



HAL
open science

Safety analysis of glecaprevir/pibrentasvir in patients with markers of advanced liver disease in clinical and real-world cohorts

Jordan J Feld, Xavier Forns, Douglas E Dylla, Hiromitsu Kumada, Victor de Ledinghen, Lai Wei, Robert S Brown, Robert Flisiak, Pietro Lampertico, Dominique Thabut, et al.

► To cite this version:

Jordan J Feld, Xavier Forns, Douglas E Dylla, Hiromitsu Kumada, Victor de Ledinghen, et al.. Safety analysis of glecaprevir/pibrentasvir in patients with markers of advanced liver disease in clinical and real-world cohorts. *Journal of Viral Hepatitis*, 2022, 29 (12), pp.1050-1061. 10.1111/jvh.13738 . hal-04409816

HAL Id: hal-04409816

<https://hal.science/hal-04409816>

Submitted on 22 Jan 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.





L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

ORIGINAL ARTICLE

Safety analysis of glecaprevir/pibrentasvir in patients with markers of advanced liver disease in clinical and real-world cohorts

Jordan J. Feld¹  | Xavier Forns²  | Douglas E. Dylla³ | Hiromitsu Kumada⁴ | Victor de Ledinghen⁵  | Lai Wei^{6,7} | Robert S. Brown Jr⁸ | Robert Flisiak⁹ | Pietro Lampertico^{10,11}  | Dominique Thabut¹² | Mark Bondin³ | Fernando Tatsch³ | Margaret Burroughs³ | John Marcinak³ | Zhenzhen Zhang³ | Amanda Emmett³ | Ira M. Jacobson¹³

¹Toronto Centre for Liver Disease, University Health Network, University of Toronto, Toronto, Ontario, Canada

²Liver Unit, Hospital Clinic, University of Barcelona, IDIBAPS and CIBEREHD, Barcelona, Spain

³AbbVie Inc., North Chicago, Illinois, USA

⁴Department of Hepatology, Toranomon Hospital, Tokyo, Japan

⁵Bordeaux University Hospital, Bordeaux, France

⁶Peking University People's Hospital, Peking University Hepatology Institute, Beijing Key Laboratory of Hepatitis C and Immunotherapy for Liver Disease, Beijing, China

⁷Beijing Tsinghua Changgung Hospital, Tsinghua University, Beijing, China

⁸Center for Liver Disease and Transplantation, Weill Cornell Medical College, New York, New York, USA

⁹Department of Infectious Diseases and Hepatology, Medical University of Białystok, Białystok, Białystok, Poland

¹⁰Division of Gastroenterology and Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, CRC "A. M. and A. Migliavacca" Center for Liver Disease, Milan, Italy

¹¹Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

¹²Groupe Hospitalier Pitié-Salpêtrière-Charles Foix, Paris, France

¹³NYU Langone Health, New York, New York, USA

Correspondence

Jordan J. Feld, Toronto Centre for Liver Disease, University Health Network, University of Toronto, Toronto, Ontario, Canada.

Email: jordan.feld@uhn.ca

Funding information

AbbVie

Abstract

Chronic hepatitis C virus (HCV) infection has the greatest health impact in patients with advanced liver disease. The direct-acting antiviral (DAA) regimen glecaprevir/pibrentasvir (G/P) is approved for treatment of HCV-infected patients without cirrhosis and with compensated cirrhosis. However, events of liver decompensation/failure have been reported in patients treated with protease-inhibitor-containing DAA regimens, often in patients with advanced liver disease. This study examines the safety of

Abbreviations: AE, Adverse event; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CC, Compensated cirrhosis; CI, Confidence interval; CKD, Chronic kidney disease; DAA, Direct-acting antiviral; eGFR, estimated glomerular filtration rate; G/P, Glecaprevir/pibrentasvir; GT, Genotype; HCC, Hepatocellular carcinoma; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; IFN, Interferon; MedDRA, Medical Dictionary for Regulatory Activities; MELD, Model for End-Stage Liver Disease; PI, Protease inhibitor; PMOS, Post-marketing observational studies; SVR, sustained virologic response; SVR12, Sustained virologic response at post-treatment Week 12; ULN, upper limit of normal.

Clinical Trial: NCT02966795, NCT02642432, NCT02738138, NCT03219216, NCT03089944, NCT03222583, NCT03235349, NCT02707952, NCT02243293, NCT03212521, NCT02446717.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Journal of Viral Hepatitis* published by John Wiley & Sons Ltd.

on-label G/P treatment in patients with compensated cirrhosis (F4 at baseline) with markers of advanced liver disease. Patients with cirrhosis were categorized into 4 sub-groups, based on different noninvasive markers of advanced liver disease identified using laboratory measures: platelet count $<$ or $\geq 100 \times 10^9/L$, and Child-Pugh score 5 or 6. Separate analyses were performed using pooled data from clinical trials and from real-world post-marketing observational studies. G/P was well tolerated in patients with platelet count $\geq 100 \times 10^9/L$ ($n = 800$), platelet count $< 100 \times 10^9/L$ ($n = 215$), a Child-Pugh score of 5 ($n = 915$) and a Child-Pugh score of 6 ($n = 95$). In the clinical trial and real-world cohorts two patients and no patients experienced a serious adverse event (AE) possibly related to study drug, respectively; three patients and no patients experienced an AE of special interest for hepatic decompensation and hepatic failure. This analysis reaffirms G/P's safety profile in indicated patients with compensated cirrhosis, including those with markers of more advanced liver disease. Increasing the number of patients treated with short-duration G/P therapy may contribute to meeting HCV elimination targets.

KEYWORDS

hepatitis C, portal hypertension, safety, thrombocytopenia

1 | INTRODUCTION

An estimated 57 million people were estimated to be infected with hepatitis C virus (HCV) globally in 2020.¹ If left untreated, HCV leads to cirrhosis in 5%–25% of patients within 10–20 years of infection, with approximately 20% of liver cancer cases and deaths estimated to result from HCV infection globally.^{2–4} Patients with cirrhosis can experience impaired liver function, portal hypertension, and the development of hepatocellular carcinoma (HCC).⁵ Successful HCV treatment is associated with an approximately 70% reduced risk of HCC (adjusted hazard ratio [HR] 0.50, 95% confidence interval [CI] 0.43–0.59 among patients with cirrhosis, and 0.32, 95% CI 0.28–0.37 among patients without cirrhosis)^{6,7} and a 61% reduced risk of liver-related mortality,⁸ compared with no HCV treatment.

