT1, 2, 4–6 cirrhotic (n = 280)	Overall (N = 1185)
Male	492 (54.4)	168 (60.0)	660 (55.7)
Age, median, *y*	52.0	60.0	54.0
<65 *y*	800 (88.4)	196 (70.0)	996 (84.1)
Race			
White	708 (78.2)	223 (79.6)	931 (78.6)
Black	67 (7.4)	27 (9.6)	94 (7.9)
Asian	112 (12.4)	28 (10.0)	140 (11.8)
Other[a]	18 (2.0)	2 (0.7)	20 (1.7)
Ethnicity			
Hispanic or Latino	92 (10.2)	35 (12.5)	127 (10.7)
Not Hispanic or Latino	813 (89.8)	245 (87.5)	1058 (89.3)
BMI, mean, kg/m^2	26.3	28.2	26.7
≥30 kg/m^2	160 (17.7)	81 (28.9)	241 (20.3)
HCV GT			
1	352 (38.9)	231 (82.5)	583 (49.2)
2	202 (22.3)	26 (9.3)	228 (19.2)
3	217 (24.0)	0	217 (18.3)
4	53 (5.9)	13 (4.6)	66 (5.6)
5	19 (2.1)	1 (0.4)	20 (1.7)
6	62 (6.9)	9 (3.2)	71 (6.0)
Fibrosis stage			
F0–F1	741/902 (82.2)	0	741/1182 (62.7)
F2	53/902 (5.9)	0	53/1182 (4.5)
F3	107/902 (11.9)	0	107/1182 (9.1)
F4	1/902 (0.1)	280 (100)	281/1182 (23.8)
HCV RNA, ≥1,000,000 *IU/mL*	547 (60.4)	190 (67.9)	737 (62.2)
Platelet count, $<100 \times 10^9$/L	6 (0.7)	48 (17.1)	54 (4.6)
APRI, ≥2	34/901 (3.8)	92/270 (34.1)	126/1171 (10.8)
FIB-4, ≥3.25	46/901 (5.1)	141/270 (52.2)	187/1171 (16.0)
History of injection-drug use[b]			
Recent, ≤12 months prior	22/624 (3.5)	2 (0.7)	24/904 (2.7)
>12 months prior	226/624 (36.2)	70 (25.0)	296/904 (32.7)
No history	376/624 (60.3)	208 (74.3)	584/904 (64.6)
Stable OST	69 (7.6)	17 (6.1)	86 (7.3)
HIV co-infection	121 (13.4)	0	121 (10.2)
History of diabetes	60 (6.6)	56 (20.0)	116 (9.8)
History of depression or bipolar disorder	206 (22.8)	8 (2.9)	214 (18.1)
Severe renal impairment	67 (7.4)	0	67 (5.7)
Concomitant PPI use	101 (11.2)	31 (11.1)	132 (11.1)
Alcohol use			
Drinker	349 (38.6)	52 (18.6)	401 (33.8)
Ex-drinker	284 (31.4)	107 (38.2)	391 (33.0)
Nondrinker	267 (29.5)	119 (42.5)	386 (32.6)
Unknown	5 (0.6)	2 (0.7)	7 (0.6)

NOTE. Data are n (%) or n/N (%) unless otherwise stated; percentages are calculated from nonmissing values.

APRI, aspartate aminotransferase to platelet ratio index; BMI, body mass index; FIB-4, fibrosis-4; GT, genotype; GTΔ3CC, population excluding genotype 3–infected patients with compensated cirrhosis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ITT, intention-to-treat; OST, opioid substitution therapy; PPI, proton pump inhibitor.

[a]Other races include American Indian, Alaska native, multiple, native Hawaiian, and other Pacific Islander categories.

[b]SURVEYOR-1 and SURVEYOR-2 trials did not capture this information and were excluded from this assessment.

Supplementary Table 2. Reasons for SVR12 Nonresponse: ITT Population, GTΔ3CC Data Set

	Treatment-naïve		
Reasons for nonresponse, n (%)	GT1–6 noncirrhotic (n = 905)	GT1, 2, 4–6 cirrhotic (n = 280)	Overall (N = 1185)
On-treatment virologic failure	1 (0.1)	0	1 (<0.1)
Relapse[a]	6/890 (0.7)	0/274	6/1164 (0.5)
Nonvirologic failure	15 (1.7)	6 (2.1)	21 (1.8)
Study-drug discontinuation	6 (0.7)	1 (0.4)	7 (0.6)
Lost to follow-up evaluation	9 (1.0)	5 (1.8)	14 (1.2)

GT, genotype; GTΔ3CC, population excluding genotype 3–infected patients with compensated cirrhosis; ITT, intention-to-treat; SVR12, sustained virologic response post-treatment week 12.

