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ORIGINAL RESEARCH

Safety and Effectiveness Using 8 Weeks of Glecaprevir/Pibrentasvir in HCV-Infected Treatment-Naïve Patients with Compensated Cirrhosis: The CREST Study

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ABSTRACT

Introduction: In clinical trials with hepatitis C virus-infected treatment-naïve (TN) patients with compensated cirrhosis (CC), glecaprevir/pibrentasvir (G/P), a fixed-dose, once-daily, pangenotypic regimen, has demonstrated sustained virologic response at posttreatment Week 12 (SVR12) > 95%. We evaluated the real-world safety and effectiveness of 8-week G/P

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therapy in TN patients with CC, including certain subgroups of interest.

Methods: The CREST study is a real-world, noninterventional, multicenter study retrospectively assessing data from Canada, Germany, Israel, Italy, and Spain. The full analysis set (FAS) designated all patients in the study; the modified analysis set (MAS) excluded patients who discontinued G/P for nonvirologic failure or who had missing SVR12 data. The primary endpoint was SVR12; safety endpoints were also assessed.

Results: A total of 386 patients were included in the FAS, 375 patients completed the study, and 325 patients were included in the MAS; 51 patients had missing SVR12 data. Overall, in the MAS and FAS, SVR12 was achieved in 99.1% and 84.2% of patients, respectively. In subgroups of interest, the percentage of patients achieving SVR12 in the MAS (and FAS) was: genotype (GT)3: 97.5% (80.6%); FibroScan® $\geq$ 12.5 kPa: 98.9% (89.3%); platelet count $< 100 \times 10^9$/l: 100% (88.2%); both platelets $< 150 \times 10^9$/l and FibroScan® $>$ 20 kPa: 100% (88.9%); aspartate aminotransferase-to-platelet ratio index $>$ 1.09: 98.7% (83.1%); fibrosis-4 index $>$ 3.25: 98.6% (84.0%); albumin $<$ 3 g/dl: 100% (91.7%); people who use drugs: 97.7% (84.3%); psychiatric disorders: 96.6% (84.8%); and human immunodeficiency virus coinfection: 100% (95.0%). Overall, 26.9% (104/386) of patients experienced an adverse event, none of which were classed as serious.

Conclusion: In this real-world cohort, 8 weeks of G/P therapy was well tolerated in TN patients with CC. SVR12 rates were similar to clinical trials, supporting 8-week treatment in TN patients with CC, including those with signs of advanced liver disease and GT3 infection.

Keywords: Compensated cirrhosis; Direct-acting antivirals; Hepatitis C virus; Real world; Treatment-naïve

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Key Summary Points

Why carry out this study?

In randomized controlled trials, 8 weeks of glecaprevir/pibrentasvir therapy produces high cure rates for most patients with hepatitis C infection

Patients in the real world may have additional comorbidities and risk factors, which are underrepresented in randomized controlled trials, such as those with genotype 3 infection, those with signs of portal hypertension (i.e., a liver stiffness > 20 kPa with a platelet count < 150 × 10^9/l; according to the Baveno VI classification), people who use drugs, and those with a psychiatric disorder

This study evaluated the real-world safety and effectiveness of 8-week glecaprevir/pibrentasvir therapy in treatment-naïve patients with compensated cirrhosis and further examined data in certain subgroups of interest

What was learned from the study?

In this real-world cohort, 8 weeks of glecaprevir/pibrentasvir therapy was well tolerated in treatment-naïve patients with compensated cirrhosis with cure rates similar to those reported in clinical trials

Until now, the evidence demonstrating the efficacy and safety of 8-week glecaprevir/pibrentasvir in these patients has been limited to the EXPEDITION-8 study and a few real-world studies; the results of this analysis supplement the clinical data and thus establish 8-week glecaprevir/pibrentasvir more firmly as an effective and well-tolerated treatment regimen in treatment-naïve patients with compensated cirrhosis, including those with genotype 3 infection and those with signs of portal hypertension

INTRODUCTION

Globally, approximately 58 million people have chronic hepatitis C virus (HCV) infection [1]. Untreated, HCV can lead to the development of cirrhosis, end-stage liver disease, hepatocellular carcinoma, and death [2, 3], with approximately 290,000 people dying in 2019 from HCV-related complications [1].

