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ORIGINAL RESEARCH

Safety of Patients with Hepatitis C Virus Treated with Glecaprevir/Pibrentasvir from Clinical Trials and Real-World Cohorts

Xavier Forns · Jordan J. Feld · Douglas E. Dylla · Stanislas Pol · Kazuaki Chayama · Jinlin Hou · Jeong Heo · Pietro Lampertico · Ashley Brown · Mark Bondin · Fernando Tatsch · Margaret Burroughs · John Marcinak · Zhenzhen Zhang · Amanda Emmett · Stuart C. Gordon · Ira M. Jacobson

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ABSTRACT

Introduction: More than 70 million people are estimated to be infected with hepatitis C virus (HCV) globally. If left untreated, HCV infection can lead to complications such as extensive liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Evolution of treatments has resulted in highly effective and well-tolerated all-oral direct-acting antivirals. The pangenotypic regimen of glecaprevir/pibrentasvir is approved for treating HCV for patients without cirrhosis or with compensated cirrhosis (CC). Guidelines have evolved to simplify treatment to enable non-specialists to manage and treat HCV-infected patients. Simultaneously, such treatment algorithms provide guidance on the pretreatment identification of small subsets of patients who may require specialist treatment and long-term follow-up for advanced liver disease, including those at risk of developing HCC. This study describes the safety profile of glecaprevir/pibrentasvir in patients identified

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X. Forns (✉)
Liver Unit, Hospital Clinic de Barcelona, IDIBAPS and CIBEREHD, University of Barcelona, Barcelona, Spain
e-mail: xforns@clinic.cat

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

D. E. Dylla · M. Bondin · F. Tatsch · M. Burroughs · J. Marcinak · Z. Zhang · A. Emmett
AbbVie Inc., North Chicago, IL, USA

S. Pol
Liver Unit, Cochin Hospital, APHP, Inserm U-1223, Institut Pasteur, Université de Paris, Paris, France

K. Chayama
Department of Gastroenterology and Metabolism, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

J. Hou
Department of Infectious Diseases, State Key Laboratory of Organ Failure Research, Guangdong Provincial Key Laboratory of Viral Hepatitis Research, Nanfang Hospital, Southern Medical University, Guangzhou, China

J. Heo
Department of Internal Medicine, College of Medicine, Pusan National University and Medical Research Institute, Busan, Republic of Korea

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

P. Lampertico
Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

using previously described noninvasive laboratory measures who may be eligible for treatment by non-liver specialists.

Methods: This post hoc analysis of glecaprevir/pibrentasvir in patients, identified by noninvasive laboratory measures, intended to exclude patients with advanced liver disease and severe renal impairment, who can be managed within non-liver specialist settings. Patients were included from clinical trials and real-world studies of glecaprevir/pibrentasvir for HCV treatment. Baseline demographics, clinical characteristics, and safety assessments, including adverse events and laboratory abnormalities, were summarized.

Results: Data across these large-scale studies confirm that glecaprevir/pibrentasvir is well tolerated across different patient populations, with fewer than 0.1% of patients experiencing a serious adverse event related to treatment drugs, and few patients developing HCC during or after treatment.

Conclusion: The safety profile of glecaprevir/pibrentasvir enhances the confidence of non-liver specialists to treat the majority of HCV-infected patients, and provides an opportunity to expand the treater pool, potentially increasing diagnosis and treatment rates for HCV, contributing to elimination of HCV.

Keywords: Hepatitis C virus; Non-specialist; Safety

Key Summary Points

Why carry out this study?

Simplification of the hepatitis C virus (HCV) care cascade and the advent of direct-acting antivirals can help to achieve the World Health Organization's (WHO) 2030 HCV elimination targets.

Guidelines have attempted to simplify treatment and enable non-liver specialists to manage and treat low-risk HCV-infected patients, who represent the majority of patients. However, non-liver specialists may have concerns over treatment safety by using simplified, noninvasive pretreatment assessments.

This study investigated the safety profile of glecaprevir/pibrentasvir in patients identified using previously described noninvasive laboratory measures who may be eligible for treatment by non-liver specialists.

What was learned from the study?

Data from large clinical trials and real-world studies included in this analysis confirm that glecaprevir/pibrentasvir is well tolerated across different patient populations, with fewer than 0.1% of patients experiencing a serious adverse event related to treatment drugs, and no significant hepatoxicity observed.

The safety profile of glecaprevir/pibrentasvir may provide clinical confidence to physicians and other non-liver specialists treating HCV with the opportunity to expand the treater pool, a necessary step to meet HCV elimination targets.

A. Brown
Imperial College Healthcare NHS Trust, London, UK

S. C. Gordon
Division of Gastroenterology and Hepatology, Henry Ford Health System and Wayne State University School of Medicine, Detroit, MI, USA

I. M. Jacobson
NYU Langone Health, New York, USA

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14438756.

INTRODUCTION

Hepatitis C virus (HCV) infection is one of the leading causes of chronic liver disease worldwide. If left untreated, HCV can lead to hepatic scarring (fibrosis), hepatic cirrhosis (extensive scarring), and increase risk for developing hepatocellular carcinoma (HCC) [1]. HCV treatment is curative, defined as sustained virologic response (SVR; unquantifiable HCV ribonucleic acid) 12 weeks after treatment completion. HCV cure prevents the development of cirrhosis and consequently is associated with reducing risk of liver-related mortality, clinical decompensation, and HCC development compared to untreated patients [1–4]. Successful HCV therapy can reduce risk of extrahepatic complications, such as cardiovascular disorders [5] and diabetes [6]. Owing to the availability of highly effective treatment, HCV elimination is possible, with the World Health Organization (WHO) aiming to reduce new viral hepatitis infections by 90% and deaths due to viral hepatitis by 65% by 2030 [7].