[a]Denominator includes patients who completed treatment with hepatitis C virus RNA less than the lower limit of quantification at the end of treatment and had post-treatment hepatitis C virus RNA data.

Supplementary Table 3. SVR12 Rates After G/P Treatment for 8 Weeks by Subgroups of Interest: GTΔ3CC Data Set

	Treatment-naïve			
	ITT		mITT[a]	
	n/N (%)	95% CI	n/N (%)	95% CI
<65 *y*	975/996 (97.9)	96.8–98.6	975/982 (99.3)	98.5–99.7
≥65 *y*	182/189 (96.3)	92.6–98.2	182/182 (100)	97.9–100
Black	91/94 (96.8)	91.0–98.9	91/91 (100)	95.9–100
Non-black	1066/1091 (97.7)	96.6–98.4	1066/1073 (99.3)	98.7–99.7
Hispanic or Latino	125/127 (98.4)	94.4–99.6	125/126 (99.2)	95.6–99.9
Not Hispanic or Latino	1032/1058 (97.5)	96.4–98.3	1032/1038 (99.4)	98.7–99.7
BMI, <30 kg/m^2	920/944 (97.5)	96.2–98.3	920/927 (99.2)	98.4–99.6
BMI, ≥30 kg/m^2	237/241 (98.3)	95.8–99.4	237/237 (100)	98.4–100
HCV GT1	572/583 (98.1)	96.7–98.9	572/572 (100)	99.3–100
HCV GT2	226/228 (99.1)	96.9–99.8	226/226 (100)	98.3–100
HCV GT3	207/217 (95.4)	91.7–97.5	207/213 (97.2)	94.0–98.7
HCV GT4	63/66 (95.5)	87.5–98.4	63/63 (100)	94.3–100
HCV GT5	19/20 (95.0)	76.4–99.1	19/20 (95.0)	76.4–99.1
HCV GT6	70/71 (98.6)	92.4–99.8	70/70 (100)	94.8–100
Fibrosis stage F0–F1	728/741 (98.2)	97.0–99.0	728/730 (99.7)	99.0–99.9
Fibrosis stage F2	51/53 (96.2)	87.2–99.0	51/53 (96.2)	87.2–99.0
Fibrosis stage F3	100/107 (93.5)	87.1–96.8	100/103 (97.1)	91.8–99.0
Fibrosis stage F4	275/281 (97.9)	95.4–99.0	275/275 (100)	98.6–100
HCV RNA, <1,000,000 *IU/mL*	439/448 (98.0)	96.2–98.9	439/440 (99.8)	98.7–100
HCV RNA, ≥1,000,000 *IU/mL*	718/737 (97.4)	96.0–98.3	718/724 (99.2)	98.2–99.6
Recent injection-drug use, ≤12 months prior[b]	21/24 (87.5)	69.0–95.7	21/21 (100)	84.5–100
Injection-drug use, >12 months prior[b]	287/296 (97.0)	94.3–98.4	287/291 (98.6)	96.5–99.5
No history of injection-drug prior[b]	576/584 (98.6)	97.3–99.3	576/579 (99.5)	98.5–99.8
On stable OST	83/86 (96.5)	90.2–98.8	83/83 (100)	95.6–100
Not on stable OST	1074/1099 (97.7)	96.7–98.5	1074/1081 (99.4)	98.7–99.7
HIV co-infection	120/121 (99.2)	95.5–99.9	120/120 (100)	96.9–100
No HIV co-infection	1037/1064 (97.5)	96.3–98.3	1037/1044 (99.3)	98.6–99.7
History of diabetes	114/116 (98.3)	93.9–99.5	114/114 (100)	96.7–100
No history of diabetes	1043/1069 (97.6)	96.5–98.3	1043/1050 (99.3)	98.6–99.7
History of depression/bipolar disorder	209/214 (97.7)	94.6–99.0	209/209 (100)	98.2–100
No history of depression/bipolar disorder	948/971 (97.6)	96.5–98.4	948/955 (99.3)	98.5–99.6
Concomitant PPI	129/132 (97.7)	93.5–99.2	129/129 (100)	97.1–100
No concomitant PPI	1028/1053 (97.6)	96.5–98.4	1028/1035 (99.3)	98.6–99.7
Severe renal impairment	65/67 (97.0)	89.8–99.2	65/65 (100)	94.4–100
No severe renal impairment	1092/1118 (97.7)	96.6–98.4	1092/1099 (99.4)	98.7–99.7
Drinker	391/401 (97.5)	95.5–98.6	391/394 (99.2)	97.8–99.7
Ex-drinker	377/391 (96.4)	94.1–97.9	377/381 (99.0)	97.3–99.6
Nondrinker	382/386 (99.0)	97.4–99.6	382/382 (100)	99.0–100