Historically, HCV therapy with interferon-based regimens had low cure rates, poor safety outcomes, and long treatment durations [4]. With the development and availability of interferon-free, direct-acting antivirals (DAAs), HCV treatment has been revolutionized to be short and well tolerated. Combinations of these drugs have been demonstrated to yield high levels of sustained virologic response (SVR) at posttreatment Week 12 (SVR12). Indeed, DAAs are now recommended for the treatment of most patients with chronic HCV infection. Moreover, simplified treatment of HCV infection is advised to support the global efforts to eliminate HCV, which is only possible with the use of pangenotypic regimens [5].

One such oral DAA-based regimen, glecaprevir/pibrentasvir (G/P), is a fixed-dose, once-daily, pangenotypic regimen approved for the treatment of patients with chronic HCV [6, 7]. In randomized controlled clinical trials, G/P demonstrated SVR12 in ≥ 93% of patients and was well tolerated [8–10]. In treatment-naïve (TN) patients with compensated cirrhosis (CC), 8 weeks of G/P therapy was approved in the US and Europe following results from the EXPEDITION-8 study where previously 12 weeks of treatment was recommended [6, 7, 9]. EXPEDITION-8 evaluated 8 weeks of G/P in 343 HCV genotype (GT) 1–6 TN patients with CC [9]. The SVR12 in patients with GT1–6 was 99.7% [334/335; 95% confidence interval (CI) 98.3–99.9] in the per-protocol (PP) population and 97.7% (335/343; 95% CI 96.1–99.3) in the intention-to-treat (ITT) population. Common adverse events (AEs) (≥ 5%) were fatigue (9%), pruritus (8%), headache (8%), and nausea (6%). Serious AEs occurred in only 2% of patients, and none of these were considered related to treatment. No AE led to drug

discontinuation, and clinically significant laboratory abnormalities were infrequent [9].

A few real-world studies have evaluated G/P in patients with CC, with a special interest in harder-to-treat groups such as those with comorbidities, those with HCV GT3 infection, people who use drugs (PWUD), those with a psychiatric disorder, and those with other barriers to treatment [11–14]. These studies have shown that SVR12 rates with G/P remain high and ≥ 98% in the PP population of GT1–6 patients [11, 12, 15]. Although these data showed G/P was well tolerated and led to high SVR12 rates, potential barriers to successful treatment, such as the presence of comorbidities and patients with other risk factors, may not always be well represented in registrational trials.

Moreover, the latest recommendations from the European Association for the Study of the Liver (EASL) for treatment of HCV state that additional data are needed to consolidate the recommendation of use of 8-week G/P in GT3 TN patients with CC and in patients with CC and signs of portal hypertension [5]. Real-world data from larger cohorts would be valuable to fully understand the benefits and potential limitations of the drug.

This study aimed to evaluate the real-world safety and effectiveness of 8 weeks of G/P therapy in TN patients with CC, including subgroups of interest such as GT3 infection, patients with comorbidities of current illicit drug use, alcohol use, or human immunodeficiency virus (HIV) coinfection, and signs of portal hypertension (i.e., a liver stiffness > 20 kPa with a platelet count < 150×10^9/l, according to the Baveno VI classification) [5].

METHODS

The CREST study is a noninterventional, multicenter observational study in HCV-infected TN patients with CC. Data were collected through a retrospective review of existing data derived from Canada, Germany, Israel, Italy, and Spain. Eligible patients were enrolled in chronologic order from participating sites by the local principal investigator. Data sources for eligible patients included all sources of study-relevant information (medical record) available to the clinical study site investigator; the medical record may include paper medical charts, electronic medical records, and clinical laboratory records. The study protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Each participating clinician signed an agreement attesting to compliance with all rules and regulations regarding the disclosure of patient information. Data were collected by the clinical study site investigator in such a manner that the identity of the patient could not be readily ascertained directly or through identifiers linked to the patient. The clinical study site investigator did not contact the subjects or re-identify patients. The study was granted an exemption from obtaining informed patient consent and approved by the Veritas Independent Review Board and the Saskatchewan Health Authority and the Ottawa Hospital Research Institute and the Hamilton Integrated Research Ethics Boards (HiREB) (Canada), the Institutional Review Board of Maccabi Healthcare Services (Israel), the Department of Medicines for Human Use of the Spanish Agency for Medicines and Health Products (AEMPS) and the Research Ethics Committee from the Medicines Gregorio Marañón General University Hospital (Spain), and the Ethics Committee of the Medical Association of Westphalia-Lippe and the Westphalian Wilhelms University Board (Germany). The study was approved by each of the institutional ethics committees for the sites in Italy.