The availability of highly effective and well-tolerated pangenotypic direct-acting antivirals (DAAs) means that sustained virologic response (SVR) can be achieved in the vast majority of patients infected with HCV, including those with more advanced liver disease.^{9,10} The DAA regimen of glecaprevir/pibrentasvir (G/P) is approved in Europe and the United States for 8 weeks of therapy in all treatment-naïve patients infected with HCV genotype (GT) 1, 2, 3, 4, 5 or 6, without cirrhosis or with compensated cirrhosis (CC).^{11,12} Clinical trials have shown G/P to be well tolerated and highly effective with an overall sustained virologic response at post-treatment Week 12 (SVR12) rate of 98%.¹³

Historically, advanced fibrosis and cirrhosis were associated with negative treatment outcomes in patients treated with interferon (IFN)-based regimens.¹⁴ The availability of IFN-free pangenotypic DAA regimens has changed the treatment paradigm, particularly in patients with advanced liver disease, with similar SVR rates seen

in patients with CC and patients without cirrhosis.¹⁴ Indeed, similar SVR rates are now reported in patients with and without cirrhosis, with 1 real-world meta-analysis of IFN-free DAA regimens reporting SVR12 rates of 97.8% in patients with cirrhosis and 97.0% in patients without cirrhosis,¹⁵ and another real-world study reporting SVR12/24 rates of 97.9% in patients with cirrhosis and 99.2% in patients without cirrhosis.¹⁶ Treatment of HCV in patients with advanced liver disease is important, as demonstrated by reduced all-cause mortality and HCC incidence in patients who achieve SVR versus those who do not.¹⁷

While there are clear benefits in treating HCV patients with advanced liver disease, there have been concerns surrounding the safety of DAA treatment, namely regimens containing an HCV NS3/4A protease-inhibitor (PI). In August 2019, the US Food and Drug Administration issued a Drug Safety Communication warning about the rare occurrence of liver failure in patients treated with PI-containing regimens, including G/P, elbasvir/grazoprevir and sofosbuvir (SOF)/velpatasvir/voxilaprevir.¹⁸ The agency identified 63 cases of hepatic decompensation, some leading to liver failure.¹⁸ However, most of these cases occurred in patients with moderate to severe liver impairment (Child-Pugh score ≥ 7), in whom PI-containing regimens are not indicated for treatment of HCV infection. It remains unclear if this was due to lack of awareness of the interdiction on treatment of decompensated cirrhotic patients with PIs, underestimation of the degree of liver disease by the treating provider, a conscious decision based on other comorbidities, lack of other therapeutic options (e.g. re-treatment), or drug–drug interactions. In cases presenting in patients with CC or without cirrhosis, the FDA also stated there was evidence of portal hypertension or other significant pre-existing risk factors

that may have contributed to clinical worsening of liver disease. Indeed, one active-comparator cohort study found that portal hypertension was significantly associated with an increased risk of decompensation (HR, 2.75; 95% CI, 1.92–3.94) regardless of whether the DAA regimen contained a PI.¹⁹ Studies have also demonstrated that decompensation events are not isolated only to patients treated with PI-containing regimens.²⁰ A retrospective analysis of propensity-score-matched cohorts treated with PI-based or non-PI-based DAAs found no increased risk of severe hepatic dysfunction (HR 1.23; 95% CI, 0.64–2.38) or hepatic decompensation (HR 1.01; 95% CI, 0.41–1.87) comparing these groups.²¹ To further evaluate the safety profile of G/P in HCV-infected patients, we herein review data from pooled clinical trials and real-world studies comparing patients with compensated cirrhosis (F4 at baseline) and with and without laboratory signs of more advanced liver disease.

2 | METHODS

2.1 | Study design and patient population

Two separate data analyses were performed. The first analysed pooled data from the following G/P clinical trials: ENDURANCE-5, 6 (NCT02966795),²² EXPEDITION-1 (NCT02642432),²³ EXPEDITION-2 (NCT02738138),²⁴ EXPEDITION-3 (NCT03219216),²⁵ EXPEDITION-8 (NCT03089944),²⁶ VOYAGE-1 (NCT03222583),²⁷ VOYAGE-2 (NCT03235349),²⁷ CERTAIN-1 (NCT02707952),²⁸ SURVEYOR-2 (NCT02243293),²⁹ APRI (NCT03212521),³⁰ and MAGELLAN-1 (NCT02446717).³¹ Separately, analysed data were pooled from real-world post-marketing observational studies (PMOS) enrolling patients from 9 countries: Austria, Belgium, France, Greece, Israel, Italy, Poland, Portugal and Switzerland. For all included studies, written informed consent was obtained from each patient, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the appropriate institutional review committee.

2.2 | Patient population

Patients with HCV GT1–6, with CC (fibrosis stage F4), who were treatment-naïve or-experienced and enrolled in G/P clinical trials, regardless of human immunodeficiency virus (HIV) coinfection, were included in these analyses. Methods for cirrhosis assessment have been reported previously, the majority of patients were diagnosed based on FibroScan® (Echosens, Waltham, MA).^{22–30,32–34} Patients with severe renal impairment, defined as chronic kidney disease (CKD) Stage 4/5, were excluded given their unique safety profile that has been described previously.^{31,35} Importantly, no events of hepatic decompensation were described in CKD patients.^{31,35} CKD stage in PMOS was determined by estimated glomerular filtration rate (eGFR). Patients were excluded from clinical trials with drug or

alcohol use that would preclude adherence to study protocols in the opinion of the investigators.

The present analysis categorizes patients into 4 subgroups, based on several different noninvasive markers of advanced liver disease. The subgroups include:

- Patients with baseline platelet count $\geq 100 \times 10^9/L$
- Patients with baseline platelet count $< 100 \times 10^9/L$
- Patients with baseline Child-Pugh score of 5
- Patients with baseline Child-Pugh score of 6

2.3 | Endpoints and assessments

Baseline demographic and clinical characteristics, including concomitant medication, were collected for all patients. Treatment-emergent adverse events (AEs) were defined as any AE with an onset date after the first dose of G/P and no more than 30 days after the last G/P dose. Treatment-emergent AEs, serious AEs, AEs including those which led to drug discontinuation and those possibly related to study drug as assessed by the study investigator, and HCC AEs of special interest (including both treatment-emergent AEs, and post-treatment AEs), and laboratory abnormalities were assessed. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), and AEs of special interest for hepatic decompensation or hepatic failure (ascites and oesophageal variceal haemorrhage) were also assessed using the MedDRA 22.1 preferred terms and were graded according to the Common Terminology Criteria for Adverse Events version 4.0. Baseline and maximum on-treatment laboratory values were cross tabulated to calculate rates of normalization.

2.4 | Statistical analysis

Analyses of safety data were performed using the integrated clinical trial and PMOS analysis sets in the intention-to-treat populations, including all patients who received at least 1 dose of G/P. Categorical variables were analysed by number and percentage; continuous variables were analysed with descriptive statistics (number of non-missing observations, mean, standard deviation, median, maximum and minimum).

