Received: 4 February 2020 | Revised: 17 April 2020 | Accepted: 17 May 2020

DOI: 10.1111/liv.14535

ORIGINAL ARTICLE

Liver INTERNATIONAL WILEY

Efficacy and safety of glecaprevir/pibrentasvir in patients with HCV genotype 5/6: An integrated analysis of phase 2/3 studies

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Abstract

Background & Aims: Hepatitis C virus (HCV) has high genetic diversity with six major genotypes (GT) GT1-6 and global distribution. HCV GT5 and 6 are rare with < 10 million people infected worldwide. Data on direct-acting antiviral use in these rare HCV genotypes are limited. The study aimed to evaluate the efficacy and safety of glecaprevir/pibrentasvir (G/P) in a pooled analysis of phase 2/3 trials in HCV GT5 or 6-infected patients without cirrhosis or with compensated cirrhosis.

Methods: Patients with chronic HCV GT5 or 6 infection received oral G/P (300 mg/120 mg) once daily for 8 or 12 weeks. The primary efficacy endpoint was sustained virological response at post-treatment week 12 (SVR12) in the intention-to-treat population.

Results: One hundred eighty-one patients were evaluated; 56 with HCV GT5 and 125 with HCV GT6. The majority were treatment-naïve (88%) and non-cirrhotic (85%). Overall SVR12 rate with 8- or 12-week G/P treatment was 98% (178/181). Eight-week treatment with G/P yielded SVR12 rates of 95% (21/22) in HCV GT5- and 99% (69/70) in HCV GT6-infected non-cirrhotic patients. Eight- and 12-week treatment of patients with compensated cirrhosis achieved SVR12 rates of 100% (10/10) and 94% (17/18) respectively. The G/P regimen was well-tolerated; 3% (6/181) Grade 3 or higher adverse events, and no serious adverse events were attributed to G/P or led to study drug discontinuation.

Abbreviations: AASLD, American Association for the Study of Liver Disease; AEs, adverse events; ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; DAA, direct-acting antiviral; G/P, glecaprevir/pibrentasvir; GT, genotype; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; ITT, intention-to-treat; LLOQ, lower limit of quantification; MedDRA, Medical Dictionary for Regulatory Activities; NGS, next-generation sequencing; NS3/4A, non-structural protein 3/4A; NS5A, non-structural protein 5A; NS5B, non-structural protein 5B; OTVF, on-treatment virologic failure; pegIFN, pegylated interferon; PTs, preferred terms; PTW, post-treatment week; RASs, resistance-associated substitutions; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; SVR12, sustained virologic response at post-treatment week 12; TW, treatment week; ULN, upper limit of normal.

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Funding information
This study was funded in full by AbbVie. The design, study conduct, analysis and financial support of this integrated analysis was provided by AbbVie.

Handling Editor: Gregory Dore

Conclusions: This integrated dataset demonstrates a high SVR12 rate following 8-week G/P treatment in patients with HCV GT5 (96%) or GT6 (99%) infection without cirrhosis or with compensated cirrhosis.

KEYWORDS
genotype 5, genotype 6, glecaprevir and pibrentasvir, hepatitis C, integrated analysis, phase 2 and 3

1 | INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a global health problem that affects approximately 71 million individuals worldwide.[1-4] Chronic HCV infection, if left untreated, can cause hepatic fibrosis, which may lead to cirrhosis.[4,5] Depending on risk factors, between 10% and 20% of all patients with chronic HCV infection develop cirrhosis over 20-30 years of HCV infection.[5] There is an increased risk for hepatocellular carcinoma (HCC) occurrence and death in the cirrhotic patient population.[5]

HCV is characterized by high genetic diversity, and the prevalence of each genotype varies by geographical location.[6] HCV genotype (GT) 1 is the most prevalent worldwide.[6] HCV GT2 and 3 infections are more common in Latin America (5% to 30%), Europe (20% to 40%) and Asia (30%-45%).[7-9] HCV GT4 is commonly found in parts of Africa and the Middle East, particularly in Egypt.[10] HCV GT5 is primarily found in South Africa, and HCV GT6 is predominantly encountered in Southeast Asia.[10,11]

HCV GT5 and 6 are the rarest of the major HCV genotypes, accounting for less than 5% of infections worldwide.[6,12] Interferon-free DAA regimens have shown high sustained virological response (SVR) rates (>95%) in HCV-infected patients, including those with HCV GT5 or 6 infection. However, because of the lower prevalence of HCV GT5 or 6 infection, the individual clinical trials for approved regimens have small numbers of patients infected with these genotypes.[11,13] Therefore, the efficacy data for GT5 or 6 patients are limited.