Pretreatment assessment guidelines in several countries, including the USA, France, Australia, and Spain, have evolved to guide non-liver specialists such as nurse practitioners and general practitioners in the management of HCV, thus increasing treatment capacity [8–13]. Guideline bodies have recently released simplified treatment algorithms that may facilitate wider treatment acceptance within primary care settings, thus reducing care cascade gaps [10]. These algorithms help identify easy-to-treat patients with less advanced liver disease or at low risk for negative liver-related outcomes. For example, the American Association for the Study of Liver Disease (AASLD) recommends simplified pretreatment assessments using noninvasive, serological, or imaging-based techniques for assessing liver fibrosis [10]. These guidelines recommend identifying patients with the likelihood of cirrhosis using Fibrosis-4 score (FIB-4) calculated by the following noninvasive measures: age, aspartate aminotransferase (AST), platelet count, and alanine aminotransferase (ALT) [10]. A FIB-4 > 3.25 is suggestive of advanced liver disease and cirrhosis [10]. Another well-accepted noninvasive measure to identify patients at low risk for developing complications was identified by the Baveno VI Consensus Workshop combining FibroScan® (Echosens, Waltham, MA) < 20 kPa and a corresponding platelet count $\geq 150 \times 10^9$/L [14]. An investigational assessment for identifying patients with a low risk of liver-related outcomes during direct-acting antiviral (DAA) treatment is a combination of albumin > 38 g/L, indicating normal synthetic function, [15] and platelet count $\geq 130 \times 10^9$/L. The aforementioned laboratory measures are feasible in primary care settings [16–18] and can identify patients without decompensated cirrhosis who could be suitable for treatment by non-liver specialists.

With the simplified pretreatment assessments, non-liver specialists' concerns may include treatment safety and effectiveness. Glecaprevir/pibrentasvir (G/P) is a fixed-dose, once-daily, all-oral combination DAA therapy approved to treat all common genotypes of chronic HCV in patients without cirrhosis or with compensated cirrhosis (CC) [19, 20]. Clinical trials have shown G/P to be well tolerated and highly effective, even in patients with CC, with an overall cure rate of 98% [21]. In light of such data, AASLD also recommends simplified 8-week G/P treatment for some patients with CC without requirement for baseline resistance testing [10].

The present analysis was conducted to describe the safety profile of G/P in patients identified using previously described noninvasive laboratory measures who may be eligible for treatment by non-liver specialists.

METHODS

Study Design

Two separate data analyses were performed using data from real-world post-marketing observational studies (PMOS) enrolling patients from Austria, Belgium, France, Greece, Israel, Italy, Poland, Portugal, and Switzerland and pooled data from the following G/P clinical trials: ENDURANCE-1 (NCT02604017), ENDURANCE-2 (active arms) (NCT02640482), ENDURANCE-3 (NCT02640157), ENDURANCE-4 (NCT02636595), ENDURANCE-5 6 (NCT02966795), EXPEDITION-1 (NCT02642432), EXPEDITION-2 (NCT02738138), EXPEDITION-3 (NCT03219216), EXPEDITION-8 (NCT03089944), VOYAGE-1 (active arms) (NCT03222583), VOYAGE-2 (NCT03235349), CERTAIN-1 (NCT02707952), CERTAIN-2 (NCT02723084), SURVEYOR-2 (parts 3 and 4) (NCT02243293), APRI (NCT03212521), and MAGELLAN-1 (part 1 arm C, part 2 arms D, E) (NCT02446717). All patients received 300/120 mg G/P taken once daily with food for 8, 12, or 16 weeks. Patients in the clinical trials were followed for 24 weeks posttreatment, and in the PMOS cohorts SVR12 data were collected. For all included studies, written informed consent was obtained from each patient, including consent to participate and permission to publish personal health information while ensuring the identity of the individual remains confidential. For all included studies, the study protocols conformed to the ethical guidelines of the 1964 Declaration of Helsinki and its later updates, and were approved by the appropriate institutional review boards.

Patient Population

For these analyses, any patients with severe renal impairment, defined as chronic kidney disease stage 4/5, were excluded. Eligibility criteria for the originating studies have been previously reported. In addition, patients with cirrhosis underwent HCC screening within 3 months prior to screening of the originating studies either by ultrasound, computed tomography scan, or magnetic resonance imaging, or had a negative ultrasound at screening. Patients with HCV genotype 1–6, without cirrhosis or with CC, treatment-naïve or experienced to interferon or pegylated interferon ± ribavirin, or sofosbuvir + ribavirin ± pegylated interferon, and human immunodeficiency virus-coinfected patients, were included in these analyses.

Patients potentially eligible for HCV treatment in non-liver specialist settings were identified using common noninvasive methods. Nonmutually exclusive patient subgroups were based on baseline laboratory measures of advanced liver disease and transient elastography:

1. Baseline FIB-4 < 3.25 [22].
2. Baseline FibroScan < 20 kPa and platelet count $\geq 150 \times 10^9$/L [14].
3. Baseline albumin > 38 g/L and platelet count $\geq 130 \times 10^9$/L.
4. Patients who met at least one of the prior criteria [10].

Endpoints and Assessments

Baseline demographics, clinical characteristics, and safety assessments, including adverse events (AE) and laboratory abnormalities, were summarized. AEs were assessed by a study investigator for a possible relationship to G/P, and were coded using Medical Dictionary for Regulatory Authorities (MedDRA) 22.1 [23]. Treatment-emergent AEs (defined as any AE that occurred after the first dose of G/P and within 30 days after the last dose of G/P) of special interest for hepatic decompensation or hepatic failure and treatment-emergent and non-treatment-emergent AEs of special interest for HCC were also assessed using MedDRA 22.1 [23] preferred terms. Baseline and maximum laboratory values were cross tabulated to calculate rates of normalization. SVR was also summarized.

Statistical Analysis

Safety results and demographic and baseline characteristics were summarized for the intent-to-treat population, which included all patients

who received at least one dose of G/P. Categorical variables were summarized by number and percentage.