3 | RESULTS

3.1 | Patient characteristics

In the clinical trial cohort, there were a total of 704 patients with platelet count $\geq 100 \times 10^9/L$, 187 patients with platelet count $< 100 \times 10^9/L$, 792 patients with a Child-Pugh score of 5 and 78 patients with a Child-Pugh score of 6. In the PMOS cohort, there were a total of 96 patients with platelet count $\geq 100 \times 10^9/L$, 28 patients

with platelet count $<100 \times 10^9/L$, 123 patients with a Child-Pugh score of 5 and 17 patients with a Child-Pugh score of 6.

Across most of the subgroups, the majority of patients were male, white race, treatment-naïve and GT1 (clinical trial cohort [Table 1](#), PMOS cohort [Table 2](#)). Concomitant medications for both the clinical trial and PMOS cohorts are available in Supplement Table 1.

At baseline in the clinical trial cohort, the platelet count $<100 \times 10^9/L$ subgroup had a greater percentage of patients with albumin <3.5 mg/L, FibroScan score of ≥ 20 kPa, Model for End-Stage Liver Disease (MELD) score of ≥ 10 , and Child-Pugh score of 6, compared with patients with platelet count $\geq 100 \times 10^9/L$ ([Table 1](#)). Similarly, as expected, patients with a Child-Pugh score of 6 had evidence of more advanced liver disease compared to patients with a Child-Pugh score of 5 ([Table 1](#)). These patterns were similar in the PMOS cohort ([Table 2](#)).

3.2 | Safety

Across the whole population, serious AEs were rare, with more AEs reported in the clinical trial cohort than the PMOS cohort, which is in line with expectations based on historical clinical trial and real-world data sets. In the clinical trial cohort, a total of 58.4%, 55.6%, 57.4% and 59.0% of patients with platelet count $\geq 100 \times 10^9/L$, platelet count $<100 \times 10^9/L$, Child-Pugh score of 5, and Child-Pugh score of 6 experienced an AE, respectively ([Table 3](#)). In the PMOS cohort, a total of 17.7%, 17.9%, 15.4% and 11.8% of patients with platelet count $\geq 100 \times 10^9/L$, platelet count $<100 \times 10^9/L$, Child-Pugh score of 5, and Child-Pugh score of 6 experienced an AE, respectively ([Table 4](#)). AEs, laboratory parameters and laboratory abnormalities are presented by patient subgroups in the clinical trial cohort in [Table 3](#), and in the PMOS cohort in [Table 4](#). The incidence of serious AEs and AEs leading to discontinuation of the study drug were similar across the patient subgroups (Supplement Table 2), and serious AEs possibly related to the study drug were rare.

In the clinical trial cohort, a total of 3 patients experienced an AE of special interest consistent with hepatic decompensation or hepatic failure, 1 with platelet count $<100 \times 10^9/L$ and 2 with platelet count $\geq 100 \times 10^9/L$. One of these patients was a protocol violation due to the presence of moderate ascites present at study screening that was not recognized and who therefore had decompensated cirrhosis (Child-Pugh >6). This patient experienced worsening ascites on Day 8 without worsening of hepatic function, and therefore, continued G/P treatment without interruption and achieved SVR without additional worsening of symptoms. The patient had a baseline FibroScan score of 26.3 kPa, MELD score ≥ 10 , Fibrosis-4 score of 3.05, platelet count of $114 \times 10^9/L$, and albumin of 2.7 g/dL. Of the other 2 patients with an AE of special interest that was consistent with hepatic decompensation or hepatic failure, 1 experienced a treatment-emergent hepatic decompensation event of ascites and the other patient, an event of oesophageal variceal haemorrhage. One of these 2 patients was a 64-year-old white male with cirrhosis, a baseline Child-Pugh score of 6, baseline thrombocytopenia (platelet

count $114 \times 10^9/L$), a medical history of portal hypertension, and known oesophageal varices, and who was a current alcohol drinker. The patient experienced a serious AE of oesophageal variceal haemorrhage on Day 22, and the Child-Pugh score did not increase to >6 . The event was not considered related to the study drug, and the patient continued treatment and achieved SVR12 with his Child-Pugh score improving to 5 after the event. The other patient who experienced ascites was a 55-year-old female who had baseline thrombocytopenia ($66 \times 10^9/L$), a history of CC with Child-Pugh score 5, and portal hypertension. The patient experienced a non-serious, Grade 1 event of ascites, with the onset on Day 86 (2 days post-treatment). The event was not considered related to the study drug by the investigator and resolved on Day 124 (40 days post-treatment).

In the clinical trial cohort, a total of 4 (0.6%) patients with platelet count $\geq 100 \times 10^9/L$ experienced HCC. There were 2 (1.1%) patients with platelet count $<100 \times 10^9/L$ who experienced HCC (including both treatment-emergent and post-treatment), all considered not related to the study drug. No patients in the PMOS cohort experienced an AE of special interest consistent with hepatic decompensation of hepatic failure, or HCC.

In both clinical trial and PMOS populations, post-baseline, Grade ≥ 3 laboratory abnormalities were rare and similar across the unique subgroups ([Tables 3](#) and [4](#)). Seven (3.8%) patients in the clinical trial cohort had post-baseline reduction in platelet count of Grade ≥ 3 , although there were no reductions seen in the PMOS cohort. No patients experienced post-baseline hypoalbuminemia. There were no cases of ALT $>3 \times$ upper limits of normal (ULN) and bilirubin $>2 \times$ ULN in the clinical trial cohort ([Table 3](#)). To meet these criteria, the elevation in laboratory values did not need to be concurrent and could be taken at any point during the treatment period. There was 1 case of ALT $>3 \times$ ULN and bilirubin $>2 \times$ ULN in the PMOS cohort, which occurred in a patient with platelet count $<100 \times 10^9/L$ and Child-Pugh score 5 ([Table 4](#)). Change in laboratory parameters from baseline to post-treatment was assessed to examine normalization ([Table 5](#)). In the clinical trial and PMOS cohorts, normalization was similar between patient subgroups, with the exception of platelets, where normalization was much lower in patients with platelet count $<100 \times 10^9/L$ compared with those with platelet count $\geq 100 \times 10^9/L$ (5.9% vs. 57.1% and 8.3% vs. 42.9%, respectively). For the clinical trial cohort, this trend was similar for alanine aminotransferase (ALT) and aspartate aminotransferase (AST), though not as pronounced, as well as for the Child-Pugh 5 and 6 subgroups.