The development of direct acting antivirals (DAAs) targeting multiple enzymes essential for the HCV replication process has remarkably improved efficacy and safety of HCV treatment, with a high rate of SVR, reduced risk of resistance and shortened duration of treatment.[14-16] Glecaprevir, a pangenotypic HCV non-structural protein 3/4A (NS3/4A) protease inhibitor, and pibrentasvir, a pangenotypic non-structural protein 5A (NS5A) inhibitor, are used in combination (glecaprevir/pibrentasvir; G/P) for treating chronic HCV infection in GT1-6-infected patients without cirrhosis or with compensated cirrhosis.[17] In individual phase 2 and 3 studies, high efficacy (SVR at post-treatment week 12 [SVR12] rate ≥ 93%) was achieved with G/P treatment in patients with HCV GT5 or 6 infection.[17-23] To help further the World Health Organisation goal of achieving HCV elimination by 2030, effective HCV treatment against all HCV genotypes is critical. Therefore, a potent pangenotypic short duration regimen that is active across the diverse array of HCV subgenotypes is necessary. Efficacy and safety of G/P in HCV GT5- or 6-infected patients have been studied across 10 AbbVie phase 2 and 3 studies[20,23,24]; the data analysis presented here integrates these data to evaluate G/P as a short duration, pangenotypic regimen.

Key points

- Hepatitis C virus genotypes 5 and 6 are rare and data on their treatment with recent therapies are limited
- The data presented here demonstrate that glecaprevir/pibrentasvir is efficacious and safe for the treatment of hepatitis C virus genotypes 5 and 6

2 | MATERIALS AND METHODS

Data were pooled from ten phase 2 and 3 studies: ENDURANCE-5/6 (N = 84), ENDURANCE-4 (NCT02636595) (N = 45), SURVEYOR-1 (N = 12), SURVEYOR-2 (N = 12), EXPEDITION-8 (N = 10), MAGELLAN-2 (N = 2), EXPEDITION-1 (N = 9), EXPEDITION-2 (NCT02738138) (N = 3), EXPEDITION-4 (NCT02651194) (N = 2) and M16-133 (N = 2). Patients received once-daily oral glecaprevir (identified by AbbVie and Enanta Pharmaceuticals; 300 mg) and pibrentasvir (120 mg), for 8 or 12 weeks depending on the design of the original study. Analyses were performed on the intention-to-treat (ITT) population, which included all patients who received at least one dose of study drug.

2.1 | Individual study oversight

All patients signed informed consent for their respective trial, and the original studies were conducted in accordance with the International Conference on Harmonization guidelines and the ethics set forth by the Declaration of Helsinki. All authors had access to all relevant study data and reviewed and approved this manuscript for submission.

2.2 | Patient population

Eligibility criteria were generally consistent across studies. Briefly, adults at least 18 years old, with chronic HCV GT5 or 6 infection, without cirrhosis or with compensated cirrhosis were enrolled. Patients were either HCV treatment-naïve or treatment-experienced with interferon (IFN) or pegylated interferon (pegIFN) with or without ribavirin (RBV) (defined as P/R treatment-experienced) or sofosbuvir (SOF) plus RBV with or without pegIFN (defined as SOF plus RBV treatment-experienced). HCV genotype was determined by the Versant® HCV Genotype Inno LiPA assay, version 2.0 or higher (LiPA, Siemens Healthcare Diagnostics, Tarrytown, NY), and subtype was determined by next-generation sequencing (NGS) followed by neighbour-joining phylogenetic analysis of NS3/4A and/or NS5A consensus nucleotide sequences from available baseline samples. If the LiPA assay was unable to genotype a sample, genotype and subtype were determined by a Sanger sequencing assay of a region of the non-structural protein 5B (NS5B) gene by the central laboratory. Among the 181 patients in the ITT population, 15 patients were missing subtype information from phylogenetic analysis due to no sample availability or technical difficulties obtaining sequence.

Presence of cirrhosis was identified by one of the following: liver biopsy; screening aspartate aminotransferase to platelet ratio index (APRI) of greater than 2 and a FibroTest result of 0.75 or greater; or screening FibroScan score 12.5 kPa or greater.

2.3 | Endpoints

The primary efficacy endpoint was SVR12, defined as having HCV RNA less than the lower limit of quantification (LLOQ) at post-treatment week 12. The number and percentages of patients achieving SVR12 were calculated for each HCV GT (GT5 and 6) and across HCV GTs. Secondary efficacy endpoints were the percentage of patients with on-treatment virological failure and post-treatment relapse. The safety endpoints were summarised for the overall population, regardless of GT, cirrhosis status or treatment duration.