RESULTS

As a result of overlap in patients defining the three individual subgroups (baseline FIB-4 < 3.25, baseline FibroScan < 20 kPa and platelet count ≥ 150 × 10^9/L, and baseline albumin > 38 g/L and platelet count ≥ 130 × 10^9/L), the results described in the text are those of the overall subgroups of patients who met at least one of the prior criteria for both clinical trial and PMOS cohorts, unless stated otherwise.

Patient Characteristics

Demographics and baseline characteristics are reported for all clinical trials and PMOS subgroups determined by the noninvasive test criteria (Table 1). The FibroScan < 20 kPa and platelet count ≥ 150 × 10^9/L patient subgroup was smaller than other subgroups for both cohorts because not all patients had baseline FibroScan conducted. For patients who met at least one of the serum test criteria, 14.2% and 6.4% of the clinical trial cohort and PMOS cohort had CC at baseline, respectively. Real-world utilization of 8-week treatment duration (89.0%) in the PMOS population accurately reflects HCV patient populations at the time data were collected. In the clinical trial cohort, 74.6% (2802/3754) of patients were taking concomitant medications; those taken by at least 5% of patients were paracetamol, ibuprofen, acetylsalicylic acid, amlodipine, and levothyroxine. In the PMOS cohort, 46.9% (634/1352) of patients were reported as taking concomitant medications, which included levothyroxine (3.9%), methadone (3.9%), and acetylsalicylic acid (3.8%).

Efficacy

SVR12 rates were at least 97.5% in the intent-to-treat clinical trial cohort and at least 97.6% in the PMOS core population with sufficient follow-up with no meaningful differences among the four subgroups (Fig. 1).

Safety

AEs, laboratory parameters, and laboratory parameter abnormalities were collected (Table 2).

Overall, in the clinical trial cohort 60.6% (2275/3754) experienced an AE, while 31.5% (1184/3754) and 0.3% (10/3754) of patients experienced an AE possibly related to the study drug and an AE leading to treatment discontinuation, respectively. Most common AEs were headache (495/3754 [13.2%]), fatigue (377/3754 [10.0%]), and nausea (254/3754 [6.8%]) in this cohort. Most common AEs leading to treatment discontinuation were angioedema (2/3754 [< 0.1%]), anxiety (2/3754 [< 0.1%]), and nausea (2/3754 [< 0.1%]). Serious AEs experienced by at least two patients in the clinical trial cohort were joint dislocation (n = 3) and angina unstable, angioedema, bile duct stone, bronchitis, gastric ulcer, and transient ischemic attack (all n = 2).

In the clinical trial cohort, 5 (0.1%) patients reported HCC during or after treatment (Supplementary Material). One (< 0.1%) patient experienced a treatment-emergent hepatic decompensation event of worsening ascites. This patient with decompensated cirrhosis had moderate ascites present at study screening by ultrasound but not recognized at that time, and therefore was considered a protocol violation. This patient continued G/P treatment without interruption and achieved SVR without additional worsening of symptoms. This patient was included in this analysis on the basis of a baseline FIB-4 of 3.05, but did not qualify for other subgroup analyses because of a baseline FibroScan of 26.3 kPa, platelet count of 114 × 10^9/L, and albumin of 27 g/L. This patient also had a FibroTest (BioPredictive, Paris, France) of 0.97, indicating cirrhosis.

In the PMOS cohort, 13.8% (187/1352) of patients experienced an AE, with 7.8% (106/1352) and 0.4% (6/1352) of patients experiencing an AE possibly related to the study drug and an AE leading to treatment discontinuation,

Table 1 Baseline characteristics in clinical trials and PMOS cohorts

n (%)	Baseline FIB-4 < 3.25		Baseline FibroScan < 20 kPa and platelet count ≥ 150 × 10^9/L		Baseline albumin > 38 g/L and platelet count ≥ 130 × 10^9/L		Met ≥ 1 serum test criteria	
	Clinical trials (*N* = 3499)	PMOS (*N* = 1153)	Clinical trials (*N* = 2197)	PMOS (*N* = 849)	Clinical trials (*N* = 3521)	PMOS (*N* = 794)	Clinical trials (*N* = 3754)	PMOS (*N* = 1352)
Sex, male	1911 (54.6)	664 (57.6)	1220 (55.5)	476 (56.1)	1895 (53.8)	493 (62.1)	2031 (54.1)	767 (56.7)
Race								
White	2164 (61.9)	1093 (94.9)	1335 (60.8)	808 (95.3)	2145 (61.0)	766 (96.5)	2292 (61.1)	1288 (95.3)
Black	176 (5.0)	41 (3.6)	89 (4.1)	24 (2.8)	160 (4.5)	14 (1.8)	186 (5.0)	44 (3.3)
Age (years)								
< 65	3045 (87.0)	969 (84.0)	1857 (84.5)	697 (82.1)	2970 (84.4)	664 (83.6)	3172 (84.5)	1122 (83.0)
≥ 65	454 (13.0)	184 (16.0)	340 (15.5)	152 (17.9)	551 (15.6)	130 (16.4)	582 (15.5)	230 (17.0)
BMI (kg/m^2)								
< 30	2893 (82.7)	529 (87.9)	1853 (84.3)	407 (88.9)	2947 (83.7)	411 (89.3)	3113 (82.9)	614 (88.0)
≥ 30	605 (17.3)	73 (12.1)	344 (15.7)	51 (11.1)	573 (16.3)	49 (10.7)	640 (17.1)	84 (12.0)
Missing	1	551	0	391	1	334	1	654
HCV genotype								
1	1599 (45.7)	615 (53.8)	979 (44.6)	444 (52.9)	1645 (46.7)	420 (53.2)	1738 (46.3)	710 (53.0)
2	852 (24.3)	120 (10.5)	499 (22.7)	96 (11.4)	843 (23.9)	88 (11.1)	910 (24.2)	137 (10.2)
3	707 (20.2)	289 (25.3)	468 (21.3)	211 (25.1)	696 (19.8)	213 (27.0)	750 (20.0)	367 (27.4)
4	164 (4.7)	112 (9.8)	123 (5.6)	84 (10.0)	158 (4.5)	66 (8.4)	169 (4.5)	119 (8.9)
5	49 (1.4)	3 (0.3)	34 (1.5)	2 (0.2)	48 (1.4)	0	51 (1.4)	3 (0.2)
6	128 (3.7)	4 (0.3)	94 (4.3)	2 (0.2)	131 (3.7)	3 (0.4)	136 (3.6)	4 (0.3)
Missing	N/A	10	N/A	10	N/A	4	N/A	12