4 | DISCUSSION

Data reported here confirm that G/P treatment has a good safety profile in patients with CC, including those with platelet count $<100 \times 10^9/L$. G/P was well tolerated in patients with platelet count $<100 \times 10^9/L$, with few patients experiencing AEs leading to treatment discontinuation and serious AEs related to the study drug (1.1% and 0.5% in the clinical trial cohort and 3.6% and 0 in the PMOS

TABLE 1 Demographics and clinical characteristics at baseline in the clinical trial population

n (%)	Baseline platelet count		Baseline Child-Pugh score	
	≥100 × 10 ⁹ /L (N = 704)	<100 × 10 ⁹ /L (N = 187)	5 (N = 792)	6 (N = 78)
Sex, male	432 (61.4)	108 (57.8)	485 (61.2)	40 (51.3)
Age, years				
<65	523 (74.3)	139 (74.3)	597 (75.4)	53 (67.9)
≥65	181 (25.7)	48 (25.7)	195 (24.6)	25 (32.1)
Race, white	460 (65.3)	111 (59.4)	501 (63.3)	56 (71.8)
BMI, kg/m ²				
<30	507 (72.0)	143 (76.5)	594 (75.0)	39 (50.0)
≥30	197 (28.0)	44 (23.5)	198 (25.0)	39 (50.0)
MELD score, median (range)	7.0 (6–22)	7.0 (6–15)	7.0 (6–15)	10.0 (6–15)
HCV genotype				
1	392 (55.7)	94 (50.3)	433 (54.7)	36 (46.2)
2	94 (13.4)	34 (18.2)	117 (14.8)	10 (12.8)
3	163 (23.2)	45 (24.1)	179 (22.6)	27 (34.6)
4	27 (3.8)	6 (3.2)	31 (3.9)	2 (2.6)
5	6 (0.9)	0	6 (0.8)	0
6	22 (3.1)	8 (4.3)	26 (3.3)	3 (3.8)
Prior HCV treatment experience				
Treatment-naive	574 (81.5)	135 (72.2)	627 (79.2)	61 (78.2)
Treatment experienced	130 (18.5)	52 (27.8)	165 (20.8)	17 (21.8)
Injection drug use				
Within prior 12 months	14 (2.0)	3 (1.6)	15 (1.9)	1 (1.3)
>12 months prior	143 (20.3)	21 (11.2)	146 (18.4)	14 (17.9)
Yes, unknown	61 (8.7)	19 (10.2)	67 (8.5)	13 (16.7)
No	486 (69.0)	144 (77.0)	564 (71.2)	50 (64.1)
Alcohol use				
Current	137 (19.5)	33 (17.6)	149 (18.8)	16 (20.5)
Former	285 (40.5)	75 (40.1)	317 (40.0)	35 (44.9)
Never	278 (39.5)	79 (42.2)	322 (40.7)	27 (34.6)
Unknown	4 (0.6)	0	4 (0.5)	0
HIV co-infection	17 (2.4)	0	15 (1.9)	0
Planned treatment duration				
8 weeks	295 (41.9)	63 (33.7)	308 (38.9)	33 (42.3)
12 weeks	368 (52.3)	99 (52.9)	429 (54.2)	34 (43.6)
16 weeks	41 (5.8)	25 (13.4)	55 (6.9)	11 (14.1)
Platelets <100 × 10 ⁹ /L	0	187 (100)	152 (19.2)	32 (41.0)
Albumin <3.5 g/dL	29 (4.1)	21 (11.2)	0	45 (57.7)
FibroScan ≥20 kPa	277 (49.0)	95 (65.5)	330 (51.0)	39 (69.6)
Missing	139	42	145	22
MELD ≥10	42 (7.0)	31 (20.9)	37 (5.5)	30 (51.7)
Missing	102	39	120	20
Baseline Grade ≥3 laboratory abnormalities				
ALT (u/L)	38/703 (5.4)	17/187 (9.1)	50/791 (6.3)	4/78 (5.1)
AST (u/L)	34/703 (4.8)	24/187 (12.8)	43/791 (5.4)	15/78 (19.2)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MELD, Model for End-Stage Liver Disease. FibroScan® is a product of Echogen, Waltham, MA.

TABLE 2 Demographics and clinical characteristics at baseline in the PMOS population

n (%)	Baseline platelet count		Baseline Child-Pugh score	
	≥100 × 10 ⁹ /L (N = 96)	<100 × 10 ⁹ /L (N = 28)	5 (N = 123)	6 (N = 17)
Sex, male	68 (70.8)	19 (67.9)	90 (73.2)	10 (58.8)
Age, years				
<65	73 (76.0)	23 (82.1)	101 (82.1)	12 (70.6)
≥65	23 (24.0)	5 (17.9)	22 (17.9)	5 (29.4)
Race, white	95 (99.0)	28 (100)	121 (98.4)	17 (100)
BMI, kg/m ²				
<30	32 (80.0)	14 (87.5)	51 (85.0)	5 (71.4)
≥30	8 (20.0)	2 (12.5)	9 (15.0)	2 (28.6)
Missing	56	12	63	10
MELD score, median (range)	7.0 (6–13)	8.0 (7–11)	7.0 (6–13)	8.0 (7–11)
HCV genotype				
1	45 (47.9)	12 (42.9)	47 (38.5)	11 (64.7)
2	13 (13.8)	2 (7.1)	16 (13.1)	0
3	31 (33.0)	13 (46.4)	53 (43.4)	5 (29.4)
4	4 (4.3)	1 (3.6)	6 (4.9)	1 (5.9)
5	1 (1.1)	0	0	0
Missing	2	0	1	0
Prior HCV treatment experience				
Treatment-naive	81 (84.4)	23 (82.1)	105 (85.4)	14 (82.4)
Treatment experienced	15 (15.6)	5 (17.9)	18 (14.6)	3 (17.6)
Injection drug use				
Within prior 12 months	5 (5.3)	0	5 (4.1)	0
>12 months prior	26 (27.4)	6 (21.4)	38 (31.1)	5 (29.4)
No	64 (67.4)	22 (78.6)	79 (64.8)	12 (70.6)
Missing	1	0	1	0
History of psychiatric disorder	16 (16.7)	1 (3.6)	15 (12.2)	1 (5.9)
Alcohol use				
Current	33 (35.1)	8 (28.6)	44 (35.8)	4 (23.5)
Former	28 (29.8)	13 (46.4)	37 (30.1)	7 (41.2)
Never	25 (26.6)	5 (17.9)	32 (26.0)	4 (23.5)
Unknown	10 (10.4)	2 (7.1)	10 (8.1)	2 (11.8)
HIV co-infection	2 (2.1)	2 (7.1)	3 (2.4)	2 (11.8)
Planned treatment duration				
8 weeks	7 (7.3)	1 (3.6)	2 (1.6)	1 (5.9)
12 weeks	85 (88.5)	25 (89.3)	115 (93.5)	16 (94.1)
16 weeks	4 (4.2)	2 (7.1)	6 (4.9)	0
Platelets <100 × 10 ⁹ /L	0	28 (100)	16 (16.8)	8 (53.3)
Missing	0	0	28	2
Albumin <3.5 g/dL	3 (5.2)	7 (38.9)	3 (4.1)	5 (62.5)
Missing	38	10	49	9
FibroScan ≥20kPa	44 (52.4)	23 (82.1)	65 (57.5)	8 (47.1)
Missing	12	0	10	0
MELD ≥10	3 (6.4)	1 (10.0)	5 (10.0)	1 (16.7)
Missing	49	18	73	11