Safety and tolerability assessments included adverse events (AEs) and laboratory abnormalities. Treatment-emergent AEs were collected from the first administration of G/P through 30 days after the last dose of G/P. AEs were recorded using the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs). Laboratory test values were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). Relatedness of AEs to G/P administration was determined by the study investigator.

2.4 | Resistance

The genes encoding full-length HCV NS3/4A or NS5A were sequenced by NGS for all patients with available baseline samples. Baseline polymorphisms were assessed relative to a subtype-specific reference sequence at a 15% detection threshold in NS3 at amino acid positions 155, 156 and 168, and in NS5A at amino acid positions 24, 28, 30, 31, 58, 92 and 93. For patients who experienced virological failure, baseline polymorphisms and treatment-emergent resistance-associated substitutions (RASs) were assessed at a 15% detection threshold at amino acid positions 36, 43, 54, 55, 56, 80, 155, 156 and 168 in NS3, and at amino acid positions 24, 28, 29, 30, 31, 32, 58, 92 and 93 in NS5A. Phylogenetic analyses were conducted on NS3/4A and/or NS5A NGS consensus sequences from samples collected at baseline and time of failure for patients who experienced virological failure in order to differentiate relapse from HCV reinfection.

2.5 | Statistical analyses

Analyses were performed on the ITT population. Categorical data were summarised with frequencies and percentages. Continuous data were summarised with medians and ranges (minimums and maximums). For the primary efficacy endpoint (SVR12), a two-sided 95% confidence interval (CI) was calculated using the Wilson's score method when the number of patients in the analysis was at least 10.

2.6 | Role of funding source

The design, study conduct, analysis and financial support of this integrated analysis were provided by AbbVie. AbbVie participated in the interpretation of data, review and approval of the content. All authors had access to all relevant data and participated in writing, review and approval of this publication.

3 | RESULTS

3.1 | Baseline characteristics and demographics

Among 181 patients with HCV GT5 (31%, 56/181) or GT6 (69%, 125/181) infection, the majority (88%; 159/181) had no prior history of HCV treatment. Most patients were male (54%, 98/181), of Asian race (65%, 115/181), and had F0-F1 stage fibrosis (69%, 123/181); 16% (28/181) had compensated cirrhosis. The majority

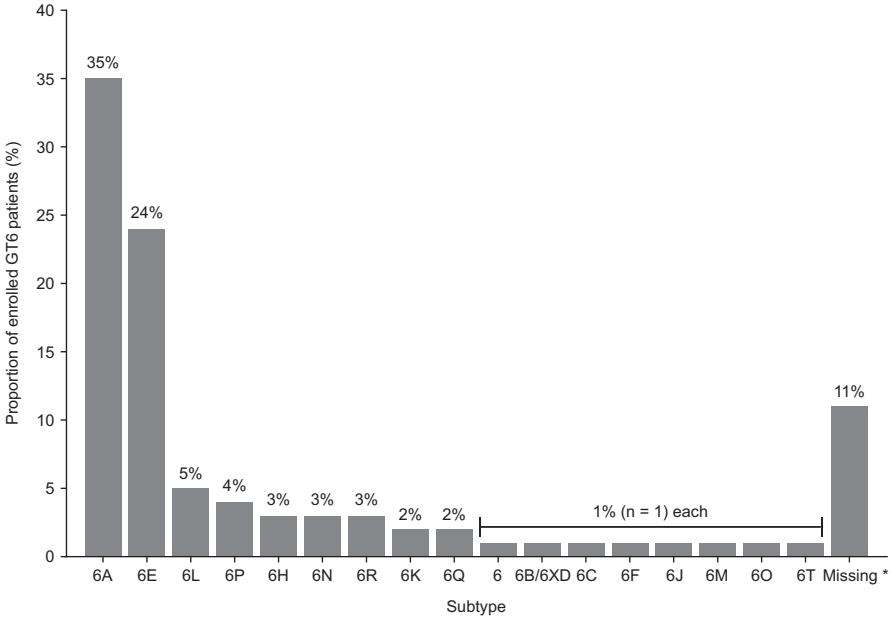

FIGURE 1 HCV Genotype 6 Subtype Distribution as Determined by Phylogenetic Analysis For 125 Enrolled Patients. *Subtype was not available by phylogenetic analysis due to sample availability or technical issues; GT, genotype

of patients (56%, 102/181) were treated with G/P for 8 weeks, and 44% (79/181) were treated with G/P for 12 weeks. Among 181 patients, there were 1 HCV GT5 subtype (5a) and 16 HCV GT6 subtypes identified. Among HCV GT6-infected patients, the predominant subtypes were 6a (35%, 44/125) and 6e (24%, 30/125) (Figure 1). One HCV GT6-infected patient with available sequence data was not assigned a subtype due to lack of homology to any of the known HCV GT6 subtypes. The majority of patients (78%, 141/181) had an HCV RNA level at baseline of 1 000 000 IU/mL or greater.