Table 1 continued

n (%)	Baseline FIB-4 < 3.25		Baseline FibroScan < 20 kPa and platelet count ≥ 150 × 10^9/L		Baseline albumin > 38 g/L and platelet count ≥ 130 × 10^9/L		Met ≥ 1 serum test criteria	
	Clinical trials (*N* = 3499)	PMOS (*N* = 1153)	Clinical trials (*N* = 2197)	PMOS (*N* = 849)	Clinical trials (*N* = 3521)	PMOS (*N* = 794)	Clinical trials (*N* = 3754)	PMOS (*N* = 1352)
Prior HCV treatment								
Treatment naïve	2683 (76.7)	986 (85.6)	1615 (73.5)	728 (85.8)	2698 (76.6)	681 (86.0)	2878 (76.7)	1153 (85.4)
Treatment experienced	816 (23.3)	166 (14.4)	582 (26.5)	120 (14.2)	823 (23.4)	111 (14.0)	876 (23.3)	197 (14.6)
Missing	N/A	1	N/A	1	N/A	2	N/A	2
Baseline fibrosis stage								
F0–1	2435 (72.0)	716 (83.1)	1623 (73.9)	722 (85.0)	2382 (70.3)	489 (81.6)	2483 (68.6)	846 (81.4)
F2	235 (7.0)	45 (5.2)	122 (5.6)	41 (4.8)	240 (7.1)	27 (4.5)	254 (7.0)	55 (5.3)
F3	320 (9.5)	52 (6.0)	262 (11.9)	59 (6.9)	340 (10.0)	47 (7.8)	365 (10.1)	72 (6.9)
F4	390 (11.5)	49 (5.7)	190 (8.6)	27 (3.2)	426 (12.6)	36 (6.0)	515 (14.2)	66 (6.4)
Missing	119	291	0	0	133	195	137	313
FIB < 3.25	3499 (100)	1153 (100)	2095 (95.4)	710 (94.5)	3277 (93.1)	674 (92.8)	–	–
FIB ≥ 3.25	0	0	102 (4.6)	41 (5.5)	244 (6.9)	52 (7.2)	–	–
Missing	N/A	N/A	N/A	98	N/A	68	–	–
HIV coinfection	186 (5.3)	62 (5.4)	118 (5.4)	51 (6.0)	173 (4.9)	38 (4.8)	189 (5.0)	76 (5.6)
Alcohol use								
Current	1073 (30.7)	402 (35.1)	708 (32.2)	310 (36.7)	1093 (31.0)	244 (31.0)	1145 (30.5)	444 (33.1)
Former	1012 (28.9)	189 (16.5)	587 (26.7)	138 (16.4)	981 (27.9)	144 (18.3)	1085 (28.9)	226 (16.8)
Never	1396 (39.9)	420 (36.7)	895 (40.7)	317 (37.6)	1429 (40.6)	285 (36.2)	1504 (40.1)	506 (37.7)

Table 1 continued

n (%)	Baseline FIB-4 < 3.25		Baseline FibroScan < 20 kPa and platelet count ≥ 150 × 10^9/L		Baseline albumin > 38 g/L and platelet count ≥ 130 × 10^9/L		Met ≥ 1 serum test criteria	
	Clinical trials (*N* = 3499)	PMOS (*N* = 1153)	Clinical trials (*N* = 2197)	PMOS (*N* = 849)	Clinical trials (*N* = 3521)	PMOS (*N* = 794)	Clinical trials (*N* = 3754)	PMOS (*N* = 1352)
Unknown	18 (0.5)	134 (11.7)	7 (0.3)	79 (9.4)	18 (0.5)	114 (14.5)	20 (0.5)	167 (12.4)
Missing	N/A	8	N/A	5	N/A	7	N/A	9
History of injection drug use								
Yes, ≤ 12 months	53 (1.5)	55 (4.8)	28 (1.3)	36 (4.2)	53 (1.5)	36 (4.6)	58 (1.5)	60 (4.5)
Yes, > 12 months	793 (22.7)	267 (23.3)	489 (22.3)	179 (21.1)	776 (22.0)	206 (26.2)	824 (21.9)	295 (22.0)
Yes, unknown	258 (7.4)	1 (< 0.1)	152 (6.9)	0	233 (6.6)	1 (0.1)	275 (7.3)	1 (< 0.1)
No	2395 (68.4)	822 (71.8)	1528 (69.5)	633 (74.6)	2459 (69.8)	543 (69.1)	2597 (69.2)	985 (73.5)
Missing	N/A	8	N/A	1	N/A	8	N/A	11
History of psychiatric disorder	N/A	124 (10.8)	N/A	100 (11.8)	N/A	80 (10.1)	N/A	143 (10.6)
Planned treatment duration								
8 weeks	2109 (60.3)	1035 (89.8)	1261 (57.4)	779 (91.8)	2099 (59.6)	714 (89.9)	2243 (59.7)	1203 (89.0)
12 weeks	1308 (37.4)	100 (8.7)	881 (40.1)	52 (6.1)	1339 (38.0)	70 (8.8)	1422 (37.9)	123 (9.1)
16 weeks	82 (2.3)	18 (1.6)	55 (2.5)	18 (2.1)	83 (2.4)	10 (1.3)	89 (2.4)	26 (1.9)
Baseline laboratory abnormalities[a]								
Platelets (10^9/L)	188 (5.4)	92 (8.0)	13 (0.6)	31 (3.7)	90 (2.6)	53 (6.7)	206 (5.5)	114 (8.4)
ALT (μ/L)	2131 (60.9)	675 (58.5)	1397 (63.6)	487 (58.4)	2209 (62.7)	495 (62.8)	2353 (62.7)	819 (61.3)
AST (μ/L)	1852 (52.9)	622 (53.9)	1249 (56.9)	413 (54.8)	1959 (55.6)	425 (58.5)	2101 (56.0)	689 (56.3)