(Continues)

TABLE 2 (Continued)

n (%)	Baseline platelet count		Baseline Child-Pugh score	
	≥100 × 10 ⁹ /L (N = 96)	<100 × 10 ⁹ /L (N = 28)	5 (N = 123)	6 (N = 17)
Baseline laboratory abnormalities Grade >3				
ALT (u/L)	6/79 (7.6)	3/24 (12.5)	9/94 (9.6)	1/13 (7.7)
AST (u/L)	7/59 (11.9)	2/17 (11.8)	9/73 (12.3)	1/10 (10.0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MELD, Model for End-Stage Liver Disease; PMOS, post-marketing observational studies. FibroScan® is a product of EchoSens, Waltham, MA.

TABLE 3 Summary of AEs, laboratory parameters and laboratory parameter abnormalities in the clinical trial population

n (%)	Baseline platelet count		Baseline Child-Pugh score	
	≥100 × 10 ⁹ /L (N = 704)	<100 × 10 ⁹ /L (N = 187)	5 (N = 792)	6 (N = 78)
Any AE	411 (58.4)	104 (55.6)	455 (57.4)	46 (59.0)
AE possibly related to DAA	217 (30.8)	53 (28.3)	238 (30.1)	25 (32.1)
AE leading to discontinuation of study drug	2 (0.3)	2 (1.1)	1 (0.1)	1 (1.3)
Serious AE	28 (4.0)	4 (2.1)	26 (3.3)	4 (5.1)
Serious AE related to DAA	1 (0.1)	1 (0.5)	1 (0.1)	0
Hepatocellular carcinoma	4 (0.6)	2 (1.1)	5 (0.6)	1 (1.3)
Deaths	3 (0.4)	1 (0.5)	3 (0.4)	1 (1.3)
AE ≥5%				
Headache	66 (9.4)	19 (10.2)	75 (9.5)	9 (11.5)
Fatigue	74 (10.5)	20 (10.7)	83 (10.5)	9 (11.5)
Nausea	42 (6.0)	9 (4.8)	47 (5.9)	3 (3.8)
Pruritus	52 (7.4)	15 (8.0)	59 (7.4)	6 (7.7)
Upper respiratory tract infection	39 (5.5)	6 (3.2)	38 (4.8)	7 (9.0)
Diarrhoea	35 (5.0)	6 (3.2)	35 (4.4)	5 (6.4)
Post-baseline Grade ≥3 laboratory abnormalities				
Platelets (10 ⁹ /L)	0/702	7/186 (3.8)	4/791 (0.5)	3/77 (3.9)
ALT (U/L)	2/703 (0.3)	0/187	2/791 (0.3)	0/78
AST (U/L)	0/703	0/187	0/791	0/78
Total bilirubin (μmol/L)	1/703 (0.1)	3/187 (1.6)	1/791 (0.1)	2/78 (2.6)
Albumin (g/dL)	0/702	0/187	0/791	0/78
Laboratory abnormalities of interest				
Bilirubin ≥2 × ULN and > baseline	6/703 (0.9)	11/187 (5.9)	7/791 (0.9)	7/78 (9.0)
ALT >3 × ULN and bilirubin >2 × ULN	0/703	0/187	0/791	0/78

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAA, direct-acting antiviral; ULN, upper limits of normal.

cohort, respectively). G/P was also well tolerated in patients with a Child-Pugh score of 5 and 6, with few patients experiencing AEs leading to treatment discontinuation (0.1% and 1.3% in the clinical trial cohort and 1.6% and 0% in the PMOS cohort, respectively) and serious AEs related to the study drug (0.1% and 0 in the clinical trial cohort and 0 in the PMOS cohort). Overall, the AE rates, including AEs leading to discontinuation and serious AEs related to the study drug in patients with platelet count <100 × 10⁹/L, were comparable to those seen in patients with platelet count ≥100 × 10⁹/L, as well as

between the Child-Pugh score 5 and 6 subgroups, in both the clinical trial and PMOS cohorts.

Overall AE rates (and rates of AEs considered possibly related to DAA therapy) were higher in the clinical trial cohort versus the PMOS cohort. This is an expected finding, as safety is often under-reported in observational studies compared with clinical trials, for which it is mandatory. As such, caution should be exercised when comparing safety outcomes reported in clinical trial and real-world data sets. Results are consistent with previously reported real-world

TABLE 4 Summary of adverse events, laboratory parameters and laboratory parameter abnormalities in the PMOS population

n (%)	Baseline platelet count		Baseline Child-Pugh score	
	≥100 × 10 ⁹ /L (N = 96)	<100 × 10 ⁹ /L (N = 28)	5 (N = 123)	6 (N = 17)
Any AE	17 (17.7)	5 (17.9)	19 (15.4)	2 (11.8)
AE possibly related to DAA	10 (10.4)	2 (7.1)	11 (8.9)	1 (5.9)
AE leading to discontinuation of study drug	1 (1.0)	1 (3.6)	2 (1.6)	0
Serious AE	2 (2.1)	1 (3.6)	3 (2.4)	0
Serious AE related to DAA	0	0	0	0
Hepatocellular carcinoma	0	0	0	0
Deaths	1 (1.0)	0	1 (0.8)	0
Most common AEs				
Fatigue	5 (5.2)	0	4 (3.3)	0
Asthenia	2 (2.1)	1 (3.6)	2 (1.6)	0
Decreased appetite	2 (2.1)	0	2 (1.6)	0
Dyspepsia	2 (2.1)	0	2 (1.6)	0
Pruritus	1 (1.0)	0	2 (1.6)	0
Post-baseline Grade ≥3 laboratory abnormalities				
Platelets (10 ⁹ /L)	0/77	0/24	0/85	0/14
ALT (u/L)	0/81	0/24	0/99	0/14
AST (u/L)	0/64	0/17	0/76	0/11
Total bilirubin (μmol/L)	0/65	0/18	0/74	0/13
Albumin (g/dL)	0/2	0/1	0/3	0/2
Laboratory abnormalities of interest				
Bilirubin ≥2 × ULN and > baseline	1/55 (1.8)	2/16 (12.5)	2/62 (3.2)	1/13 (7.7)
ALT >3 × ULN and bilirubin >2 × ULN	0/55	1/16 (6.3) ^a	1/62 (1.6) ^a	0/13

^aOne patient experienced an ALT increase from 73 IU/mL at baseline to 159 IU/mL (>3 × ULN) and a total bilirubin increase from 0.7 μmol/L at baseline to 3.68 μmol/L (>2 × ULN) concurrently on treatment Day 43, at the same time as the onset of SAEs of respiratory tract infection and cardiac failure lasting for 16 days. The patient prematurely discontinued study drug because of SAEs but achieved SVR12.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAA, direct-acting antiviral; ULN, upper limits of normal.