Study Population

Chronic HCV-infected patients aged ≥ 12 years who were TN and had CC (documented as Child-Pugh A as determined per the clinical study investigator), treated for 8 weeks with G/P, were included in the study; patients were also required to start G/P treatment on or after January 1, 2018. Patients were excluded from the study if there were insufficient or limited source data confirming the patient's HCV

status, treatment history, and cirrhosis status or if they had any historical clinical evidence of hepatocellular carcinoma, decompensated cirrhosis, or events possibly related to liver decompensation, including any current or past evidence of Child-Pugh B or C classification. Patients were also excluded if they were still on G/P treatment and still in the follow-up period prior to a treatment outcome evaluation. All patients enrolled in the study who were eligible as per inclusion and exclusion criteria were designated to the full analysis set (FAS). The modified analysis set (MAS) excluded patients who discontinued G/P for reasons other than virologic failure and/or who had missing data to document the primary endpoint. The primary endpoint was effectiveness determined by SVR12, defined as HCV ribonucleic acid (RNA) less than the lower limit of quantification 12 weeks after end of treatment with G/P in the MAS. A window of 10–26 weeks posttreatment was deemed acceptable for determination of primary and secondary endpoints. Exploratory objectives included determining treatment factors that may be associated with HCV treatment failure such as, but not limited to, nonprescribed illicit drug use, comorbidities, concomitant medication therapy, and subgroup analyses in patients of interest (PWUD, GT3, HIV/HCV coinfection).

Statistical Analyses

Demographic and baseline characteristics of the patients were summarized using descriptive statistics. Categorical variables were summarized using frequency tables, and quantitative variables were summarized using mean [± standard deviation (SD)] and median [interquartile range (IQR), Q1–Q3] values. Descriptive analyses were also performed for subgroups of interest. The primary effectiveness endpoint was assessed by the percentage and the exact Clopper-Pearson 95% CI [16] of patients achieving SVR12; in the FAS population, this was computed using nonresponder imputation. For quantitative secondary endpoints, the median (IQR, Q3–Q1) were computed.

RESULTS

A total of 386 patients were included in the FAS, out of which 375 (97.2%) patients completed the study (Fig. 1). Eleven patients discontinued treatment prematurely: six due to noncompliance; three were lost to follow-up; one discontinued treatment due to an AE; one discontinued treatment for an unknown reason. Of the 375 patients who completed the study, 325 (86.7%) were then included in the MAS and 51 (15.7%) had missing data and were unable to be assessed for SVR12 (Fig. 1). One patient who discontinued treatment had data to assess SVR12.

Baseline Characteristics

Of the patients included in the FAS, 58.3% (225/386) were infected with HCV GT1 and 26.2% (101/386) were infected with GT3 (Table 1). Among the patients with missing data, 60.8% (31/51) had GT1 infection and 37.3% (19/51) had GT3 infection. At treatment initiation, 16.3% (63/386) of patients had a comorbidity of current alcoholism, 23.6% (91/386) reported current drug addiction, 9.1% (35/386) had psychiatric disorders, and 5.2% (20/386) had HIV coinfection (Table 2). Noninvasive methodologies were used to assess cirrhosis in 99% of patients (382/386) with the most common being fibrosis-4 (FIB-4) index (64.4%; 246/382), aspartate aminotransferase-to-platelet ratio index (APRI; 57.9%; 221/382), and FibroScan® (EchoSens, Paris, France) (52.1%; 199/382) (Table 3). The most prescribed concomitant medications included therapy for drug addiction, antihypertensives, and analgesics. The top ten medications by class and name are enumerated in Table 2.

Efficacy

Overall, SVR12 was achieved in 99.1% (322/325; 95% CI: 97.3–99.8) of patients in the MAS and 84.2% (325/386; 95% CI: 80.2–87.7) of patients in the FAS populations (Fig. 2). The percentage of patients achieving SVR12 in the MAS (and FAS), broken down by GT, was as follows: GT1:

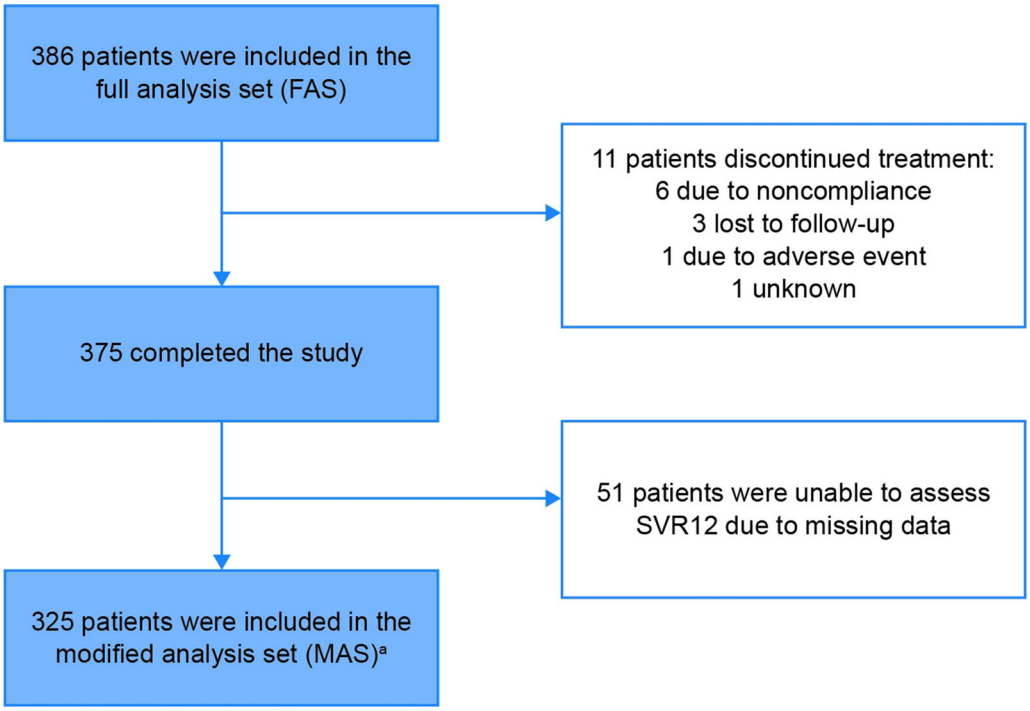

Fig. 1 Study schematic. *SVR12* sustained virologic response at posttreatment Week 12. [a]One patient who discontinued treatment but had data to assess SVR12 was included in the MAS

99.5% (85.6%); GT2: 100% (90.5%); GT3: 97.5% (80.6%); GT4: 100% (93.3%); GT5: 100% (100%). In patient subgroups of interest, the percentage of patients achieving SVR12 in the MAS (and FAS) was as follows: FibroScan ≥ 12.5 kPa: 98.9% (89.3%); platelet count < 100 × 10^9/l: 100% (88.2%); both platelets < 150 × 10^9/l and FibroScan > 20 kPa: 100% (88.9%); APRI > 1.09: 98.7% (83.1%); FIB-4 index > 3.25: 98.6% (84.0%); albumin < 3 g/dl: 100% (91.7%); PWUD: 97.7% (84.3%); psychiatric disorder: 96.6% (84.8%); and HIV coinfection: 100% (95.0%) (Fig. 3).

Safety

Overall, 26.9% (104/386) of patients experienced an AE and 1.3% (5/386) experienced a serious AE (SAE). None of the SAEs were drug-related. Only one patient (0.3%) reported discontinuation of G/P due to an AE (Table 4). The most common AEs experienced were fatigue (9.8%, 38/386) and headache (6.2%, 24/386). Of the 370 patients with documented laboratory data available, 2.7% (10/370) patients experienced aspartate aminotransferase (AST) levels higher than five times the upper limit of normal.

DISCUSSION

G/P has been approved by the US Food and Drug Administration, the European Medicines Agency, and many other drug authorities around the world for use with a shortened treatment duration of 8 weeks in TN patients with chronic HCV GT1-6 infection without cirrhosis or with CC (Child–Pugh A) [6, 7].

Real-world data from large cohorts such as this study are valuable to fully understand whether the benefits of a therapeutic approach will be translated into routine clinical practice. EASL Clinical Practice Guidelines 2020 on treatment of HCV highlighted that in TN patients infected with GT3 with CC (Child-Pugh A), treatment with G/P can be shortened to 8 weeks, but more data are needed to consolidate this recommendation. Moreover,