Table 1 continued

n (%)	Baseline FIB-4 < 3.25		Baseline FibroScan < 20 kPa and platelet count ≥ 150 × 10^9/L		Baseline albumin > 38 g/L and platelet count ≥ 130 × 10^9/L		Met ≥ 1 serum test criteria	
	Clinical trials (*N* = 3499)	PMOS (*N* = 1153)	Clinical trials (*N* = 2197)	PMOS (*N* = 849)	Clinical trials (*N* = 3521)	PMOS (*N* = 794)	Clinical trials (*N* = 3754)	PMOS (*N* = 1352)
Alkaline phosphatase (μ/L)	148 (4.2)	–	90 (4.1)	–	155 (4.4)	–	180 (4.8)	–
Total bilirubin (μmol/L)	150 (4.3)	64 (6.7)	85 (3.9)	52 (7.4)	145 (4.1)	48 (6.5)	163 (4.3)	77 (6.9)
Albumin (g/L)	155 (4.4)	56 (7.0)	108 (4.9)	36 (6.4)	157 (4.5)	42 (5.3)	168 (4.5)	71 (7.7)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, *FIB-4* Fibrosis-4 score, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *N/A* not assessed, *PMOS* post-marketing observation studies. FibroScan® is a product of Echosens (Waltham, MA)

[a] Laboratory abnormalities were values less than the lower limit of normal or greater than the upper limit of normal

respectively. No serious AEs occurred in at least two patients in this cohort. Most common AEs were fatigue (34/1352 [2.5%]), asthenia (33/1352 [2.4%]), and headache (30/1352 [2.2%]). Most common AE leading to treatment discontinuation was nausea (2/1352 [0.1%]). No patients in this cohort reported HCC or experienced treatment-emergent hepatic decompensation events.

When comparing safety data across the three analysis subgroups, no apparent differences in the number of AEs, treatment-related AEs, or serious AEs were observed within the clinical trial and PMOS cohorts. The most common AEs were consistent across subgroups in each cohort.

Laboratory Assessments

At baseline in the clinical trial cohort, 4.7% (175/3754) of patients had thrombocytopenia (low platelets) and 0.1% (5/3754) had hypoalbuminemia (low albumin). There were 62.6% (2351/3754), 56.0% (2101/3754), 4.1% (155/3754), and 3.1% (116/3754) of patients at baseline who had elevated ALT, AST, alkaline phosphatase, and total bilirubin, respectively. In the PMOS cohort at baseline, 6.1% (83/1352) of patients had thrombocytopenia and 4.3% (40/926) had hypoalbuminemia. There were 61.0% (816/1337), 56.0% (685/1223), and 5.0% (56/1116) of patients at baseline who had elevated ALT, AST, and bilirubin, respectively. Post-baseline grade 3 and 4 laboratory abnormalities were rare across all patient populations, and similar for the three unique subgroups. In the clinical trial cohort, 0.2% of patients experienced post-baseline grade ≥ 3 ALT, AST, or bilirubin (Table 2). In the PMOS cohort, 0.2% and 0.1% of patients experienced post-baseline grade ≥ 3 ALT and AST, respectively (Table 2). There were no post-baseline abnormalities for platelets or albumin. To assess the impact of G/P treatment on laboratory parameters, the change from baseline to maximum laboratory values during the treatment period was assessed to examine normalization of these parameters (Table 3). After treatment, the majority of patients in the clinical trial dataset had