G/P data, which showed low rates of severe AEs and AEs of special interest.^{36,37}

In both cohorts, normalization of laboratory parameters was observed across the subgroups. Platelet normalization was rare; however, as low platelet count is a consequence of portal hypertension, platelet count rarely normalizes, even in patients who undergo a liver transplant as the spleen remains large. AST and ALT elevation was transient, often below Grade 3, returned to normal after treatment completion, and was not associated with other findings that would suggest liver decompensation. Therefore, this can reassure non-liver specialists that in most cases AST and ALT elevations are limited and do not suggest liver decompensation.^{38,39} The analysis of safety data from subgroups defined by individual noninvasive measures (such as baseline platelet count and Child-Pugh score) affords comparison of the utility/interchangeability of individual measures for identifying patients at low risk for liver-related outcomes. The overlap and similar safety profile observed in the patient subgroups of platelet count < or ≥ 100 × 10⁹/L and Child-Pugh score of 5 or 6, demonstrates the similar safety of patients with CC, regardless of markers of portal hypertension or synthetic dysfunction, compared with those without markers.

While this analysis has strengths, including sample size and use of both clinical trial and PMOS populations, some limitations should be acknowledged. Firstly, there was a lack of available laboratory data and MELD score values for the PMOS cohort compared with the clinical trial cohort due to differences in real-world clinical monitoring practices compared with controlled clinical trials. Another limitation is that the small number of liver-related AEs and AEs that led to treatment discontinuation means it is not possible to use these data to identify risk factors for the occurrence of liver-related events. In addition, subgroups contained some overlap, as they were not mutually exclusive, and the number of patients with Child-Pugh score of 6 was relatively small. Lastly, because the population was exclusively those with compensated cirrhosis, the proportion of patients with recent illicit drug use was low, though should be anticipated because active drug users are generally younger and without long-term HCV infection that would facilitate liver disease progression to cirrhosis.

The results presented here are supported by other studies that concluded that G/P is well tolerated in patients with advanced renal disease, HIV and solid organ transplants.^{40,41} In summary, the findings of the present post hoc analysis confirm the known safety profile

TABLE 5 Change in laboratory values from baseline to on-treatment post-baseline visits among patient subgroups with available data, n/N

	Clinical trials		PMOS	
	Baseline platelet count		Baseline platelet count	
	$\geq 100 \times 10^9/L$ (N = 704)	$< 100 \times 10^9/L$ (N = 187)	$\geq 100 \times 10^9/L$ (N = 96)	$< 100 \times 10^9/L$ (N = 28)
Laboratory parameter from baseline to post-baseline	Baseline Child-Pugh score	Baseline Child-Pugh score	Baseline Child-Pugh score	Baseline Child-Pugh score
	5 (N = 792)	6 (N = 78)	5 (N = 123)	6 (N = 17)
Platelets $10^9/L$				
Low to normal	133/233 (57.1)	11/186 (5.9)	13/51 (25.5)	2/24 (8.3)
Normal to low	8/465 (1.7)	0/0	3/26 (11.5)	0/0
Alanine aminotransferase				
High to normal	271/575 (47.1)	53/164 (32.3)	21/66 (31.8)	18/23 (78.3)
Normal to high	3/127 (2.4)	1/23 (4.3)	0/12	0/1
Aspartate aminotransferase				
High to normal	293/604 (48.5)	64/178 (36.0)	17/75 (22.7)	12/16 (75.0)
Normal to high	4/99 (4.0)	0/9	0/3	0/1
Alkaline phosphatase				
High to normal	18/99 (18.2)	3/38 (7.9)	6/34 (17.6)	-
Normal to high	63/601 (10.5)	24/149 (16.1)	10/44 (22.7)	-
Bilirubin				
High to normal	10/55 (18.2)	4/47 (8.5)	1/26 (3.8)	3/7 (42.9)
Normal to high	93/647 (14.4)	34/140 (24.3)	15/52 (28.8)	2/10 (20.0)
Direct bilirubin				
High to normal	29/169 (17.2)	8/73 (11.0)	2/37 (5.4)	2/5 (40.0)
Normal to high	113/526 (21.5)	32/111 (28.8)	15/39 (38.5)	0/1
Albumin				
Low to normal	7/8 (87.5)	5/5 (100)	9/9 (100)	0/0
Normal to low	0/686	1/177 (0.6)	0/68	0/2

Abbreviation: PMOS, post-marketing observational studies.

in CC patients with more advanced liver disease, treated with G/P according to the label. Therefore, these data provide reassurance that when prescribed per label in patients with CC, even in those with platelet count $<100 \times 10^9/L$, G/P can be safely used with appropriate long-term follow-up to monitor for development of HCC.^{14,42} It is because of this long-term monitoring that patients demonstrating clinical signs of advanced liver disease may preferentially benefit from HCV care by experienced centers. However, simplified treatment algorithms may be particularly useful in countries, such as the United States and France, which allow HCV treatment in the community setting.⁴²⁻⁴⁴ In addition, expanding the pool of patients eligible for shorter duration G/P therapy to include those with CC has the potential to support the global goal of HCV elimination.^{41,45}

4.1 | Significance Statement

Although DAAs with good efficacy and safety profiles are available for the treatment of chronic hepatitis C, events of liver decompensation/failure have been reported with protease-containing DAA regimens.

These data from clinical trial and real-world PMOS cohorts provide additional reassurance around the safety of G/P in patients with compensated cirrhosis, including those with platelet count $<100 \times 10^9/L$, reaffirming the potential for this patient population to be treated safely and effectively with 8 weeks G/P.

AUTHOR CONTRIBUTIONS

All authors had access to relevant data and participated in the writing, review and approval of the manuscript. JJF, XF, DED, MB, FT, MB, JM, ZZ, AE and IMJ contributed to study concept and design. All authors contributed to acquisition of data; analysis and interpretation of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content. JF is acting as the guarantor of this manuscript and all authors approved this final version.