Table 1 Baseline demographics and clinical characteristics

Characteristic	Total population $N = 386$
Male, *n* (%)	247 (64.0)
Age, years, mean (SD)	55.1 (12.3)
HCV GT, *n* (%)	
1	225 (58.3)
2	22 (5.7)
3	101 (26.2)
4	17 (4.4)
5	1 (0.3)
Other/mixed/unknown	20 (5.2)
Race, *n* (%)	
White	356 (92.2)
Black or African American	6 (1.6)
Other	24 (6.2)
HCV RNA, median, (Q1–Q3) $\log_{10}$ IU/ml[a]	6.1 (5.6–6.6)
FibroScan score, kPa[b]	
Mean ± SD	16.8 (11.3)
APRI score[c]	
Mean ± SD	2.4 (2.5)
FIB-4 index[d]	
Mean ± SD	4.5 (3.5)
Platelets, median (range) (10^9/l)[e]	156.5 (17.5–512)
Platelets $< 100 \times 10^9$, *n* (%)[f]	17 (11.5)
Bilirubin, median (Q1–Q3) (mg/dl)[g]	0.62 (0.50–0.89)
Albumin, median (Q1–Q3) (g/dl)[h]	4.1 (3.8–4.4)
ALT, median, (Q1–Q3) (U/l)[i]	103.4 (46.0–278.8)
Encephalopathy grade[j]	
None	351 (90.9)
1 or 2	0
3 or 4	0
Unknown	33 (8.5)
Ascites[k]	
None	339 (87.8)
Slight	1 (0.3)
Moderate to severe	0
Unknown	44 (11.4)
Baseline polymorphisms (NS3, NS5A, NS5B), *n* (%)[l]	
NS3	3 (1.5)
NS5A	3 (1.5)
NS5b	0
Unknown	171 (88.6)

Data are *n* (%) unless stated otherwise; percentages are calculated from nonmissing values

ALT alanine aminotransferase, *GT* genotype, *HCV* hepatitis C virus, *RNA* ribonucleic acid, *SD*, standard deviation

Weighted average of chart review; German and Israeli data medians (Q1–Q3)

n value could be derived from either chart review, German registry, Israeli registry, or a combination of the three based on data available

[a] $N = 376$

[b] $N = 196$. FibroScan® (EchoSens, Paris, France)

[c] $N = 221$

[d] $N = 230$

[e] $N = 375$

[f] $N = 148$

[g] $N = 355$

[h] $N = 236$

[i] $N = 375$

[j] $N = 386$

[k] $N = 386$

[l] $N = 193$

Table 2 Comorbidities and concomitant medications

Characteristic, *n* (%)	Total population *N* = 386
Comorbidities present at treatment initiation[a]	
Hypertension	106 (27.5)
Drug addiction	91 (23.6)
Alcoholism	63 (16.3)
Depression	41 (10.6)
Diabetes mellitus	40 (10.4)
Psychiatric disorders	35 (9.1)
HIV coinfection	20 (5.2)
HBV coinfection	10 (2.6)
Concomitant medications by class (top 10)	
Other nervous system drugs	81 (28.9)
Analgesics	79 (28.2)
Agents acting on the renin-angiotensin system	71 (25.4)
Psycholeptics	55 (19.6)
Drugs for obstructive airway diseases	50 (17.9)
Drugs for acid-related disorders	50 (17.9)
Beta blocking agents	47 (16.8)
Psychoanaleptics	46 (16.4)
Drugs use in diabetes	45 (16.1)
Systemic antivirals	39 (13.9)
Calcium channel blockers	39 (13.9)
Concomitant medications by name (top 10)	
Methadone	44 (15.7)
Amlodipine	29 (10.4)
Acetylsalicylic acid	28 (10.0)
Levomethadone hydrochloride	26 (9.3)
Bisoprolol	22 (7.9)
Metformin	20 (7.1)
Ramipril	20 (7.1)
Omeprazole	19 (6.8)
Hydrochlorothiazide	16 (5.7)
Paracetamol	14 (5.0)

HBV hepatitis B virus, *HIV* human immunodeficiency virus

[a]Multiple selection was allowed in the case report form for this variable, so aggregate percentage may exceed 100%

Table 3 Methods used to determine cirrhosis

Methodology, *n* (%)	Total population (*N* = 386)
Liver biopsy[a]	4 (2.6)
Noninvasive measure of fibrosis[b,c]	382 (99.0)
FIB-4 index	246 (64.4)
APRI	221 (57.9)
FibroScan® (EchoSens, Paris, France)	199 (52.1)
Others	25 (6.5)

APRI aspartate aminotransferase-to-platelet ratio index; *FIB-4* fibrosis-4

[a]*N* = 155

[b]Percentages calculated using the number of patients undergoing a noninvasive measure of fibrosis (382) as the denominator

[c]Multiple selection was allowed in the case report form for this variable, so aggregate percentage may exceed 100%

effectiveness of 8-week G/P in patients with CC and signs of portal hypertension (i.e., liver stiffness > 20 kPa and platelets < 150 × 10^9/l) remains to be determined [5].