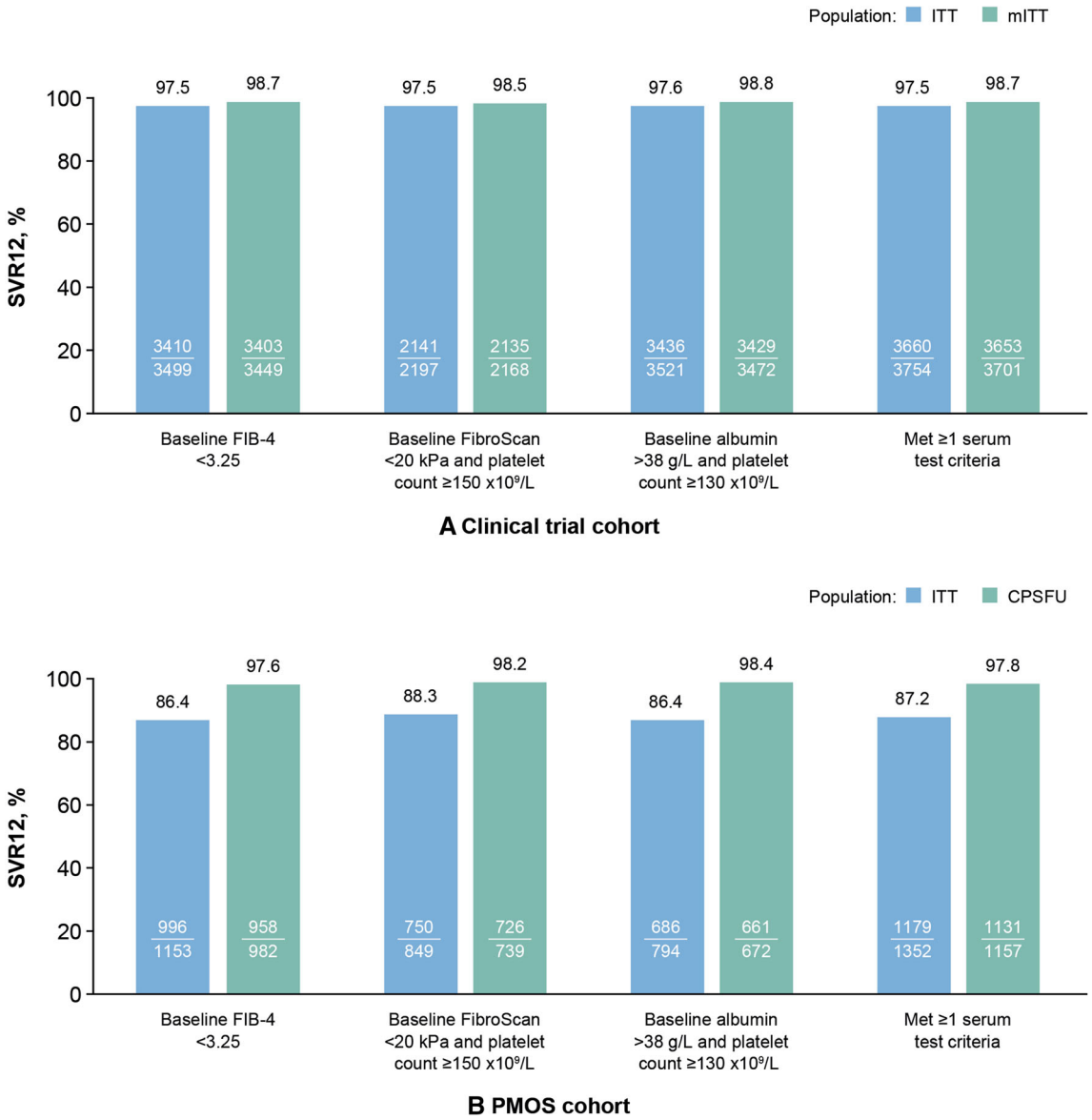

Fig. 1 SVR12 rates in the patient populations in the clinical trial cohort (**a**) and PMOS cohort (**b**). CPSFU population included patients from the core population, excluding those who did not have an HCV RNA evaluation after posttreatment day 70 for reasons not related to effectiveness or safety (lost to follow-up or unavailable HCV RNA data). Patients included in the CPSFU had one of the following: HCV RNA data after posttreatment day 70 (not included if the drug end date was unknown), virologic failure (on-treatment virologic failure or posttreatment relapse), discontinued the study because of an AE, and had HCV RNA < 50 IU/mL at the last measurement. mITT population excluded patients who did not achieve SVR for reasons other than virologic failure (e.g., patients who discontinued early or were lost to follow-up). AE adverse event, CPSFU core population with sufficient follow-up, FIB-4 Fibrosis-4 score, HCV hepatitis C virus, ITT intention-to-treat, mITT modified intention-to-treat, PMOS post-marketing observation studies, RNA ribonucleic acid, SVR12 sustained virologic response at posttreatment week 12. FibroScan® is a product of Echosens (Waltham, MA)

Table 2 Summary of AEs and laboratory parameter abnormalities in clinical trials and PMOS cohorts

n (%)	Baseline FIB-4 < 3.25		Baseline FibroScan < 20 kPa and platelet count ≥ 150 × 10^9/L		Baseline albumin > 38 g/L and platelet count ≥ 130 × 10^9/L		Met ≥ 1 serum test criteria	
	Clinical trials (*N* = 3499)	PMOS (*N* = 1153)	Clinical trials (*N* = 2197)	PMOS (*N* = 849)	Clinical trials (*N* = 3521)	PMOS (*N* = 794)	Clinical trials (*N* = 3754)	PMOS (*N* = 1352)
Any AE[a]	2135 (61.0)	170 (14.7)	1363 (62.0)	110 (13.0)	2140 (60.8)	112 (14.1)	2275 (60.6)	187 (13.8)
AE possibly related to DAA	1119 (32.0)	95 (8.2)	742 (33.8)	65 (7.7)	1110 (31.5)	62 (7.8)	1184 (31.5)	106 (7.8)
AE leading to discontinuation of study drug	10 (0.3)	5 (0.4)	6 (0.3)	5 (0.6)	10 (0.3)	1 (0.1)	10 (0.3)	6 (0.4)
Serious AE	59 (1.7)	8 (0.7)	33 (1.5)	4 (0.5)	60 (1.7)	5 (0.6)	66 (1.8)	8 (0.6)
Serious AE related to DAA	3 (< 0.1)	0/1153	1 (< 0.1)	0/849	3 (< 0.1)	0/794	3 (< 0.1)	0/1352
Deaths	5 (0.1)	5 (0.4)	4 (0.2)	4 (0.5)	5 (0.1)	4 (0.5)	7 (0.2)	5 (0.4)
AE ≥ 3% in clinical trial cohort								
Headache	472 (13.5)	25 (2.2)	321 (14.6)	16 (1.9)	470 (13.3)	19 (2.4)	495 (13.2)	30 (2.2)
Fatigue	361 (10.3)	32 (2.8)	237 (10.8)	26 (3.1)	347 (9.9)	19 (2.4)	377 (10.0)	34 (2.5)
Nausea	236 (6.7)	14 (1.2)	149 (6.8)	8 (0.9)	237 (6.7)	11 (1.4)	254 (6.8)	15 (1.1)
Nasopharyngitis	165 (4.7)	3 (0.3)	105 (4.8)	0/849	168 (4.8)	2 (0.3)	172 (4.6)	3 (0.2)
Pruritus	149 (4.3)	8 (0.7)	99 (4.5)	5 (0.6)	154 (4.4)	5 (0.6)	170 (4.5)	10 (0.7)
Upper respiratory tract infection	156 (4.5)	1 (< 0.1)	113 (5.1)	1 (0.1)	157 (4.5)	0/794	168 (4.5)	1 (< 0.1)
Diarrhea	159 (4.5)	8 (0.7)	91 (4.1)	6 (0.7)	156 (4.4)	4 (0.5)	165 (4.4)	8 (0.6)
Dizziness	95 (2.7)	5 (0.4)	68 (3.1)	3 (0.4)	99 (2.8)	3 (0.4)	106 (2.8)	5 (0.4)
Post-baseline grade ≥ 3 laboratory abnormalities								
ALT (μ/L)	6/3493 (0.2)	2/920 (0.2)	2/2195 (< 0.1)	1/707 (0.1)	6/3516 (0.2)	0/632	6/3748 (0.2)	2/1077 (0.2)