NOTE. n/N shows the number of patients with SVR12/total number of patients in each subgroup.

BMI, body mass index; G/P, glecaprevir/pibrentasvir; GT, genotype; GTΔ3CC, population excluding genotype 3–infected patients with compensated cirrhosis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ITT, intention-to-treat; mITT, modified intention-to-treat; OST, opioid substitution therapy; PPI, proton-pump inhibitor; SVR12, sustained virologic response at post-treatment week 12.

[a]mITT population excluded patients with nonvirologic failure.

[b]SURVEYOR-1 and SURVEYOR-2 trials did not capture this information, thus they were excluded from this assessment.

Supplementary Table 4. SVR12 Rates After G/P Treatment for 8 Weeks in Treatment-Naïve, Noncirrhotic Patients

	Treatment-naïve noncirrhotic[a]			
	ITT		mITT[b]	
	n/N (%)	95% CI	n/N (%)	95% CI
GT1	347/352 (98.6)	96.7–99.4	347/347 (100)	98.9–100
GT2	200/202 (99.0)	96.5–99.7	200/200 (100)	98.1–100
GT3	207/217 (95.4)	91.7–97.5	207/213 (97.2)	94.0–98.7
GT4	50/53 (94.3)	84.6–98.1	50/50 (100)	92.9–100
GT5	18/19 (94.7)	75.4–99.1	18/19 (94.7)	75.4–99.1
GT6	61/62 (98.4)	91.4–99.7	61/61 (100)	94.1–100
Overall	883/905 (97.6)	96.3–98.4	883/890 (99.2)	98.4–99.6

NOTE. n/N shows the number of patients with SVR12/total number of patients in each subgroup.
G/P, glecaprevir/pibrentasvir; GT, genotype; GTΔ3CC, population excluding genotype 3–infected patients with compensated cirrhosis; ITT, intention-to-treat; mITT, modified intention-to-treat; SVR12, sustained virologic response at post-treatment week 12.
[a]Population is the same in the GT1 to 6 and GTΔ3CC data sets.
[b]mITT population excluded patients with nonvirologic failure.

Supplementary Table 5. Treatment-Emergent Adverse Events and Postbaseline Clinical Laboratory Abnormalities: ITT Population, GTΔ3CC Data Set

	Treatment-naïve		
	GT1–6 noncirrhotic (n = 905)	GT1, 2, 4–6 cirrhotic (n = 280)	Overall (N = 1185)
AEs, n (%)			
Any AE	563 (62.2)	134 (47.9)	697 (58.8)
Any serious AE	24 (2.7)	6 (2.1)	30 (2.5)
Any serious AE possibly related to G/P	0	0	0
Any AE leading to G/P discontinuation	2 (0.2)	0	2 (0.2)
Any serious AE leading to G/P discontinuation	2 (0.2)	0	2 (0.2)
Deaths[a]	2 (0.2)	0	2 (0.2)
AEs in ≥10% patients in any group			
Headache	120 (13.3)	23 (8.2)	143 (12.1)
Fatigue	115 (12.7)	24 (8.6)	139 (11.7)
Laboratory abnormalities, n/N (%)			
Alanine aminotransferase			
Grade ≥3	0/903	0/279	0/1182
Aspartate aminotransferase			
Grade ≥3	1/903 (0.1)	0/279	1/1182 (<0.1)
Total bilirubin			
Grade ≥3	4/903 (0.4)	0/279	4/1182 (0.3)

NOTE. n/N shows number of patients with respective parameter/number of patients with available data.
AE, adverse event; GT, genotype; G/P, glecaprevir pibrentasvir; GTΔ3CC, population excluding genotype 3–infected patients with compensated cirrhosis; ITT, intention-to-treat.
[a]Includes non–treatment-emergent deaths.