Here we report the real-world effectiveness data of G/P 8-week treatment in HCV TN patients with CC from Canada, Germany, Israel, Italy, and Spain. We evaluated 386 patients from these five countries in a retrospective study via analysis of medical charts and review of registry data. Overall, the SVR12 rate was > 99% in the MAS population of GT1–6 patients. In patients with GT3, the SVR12 rate was 97.5% compared with SVR12 rates exceeding 99% for GT1, 2, 4, and 5. In particular, in the

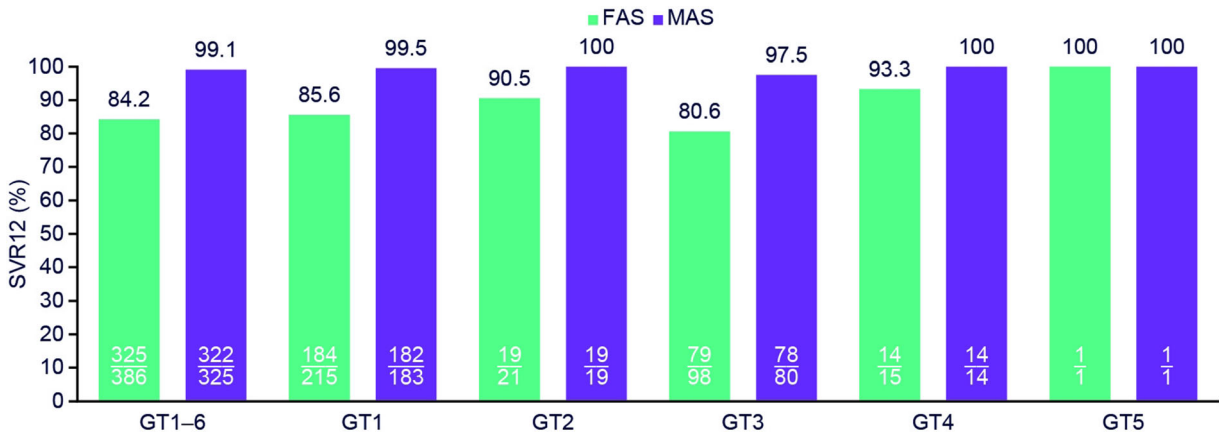

Fig. 2 Percentage of patients achieving SVR12 in the MAS and FAS, overall, and by GT. *FAS* full analysis set, *GT* genotype, *MAS* modified analysis set, *SVR12* sustained virologic response at posttreatment Week 12

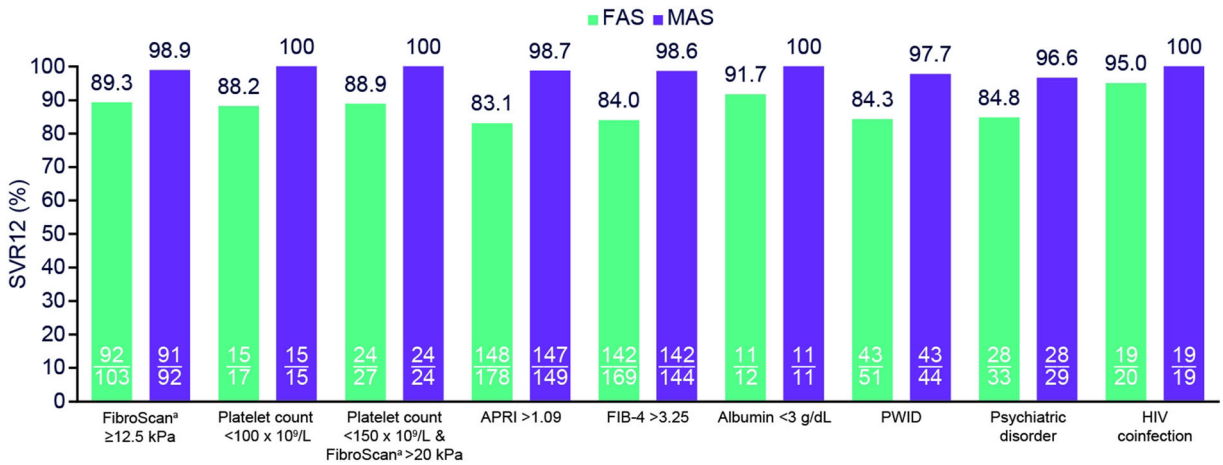

Fig. 3 Percentage of patients achieving SVR12 by subgroups of interest. *APRI* aspartate aminotransferase-to-platelet ratio index, *FAS* full analysis set, *FIB-4* fibrosis-4, *HIV* human immunodeficiency virus, *MAS* modified analysis set, *PWUD* patients who use drugs, *SVR12* sustained virologic response at posttreatment Week 12. [a]FibroScan® (EchoSens, Paris, France)