ACKNOWLEDGEMENTS

AbbVie funded the original clinical studies and participated in the design, research, analysis, data collection, interpretation of data, reviewing, and approval of this analysis. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Medical writing support was provided by Annie Massa, MBiolSci, and Tom Owen, PhD, of Fishawack Communications, Ltd; and funded by AbbVie. Glecaprevir was identified by AbbVie and Enanta.

FUNDING INFORMATION

AbbVie sponsored the study, contributed to its design, and participated in the collection, analysis, and interpretation of the data, and in the writing, reviewing, and approval of the manuscript. Medical writing support was provided by Annie Massa, MBiolSci, and Tom Owen, PhD, of Fishawack Communications, Ltd; and funded by AbbVie. Glecaprevir was identified by AbbVie and Enanta.

CONFLICT OF INTEREST

Jordan J Feld: Research support/consultant: AbbVie, Arbutus, Enanta, Gilead, Janssen, Merck, and Roche. Xavier Forns: Advisor for AbbVie and Gilead Douglas E Dylla, Mark Bondin, Fernando Tatsch, Margaret Burroughs, John Marcinak, Zhenzhen Zhang, Amanda Emmett: Employees of AbbVie and may hold stock/share options. Hiromitsu Kumada: Honoraria: MSD K.K., Sumitomo Dainippon Pharma Co., Ltd., Eisai Co., Ltd., AbbVie GK., Gilead Sciences Inc. Victor de Ledinghen: AbbVie, Echosens, Gilead, Hologic, Intercept Pharma, MSD, MYR-Pharma, Siemens, Tillotts. Lai Wei: Consulting for Gilead Sciences, Johnson & Johnson, Pfizer, and Roche; and research grants to the institution from AbbVie and Gilead Sciences. Robert S Brown Jr: Research support from AbbVie, Gilead, Merck, Intercept, and Bristol-Myers Squibb, and has acted as an advisor for AbbVie, Bristol-Myers Squibb, Gilead, Intercept, Merck, Shionogi, and Dova. Robert Flisiak: Advisor for AbbVie, Gilead, and Merck. Pietro Lampertico: Speaker bureau and/or advisory board: AbbVie, Alnylam, Arrowhead, Bristol-Myers Squibb, Eiger BioPharmaceuticals, Gilead Sciences, GSK, Janssen, MSD, MYR Pharmaceuticals, Roche, and Spring Bank. Dominique Thabut: Consultant for AbbVie, Alfasigma, Gilead, Gore, Medday, MSD. Ira M Jacobson: Grant/research support: Assembly Biosciences, Bristol-Myers Squibb, Eli Lilly, Gilead, Genfit, Enanta, and Janssen; consultant/advisor: AbbVie, Arrowhead, Atea, Assembly Biosciences, Bristol-Myers Squibb, Intercept, Janssen, Gilead, GSK, Merck, Novo Nordisk, Poptest, Redhill, and Siemens.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

For all included studies, written informed consent was obtained from each patient, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the appropriate institutional review committee.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Permission was obtained to reproduce material where appropriate.

ORCID

Jordan J. Feld  <https://orcid.org/0000-0003-2640-2211>

Xavier Forns  <https://orcid.org/0000-0002-8188-1764>

Victor de Ledinghen  <https://orcid.org/0000-0001-6414-1951>

Pietro Lampertico  <https://orcid.org/0000-0002-1026-7476>

REFERENCES

- Blach S, Dugan E, Razavi-Shearer D, et al. Global status update on the HCV prevalence and cascade of care entering 2020. *Hepatology*. 2021;74(S1):68A.
- Thomas DL, Seeff LB. Natural history of hepatitis C. *Clin Liver Dis*. 2005;9(3):383-398. vi.