Table 2 continued

n (%)	Baseline FIB-4 < 3.25		Baseline FibroScan < 20 kPa and platelet count ≥ 150 × 10^9/L		Baseline albumin > 38 g/L and platelet count ≥ 130 × 10^9/L		Met ≥ 1 serum test criteria	
	Clinical trials (*N* = 3499)	PMOS (*N* = 1153)	Clinical trials (*N* = 2197)	PMOS (*N* = 849)	Clinical trials (*N* = 3521)	PMOS (*N* = 794)	Clinical trials (*N* = 3754)	PMOS (*N* = 1352)
AST (μ/L)	7/3493 (0.2)	1/862 (0.1)	4/2195 (0.2)	1/617 (0.2)	7/3516 (0.2)	0/583	7/3748 (0.2)	1/958 (0.1)
Alkaline phosphatase (μ/L)	0/3493	–	0/2195	–	0/3516	–	0/3748	–
Bilirubin (μmol/L)	9/3493 (0.3)	0/735	7/2195 (0.3)	0/561	9/3516 (0.3)	0/539	9/3748 (0.2)	0/859
Laboratory abnormalities of interest								
Bilirubin ≥ 2 × ULN and > baseline	32/3492 (0.9)	8/682 (1.2)	21/2194 (1.0)	9/536 (1.7)	34/3515 (1.0)	7/498 (1.4)	35/3747 (0.9)	12/790 (1.5)
ALT > 3 × ULN and total bilirubin > 2 × ULN	2/3492 (< 0.1)	0/682	2/2194 (< 0.1)	0/536	3/3515 (< 0.1)	0/498	3/3747 (< 0.1)[b]	0/790

AE adverse event, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *DAA* direct-acting antivirals, *FIB-4* Fibrosis-4 score, *GGT* gamma-glutamyl transpeptidase, *G/P* glecaprevir/pibrentasvir, *MEDDRA* Medical Dictionary for Regulatory Authorities, *PMOS* post-marketing observation studies, *ULN* upper limit of normal. FibroScan® is a product of Echosens (Waltham, MA)

[a] AEs were assessed by a study investigator for a possible relationship to G/P and were coded using MEDDRA 22.1

[b] These cases do not represent drug-induced liver injury. One patient experienced a transient increase in ALT on day 29 with no concurrent increase in bilirubin or an increase in grade of ALT before normalization. This patient had rapid decline in ALT from baseline 1143 to 90 μ/L on day 15 (first nadir) before transient ALT increase to 111 μ/L on day 29. Total bilirubin declined from day 15 (42 μmol/L) to day 29 (40 μmol/L). A second patient had grade 3 ALT, AST, and GGT values, as well as elevation of alkaline phosphatase on day 87. On day 106 an ultrasound revealed two gallstones without evidence of biliary dilation. The investigator considered the events of ALT, AST, and total bilirubin increase as having reasonable possibility of being related to the study drug, but not consistent with drug-induced liver injury. A third patient experienced a post-nadir increase in ALT to ≥ 3 × ULN and total bilirubin > 2 × ULN. The increase in ALT was minimal (8 μ/L on day 15) and the total bilirubin elevations were predominately indirect and present at baseline. The total bilirubin elevation ≥ 2 × ULN on day 57 was in the context of a sample with hemolysis

Table 3 Change in laboratory measures from baseline among patients who met at least one serum test criteria and with available data, *n*/*N* (%)

	Clinical trials (*N* = 3754)	PMOS (*N* = 1352)
Platelets[a]		
Low to normal	120/174 (69.0)	36/63 (57.1)
Normal to low	15/3538 (0.4)	18/918 (2.0)
Alanine aminotransferase[b]		
High to normal	1549/2349 (65.9)	599/663 (90.3)
Normal to high	34/1397 (2.4)	7/401 (1.7)
Aspartate aminotransferase[c]		
High to normal	1585/2100 (75.5)	456/513 (88.9)
Normal to high	58/1648 (3.5)	9/406 (2.2)
Bilirubin[d]		
High to normal	21/116 (18.1)	12/40 (30.0)
Normal to high	299/3585 (8.3)	56/746 (7.5)
Direct bilirubin[e]		
High to normal	63/204 (30.9)	24/65 (36.9)
Normal to high	233/3176 (7.3)	36/209 (17.2)
Albumin[f]		
Low to normal	4/5 (80.0)	–
Normal to low	0/3580	–

PMOS post-marketing observation studies
[a] Lower limit of normal is 140
[b] Upper limit of normal is 32 for women and 43 for men
[c] Upper limit of normal is 34 for women and 36 for men
[d] Upper limit of normal is 1.2 mg/dL
[e] Upper limit of normal is 0.3 mg/dL
[f] Lower limit of normal is 33 g/L, data collection for albumin in the PMOS cohort was insufficient to report

normalized for platelets, ALT, and AST (69.0%, 65.9%, and 75.5%, respectively), while 18.1%, 30.9%, and 80.0% of patients had normalized levels of bilirubin, direct bilirubin, and albumin, respectively (Table 3). Correspondingly, after treatment, the majority of patients in the PMOS dataset had normalized levels of platelets, ALT, and AST (57.1%, 90.3%, and 88.9%, respectively), while 30.0% and 36.9% of patients had normalized levels of bilirubin and direct bilirubin, respectively (Table 3).