registration trial EXPEDITION-8 of TN patients with HCV GT1–6 and CC, 8 weeks of G/P led to SVR12 rates of 99.7% and 97.7% in the PP and ITT populations, respectively, including 98.4% in patients with GT3 [9]. These randomized clinical trial data informed the approval of 8-week G/P in this population and are supported by the real-world data reported here. Consistency was also demonstrated with other real-world studies, with uniformly high rates of SVR12 irrespective of GT reported in TN patients with CC treated with 8-week G/P, demonstrating the reproducibility of G/P efficacy in real-world practice [11, 15].

Patients in subgroups of interest such as those with low platelets or with high FibroScan, FIB-4 index, or APRI scores had similar rates of SVR12, supporting the use of 8-week therapy in patients with CC. The favorable safety profile of G/P in this real-world cohort was consistent with that reported in previous clinical trials and real-world studies of G/P for patients with CC

Table 4 AEs and postbaseline laboratory abnormalities

Patients with AEs, *n* (%)	Total population *N* = 386
Any AE	104 (26.9)
SAEs	5 (1.3)
AEs leading to drug discontinuation	1 (0.3)
Any drug-related SAEs	0
AEs occurring in ≥ 5% of patients	
Fatigue	38 (9.8)
Headache	24 (6.2)
ALT > 5 × ULN[a]	0
AST > 5 × ULN[a]	10 (2.7)

AE adverse event, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *SAE* serious adverse event, *ULN* upper limit of normal
[a]*N* = 370

[8, 12], including EXPEDITION-8, where no serious drug-related AEs or discontinuations due to AEs were reported [9]. Furthermore, the high SVR12 rates observed in patients traditionally considered as being underserved are in line with the findings from studies which have demonstrated that G/P treatment was highly effective in patients with substance abuse and psychiatric comorbidities [13, 14, 17].

It is important to note that there are limitations to this study. Consistent with all retrospective data reviews and real-world studies, not all information is readily available for all patients; therefore, some patients may be lost to follow-up without a properly documented reason, making it difficult to fully understand the barriers to treatment completion. Indeed, one patient discontinued G/P treatment because of an AE but the specific AE could not be collected by the study site. Moreover, the natures of the SAEs could not be documented. While SVR12 rates were high during this study, 13.2% (51/386) patients were not included in the MAS because of unavailability of SVR12 data. This may be an accurate reflection of the experiences encountered by health care providers in clinical practice and does not indicate that treatment should be withheld from such patients. The baseline genotypes of those in whom SVR12 was not ascertained were no different from those recorded in the MAS group. There is no reason to believe that a substantially different SVR12 rate would have been achieved had it been measured. As patients with identified decompensated Child-Pugh B or C cirrhosis are contraindicated or not recommended for treatment with G/P, these patients were expressly excluded from this analysis based on a current or prior history of hepatic decompensation. Though the methodology to assess cirrhosis was documented for every patient from the medical charts, patient cirrhosis status included in the study were physician reported. Laboratory abnormalities including AST levels posttreatment were not always captured for all patients, so it was not possible to document the outcomes of those with abnormal laboratory levels. Since data were merged from consolidated study reports from two registries and patient charts, it was difficult to calculate overall medians and IQR for non-parametric variables such as APRI, FIB-4, and Fibroscan scores; therefore, mean values have been presented.

CONCLUSION

In this real-world analysis of HCV GT1–6 patients with CC, including patients with GT3 infection or comorbidities such as HIV, psychiatric disorders, PWUD, platelets $< 100 \times 10^9$/l or both, FibroScan ≥ 12.5 kPa, and platelets $< 150 \times 10^9$/l, 8 weeks of G/P was well tolerated and effective, supporting the use of 8 weeks of therapy in these populations who may be underrepresented in the clinical trial populations. Successful simplified treatment of such populations will be critical if the World Health Organization HCV elimination targets are to be achieved. Until now, the evidence demonstrating the efficacy and safety of 8-week G/P in these patients has been limited to the EXPEDITION-8 study and a few real-world studies. The results of this analysis extend the clinical trial results supporting the use of 8-week G/P in all patients with CC, regardless of any comorbidities or other factors that may affect treatment

response and thus establish 8-week G/P more firmly as an effective and well-tolerated treatment regimen.