3. Global Burden of Disease Liver Cancer Collaboration, Akinemiju T, Abera S, Alam N, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and National Level: results from the global burden of disease study 2015. *JAMA Oncol.* 2017;3(12):1683-1691.
4. Liu Z, Jiang Y, Yuan H, et al. The trends in incidence of primary liver cancer caused by specific etiologies: results from the global burden of disease study 2016 and implications for liver cancer prevention. *J Hepatol.* 2019;70(4):674-683.
5. Schuppan D, Afdhal NH. Liver cirrhosis. *Lancet.* 2008;371(9615):838-851.
6. Janjua NZ, Wong S, Darvishian M, et al. The impact of SVR from direct-acting antiviral- and interferon-based treatments for HCV on hepatocellular carcinoma risk. *J Viral Hepat.* 2020;27:781-793.
7. Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. *J Hepatol.* 2017;S0168-8278(17):32273-32280.
8. Carrat F, Fontaine H, Dorival C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. *Lancet.* 2019;393(10179):1453-1464.
9. World Health Organization (WHO). *Global Hepatitis Report.* WHO Publication; 2017. <http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf>. Accessed May 2020.
10. Gelson W, Alexander G. Is elimination of hepatitis C from the UK by 2030 a realistic goal? *Br Med Bull.* 2017;123(1):59-67.
11. Maviret EU. *Maviret.* 2020; https://www.ema.europa.eu/en/documents/product-information/maviret-epar-product-information_en.pdf. Accessed May 2020.
12. Mavyret US. *Mavyret US.* 2019; https://www.rxabbvie.com/pdf/mavyret_pi.pdf. Accessed May 2020.
13. Zuckerman E, Gutierrez JA, Dylla DE, et al. Eight weeks treatment with Glecaprevir/Pibrentasvir is safe and efficacious in an integrated analysis of treatment-naïve patients with hepatitis C virus infection. *Clin Gastroenterol Hepatol.* 2020;18:2544-2553.
14. Carmona I, Cordero P, Ampuero J, Rojas A, Romero-Gomez M. Role of assessing liver fibrosis in management of chronic hepatitis C virus infection. *Clin Microbiol Infect.* 2016;22(10):839-845.
15. Lampertico P, Carrion JA, Curry M, et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of patients with chronic HCV infection: a meta-analysis. *J Hepatol.* 2020;72(6):1112-1121.
16. Mangia A, Milligan S, Khalili M, et al. Global real-world evidence of sofosbuvir/velpatasvir as simple, effective HCV treatment: analysis of 5552 patients from 12 cohorts. *Liver Int.* 2020;40:1841-1852.
17. Backus LI, Belperio PS, Shahoumian TA, Mole LA. Impact of sustained virologic response with direct-acting antiviral treatment on mortality in patients with advanced liver disease. *Hepatology.* 2019;69(2):487-497.
18. US FDA. FDA warns about rare occurrence of serious liver injury with use of hepatitis C medicines mavyret, zepatier, and vosevi in some patients with advanced liver disease. 2019.
19. Wegrzyn L, Huisingh C, Porcalla A, et al. No identified association between glecaprevir/pibrentasvir use and risk of hepatic decompensation in HCV-infected patients with compensated cirrhosis at baseline: an active comparative cohort study. *Presented at Hep Dart.* 2019;P38.
20. Pereira Guedes T, Fragoso P, Lemos C, et al. Long-term follow-up of advanced liver disease after sustained Virological response to treatment of hepatitis C with direct-acting antivirals: outcomes from a real-world Portuguese cohort. *GE Port J Gastroenterol.* 2020;27(3):149-159.
21. Torgersen J, Newcomb CW, Carbonari DM, et al. Protease inhibitor-based direct-acting antivirals are associated with increased risk of aminotransferase elevations but not hepatic dysfunction or decompensation. *J Hepatol.* 2021;75(6):1312-1322.
22. 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(1):45-51.
23. Fornis X, Lee SS, Valdes J, et al. Glecaprevir plus pibrentasvir for chronic hepatitis C virus genotype 1, 2, 4, 5, or 6 infection in adults with compensated cirrhosis (EXPEDITION-1): a single-arm, open-label, multicentre phase 3 trial. *Lancet Infect Dis.* 2017;17(10):1062-1068.
24. Rockstroh JK, Lacombe K, Viani RM, et al. Efficacy and safety of Glecaprevir/Pibrentasvir in patients coinfecting with hepatitis C virus and human immunodeficiency virus type 1: the EXPEDITION-2 study. *Clin Infect Dis.* 2018;67(7):1010-1017.
25. Peribanez-Gonzalez M, Cheinquer H, Rodrigues L, et al. Efficacy and safety of glecaprevir/pibrentasvir in treatment-naïve adults with chronic hepatitis C virus genotypes 1-6 in Brazil. *Ann Hepatol.* 2021;20:100257.
26. Brown RS Jr, Buti M, Rodrigues L, et al. Glecaprevir/pibrentasvir for 8weeks in treatment-naïve patients with chronic HCV genotypes 1-6 and compensated cirrhosis: the EXPEDITION-8 trial. *J Hepatol.* 2020;72(3):441-449.
27. Wei L, Wang G, Alami NN, et al. Glecaprevir-pibrentasvir to treat chronic hepatitis C virus infection in Asia: two multicentre, phase 3 studies- a randomised, double-blind study (VOYAGE-1) and an open-label, single-arm study (VOYAGE-2). *Lancet Gastroenterol Hepatol.* 2020;5(9):839-849.
28. Krishnan P, Schnell G, Tripathi R, et al. Integrated resistance analysis of CERTAIN-1 and CERTAIN-2 studies in hepatitis C virus-infected patients receiving Glecaprevir and Pibrentasvir in Japan. *Antimicrob Agents Chemother.* 2018;62(2):e02217-17.
29. 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(2):263-271.
30. Fontana RJ, Lens S, McPherson S, et al. Efficacy and safety of 8weeks of Glecaprevir/Pibrentasvir in treatment-naïve, HCV-infected patients with APRI ≤ 1 in a single-arm, open-label, Multicenter Study. *Adv Ther.* 2019;36(12):3458-3470.
31. Gane E, Lawitz E, Pugatch D, et al. Glecaprevir and Pibrentasvir in patients with HCV and severe renal impairment. *N Engl J Med.* 2017;377(15):1448-1455.
32. Zeuzem S, Foster GR, Wang S, et al. Glecaprevir-Pibrentasvir for 8 or 12weeks in HCV genotype 1 or 3 infection. *N Engl J Med.* 2018;378(4):354-369.
33. Asselah T, Kowdley KV, Zadeikis N, et al. Efficacy of Glecaprevir/Pibrentasvir for 8 or 12weeks in patients with hepatitis C virus genotype 2, 4, 5, or 6 infection without cirrhosis. *Clin Gastroenterol Hepatol.* 2018;16(3):417-426.
34. Poordad F, Felizarta F, Asatryan A, et al. Glecaprevir and pibrentasvir for 12weeks for hepatitis C virus genotype 1 infection and prior direct-acting antiviral treatment. *Hepatology.* 2017;66(2):389-397.
35. Lawitz E, Flisiak R, Abunimeh M, et al. Efficacy and safety of glecaprevir/pibrentasvir in renally impaired patients with chronic HCV infection. *Liver Int.* 2020;40(5):1032-1041.
36. Ippolito AM, Milella M, Messina V, et al. HCV clearance after direct-acting antivirals in patients with cirrhosis by stages of liver impairment: the ITAL-C network study. *Dig Liver Dis.* 2017;49(9):1022-1028.
37. Berge E, Arencibia A, Oton E, Cejas L, Acosta S, Perez F. Clinical outcomes of direct-acting antiviral therapy in patients with compensated hepatitis C virus-related cirrhosis. *Hepatoma Res.* 2017;3:209-214.
38. Chahal HS, Marseille EA, Tice JA, et al. Cost-effectiveness of early treatment of hepatitis C virus genotype 1 by stage of liver fibrosis in a US treatment-naïve population. *JAMA Intern Med.* 2016;176(1):65-73.
39. Royal College of General Practitioners. Guidance for the prevention, testing, treatment and management of hepatitis C in primary care. 2007.

40. Hsu SJ, Chiu MC, Fang YJ, et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir in Asian patients with chronic hepatitis C. *J Formos Med Assoc.* 2019;118(8):1187-1192.
41. Cotter TG, Jensen DM. Glecaprevir/pibrentasvir for the treatment of chronic hepatitis C: design, development, and place in therapy. *Drug des Devel Ther.* 2019;13:2565-2577.
42. AASLD-IDS A Hepatitis C Guidance Panel. Hepatitis C guidance 2019 update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America recommendations for testing, managing, and treating hepatitis C virus infection. *Hepatology.* 2019;71(2):686-721.
43. Alcorn K. France Switches to Simplified Pangenotypic Hepatitis C Treatment. 2019; <https://www.worldhepatitisalliance.org/latest-news/infohep/3435331/france-switches-simplified-pangenotypic-hepatitis-c-treatment>. Accessed March 2020.
44. Huppe D, Serfert Y, Buggisch P, et al. 4 years of direct-acting antivirals (DAAs) in the German hepatitis C-registry (DHC-R). *Z Gastroenterol.* 2019;57(1):27-36.
45. Ferenci P. Are all cirrhotic patients equal? *J Hepatol.* 2020;72(3):389-390.

How to cite this article: Feld JJ, Fornis X, Dylla DE, et al. Safety analysis of glecaprevir/pibrentasvir in patients with markers of advanced liver disease in clinical and real-world cohorts. *J Viral Hepat.* 2022;29:1050-1061. doi: [10.1111/jvh.13738](https://doi.org/10.1111/jvh.13738)