DISCUSSION

Revisions made to HCV testing algorithms and the advent of DAAs allow for the simplification of treatment for patients with HCV [24, 25]. Screening and treatment recommendations have expanded to be more inclusive, and in some cases recommend non-liver specialist treatment in low-risk patients with HCV, which represent the majority of patients [10]. This will increase treatment capacity, which may help to

achieve the WHO's 2030 HCV elimination targets [26]. Some patients with advanced liver disease may require specialist care, including patients at risk for decompensation events and HCC [10]. Published data have begun demonstrating that non-liver specialist treatment of HCV-infected patients with DAAs can be as effective as specialist care, provided that non-specialists receive appropriate training in the screening and treatment of HCV infection. The ASCEND study showed that task shifting HCV treatment to non-liver specialists was effective and well tolerated with no significant difference in SVR rate [27]. These results are supported by multiple studies that show HCV treatment through primary care is effective and may increase treatment uptake [28–30]. Despite these early data from non-liver specialist settings, concerns regarding safe use of HCV medications may remain, creating barriers for non-liver specialist HCV treatment uptake [31].

Data presented here describe the safety of G/P in low-risk patients with HCV identified by noninvasive techniques from both the clinical trial and PMOS cohorts. Overall, G/P was well tolerated in both cohorts with few patients experiencing AEs leading to treatment discontinuation (0.3% and 0.4% in the clinical trial cohort and PMOS cohort, respectively), low rates of serious AEs (1.8% and 0.6%, respectively), and no significant hepatotoxicity observed. Fewer patients in the PMOS cohort had compensated cirrhosis compared with the clinical trial cohort. This difference could explain the higher number of decompensation events and patients with HCC observed in the clinical trial cohort. Safety data from this large analysis provide additional evidence for non-specialist treatment following pretreatment assessment to identify low-risk patients through noninvasive diagnostics described by the three unique subgroups. Data derived from PMOS cohorts reinforce results that may be expected outside of clinical trial protocols; however, alone they may be limited by the underreporting of safety events typically present in observational studies versus more controlled clinical trials.

Comparisons between demographics and baseline characteristics of patients from the clinical trial and PMOS cohorts should be treated with caution because those in the clinical trials may not accurately represent real-world populations in regard to proportions with specific comorbidities or treatment durations studied. In this particular instance, fewer patients were administered 8-week G/P in the clinical trial cohort as a result of clinical trial designs aiming to identify optimal treatment duration across different patient subpopulations. However, G/P safety has been demonstrated to be similar regardless of treatment duration [19, 20].

Each noninvasive measure assessed here demonstrated a similar safety profile for G/P. The overlap and similar safety profile observed in patient subgroups qualified for the analysis by FIB-4 < 3.25 or albumin > 38 g/L and platelet count $\geq 130 \times 10^9$L suggest that either assessment would be sufficient to identify patients at risk for liver-related outcomes. Similar safety profiles were also observed across the FibroScan subgroup, but applicability and significance of this finding may be limited by lack of universal non-liver specialist access to this instrument.

A limitation to consider for FIB-4 eligibility is the finding of one patient in the clinical trial subgroup ($N = 3499$) who had baseline Child–Pugh B decompensated cirrhosis and experienced worsening of ascites. Despite being a protocol violation, this patient would have qualified for simplified treatment by FIB-4 in clinical practice, but not by the other two assessments. This may be explained because FIB-4 does not assess liver stiffness or symptoms of portal hypertension like the other two test criteria do, and relies more heavily on AST in its calculation, which was within the normal range for this patient. While not validated and perhaps a limitation, our observation of no hepatic decompensation events in patients identified by albumin > 38 g/L and platelet count $\geq 130 \times 10^9$/L criteria is consistent with the publication first describing these criteria. In that analysis, no patient with CC experienced hepatic decompensation events during G/P treatment [32]. Other limitations to consider are short duration of post-SVR monitoring for negative liver outcomes, missing baseline laboratory

values in the PMOS cohort, and nonmutual exclusiveness of the subgroups meaning it is not possible to quantify how many of the criteria each patient met. A further limitation of this analysis is that in both clinical trial and PMOS cohorts, patients were assessed and treated by HCV specialists; more information is needed to confirm whether non-specialists would accurately identify patients with advanced fibrosis and both compensated and decompensated cirrhosis.

CONCLUSIONS

G/P treatment was well tolerated across the subgroups, including some patients with CC, consistent with pivotal clinical trial safety data [33] and real-world evidence [34] of G/P treatment in patients with CC. These data should provide reassurance that specialist intervention is not necessary for low-risk patients and reinforce the wider adoption of noninvasive screening tools in primary care settings. Non-liver specialists can be reassured that G/P, when prescribed per label, can be safely used in patients in combination with post-SVR HCC screening and awareness of potential drug–drug interactions [10, 35, 36]. In addition, these data may impact treatment guidelines, particularly in countries adopting decentralized HCV care, working towards simplified 8-week treatment for the majority of patients with HCV. These results may provide clinical confidence to physicians and other non-liver specialists treating HCV with the opportunity to expand the treater pool, a necessary step to meet elimination targets [31].

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Compliance with Ethics Guidelines. For all included studies, written informed consent was obtained from each patient, including consent to participate and permission to publish personal health information while maintaining the identity of the individual confidential. For all included studies, the study protocols conformed to the ethical guidelines of the 1964 Declaration of Helsinki and its later amendments, and were approved by the appropriate institutional review boards.

Data Availability. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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