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Compliance With Ethics Guidelines. The study protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Each participating clinician signed an agreement attesting to compliance with all rules and regulations regarding the disclosure of patient information. Data were collected through a retrospective review of existing data recorded by the investigator in such a manner that the identity of the

human subjects could not be readily ascertained directly or through identifiers linked to the subjects. The investigator did not contact the subjects, and the investigator did not re-identify subjects. The study was granted an exemption from obtaining informed patient consent and approved by the Veritas Independent Review Board and the Saskatchewan Health Authority and the Ottawa Hospital Research Institute and the Hamilton Integrated Research Ethics Boards (HiREB) (Canada), the Institutional Review Board of Maccabi Healthcare Services (Israel), the Department of Medicines for Human Use of the Spanish Agency for Medicines and Health Products (AEMPS) and the Research Ethics Committee from the Medicines Gregorio Marañón General University Hospital (Spain), and the Ethics Committee of the Medical Association of Westphalia-Lippe and the Westphalian Wilhelms University Board (Germany). The study was approved by each of the institutional ethics committees for the sites in Italy.

Data Availability. German data were derived from the German Hepatitis C-Registry (Deutsches Hepatitis C-Register) a project of the German Liver Foundation (Deutsche Leberstiftung), managed by Leberstiftungs-GmbH Deutschland in cooperation with the Association of German gastroenterologists in private practice (bng). The German Hepatitis C-Registry is financially supported by AbbVie Deutschland GmbH & Co. KG, Gilead Sciences GmbH, MSD Sharp & Dohme GmbH, as well as Bristol-Myers Squibb GmbH & Co. KGaA and Janssen-Cilag GmbH (each until July 14, 2020) and Roche Pharma AG (until July 14, 2017). Israel data were collected from Maccabi Healthcare Services, a state-mandated non-for-profit health provider. AbbVie is committed to responsible data sharing regarding the clinical trials they sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This clinical trial data can be requested by any qualified researcher who engages in rigorous, independent scientific research. Data will be provided following review and approval of a research proposal, Statistical Analysis Plan, and execution of a Data Sharing Agreement. Data requests can be submitted at any time where 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.

REFERENCES

1. World Health Organization (WHO). Hepatitis C fact sheet. 2021. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c. Cited 04 Oct 2021

2. Polaris Observatory, H. C. V. Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol. 2015;2017(2):161–76.

3. Webster DP, Klenerman P, Dusheiko GM. Hepatitis C. Lancet. 2015;385:1124–35.

4. Kronenberger B, Zeuzem S. Current and future treatment options for HCV. Ann Hepatol. 2009;8:103–12.

5. European Association for the Study of the Liver, Clinical Practice Guidelines Panel Chair, EASL Governing Board representative, Panel members. EASL recommendations on treatment of hepatitis C: Final update of the series. J Hepatol. 2020;73:1170–218.

6. AbbVie. Maviret EU Summary of product characteristics. 2021. https://www.ema.europa.eu/en/documents/product-information/maviret-epar-product-information_en.pdf. Cited 04 Oct 2021

7. AbbVie. Mavyret US Package Insert. 2021. https://www.rxabbvie.com/pdf/mavyret_pi.pdf. Cited 04 Oct 2021

8. 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;378:354–69.

9. Brown RS Jr, Buti M, Rodrigues L, et al. Glecaprevir/pibrentasvir for 8weeks in treatment-naive patients with chronic HCV genotypes 1–6 and compensated cirrhosis: The EXPEDITION-8 trial. J Hepatol. 2020;72:441–9.

10. 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;16:417–26.

11. Flamm SL, Kort J, Marx SE, et al. Effectiveness of 8-week glecaprevir/pibrentasvir for treatment-naive, compensated cirrhotic patients with chronic hepatitis C infection. Adv Ther. 2020;37:2267–74.

12. Klinker H, Naumann U, Rossle M, et al. Glecaprevir/pibrentasvir for 8 weeks in patients with compensated cirrhosis: safety and effectiveness data from the German Hepatitis C-Registry. Liver Int. 2021;41:1518–22.

13. 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. Hepatology. 2019;70:954A-A955.

14. Aghemo A, Horsmans Y, Bourgeois S, et al. Real-world outcomes in historically underserved patients with chronic hepatitis C infection treated with glecaprevir/pibrentasvir. Infect Dis Ther. 2021. https://doi.org/10.1007/s40121-021-00455-1.

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;70:379–87.

16. Clopper C, Pearson E. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26:404–13.

17. Back D, Belperio P, Bondin M, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients with chronic HCV infection and psychiatric disorders: An integrated analysis. J Viral Hepat. 2019;26:951–60.