Some differences in baseline characteristics were noted between those with HCV GT5 infection and those with HCV GT6 infection. Patients with HCV GT5 infection were generally older and of white ethnicity, while patients with HCV GT6 infection were younger and mostly of Asian ethnicity (Table 1). Among 156 patients with available sequence data for both NS3/4A and NS5A at baseline, 19% (30/156) had baseline polymorphisms in NS3 and 43% (67/156) had polymorphisms in NS5A; 4% (7/156) had polymorphisms in both NS3 and NS5A (Table 1). The majority of baseline polymorphisms in NS3 were detected in GT5-infected patients (27/30), while the highest prevalence of NS5A polymorphisms were detected in GT6-infected patients (60/67).

3.2 | Efficacy

Overall, 98% of patients (178/181, 95% CI: 95.2%-99.4%) achieved SVR12. The SVR12 rates for HCV GT5- and 6-infected patients were 98% (55/56, 95% CI: 90.6%-99.7%) and 98% (178/181, 95% CI: 94.4%-99.6%), respectively. HCV GT5-infected patients without cirrhosis treated with G/P for 8 weeks and 12 weeks had 95% (21/22, 95% CI: 78.2%-99.2%) and 100% (28/28, 95% CI: 87.9%-100%) SVR12 rates, respectively. The SVR12 rates for HCV GT5-infected patients with compensated cirrhosis treated with G/P for 8 weeks and 12 weeks were 100% (1/1) and 100% (5/5), respectively (Figure 2). For GT6-infected patients without cirrhosis, the SVR12 rates were 99% (69/70, 95% CI: 92.3%-99.7%) and 100% (33/33, 95% CI: 89.6%-100%) with 8 and 12 weeks of G/P treatment, respectively; for GT6-infected patients with compensated cirrhosis, the rates were 100% (9/9) and 92% (12/13, 95% CI: 66.7%-98.6%) with 8 and 12 weeks of G/P treatment, respectively (Figure 2).

One treatment-naïve patient with HCV GT5 infection without cirrhosis experienced relapse at post-treatment week 12. On-treatment virological failure was reported at treatment week 12 in one treatment-naïve patient with GT6 infection with compensated cirrhosis. Of the patients who achieved SVR12, one treatment-naïve patient with HCV GT6 infection without cirrhosis experienced relapse at post-treatment week 24; this patient was determined to be a late relapse based on NS5A sequencing and phylogenetic analysis. Additional details on the three patients who experienced virological failure, including baseline polymorphisms and treatment-emergent RASs, are presented in Table 2.

3.3 | Adverse events and laboratory abnormalities

Across all patients with GT5 or 6 infection, AEs occurring in ≥ 10% of patients were fatigue (16%, 29/181) and headache (15%, 27/181). The rate of G/P discontinuation due to AEs was low (1%, 2/181). Serious AEs occurred in 4% (7/181) of patients, none of which were considered related to G/P by investigators. Across all patients, no grade 3 or higher laboratory abnormalities in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin occurred. The G/P regimen was well-tolerated, with mostly mild or moderate treatment-emergent AEs (Table 3).

TABLE 1 Baseline demographics and disease characteristics of HCV GT5- and 6-infected patients

Characteristic	GT5 N = 56[a]	GT6 N = 125	Total N = 181
Male, n (%)	29 (52)	69 (55)	98 (54)
Age, median (range), years	64.5 (20-76)	54 (28-79)	56 (20-79)
BMI, median (range), Kg/m^2	28 (19.8-43.5)	23.4 (17.2-40)	24.3 (17.2-43.5)
Race, n (%)			
Asian	3 (6)	112 (90)	115 (65)
White	43 (81)	11 (9)	54 (30)
Black or African American	5 (9)	0	5 (3)
American Indian or Alaska Native	0	1 (1)	1 (1)
Multi-race	2 (4)	1 (1)	3 (2)
Missing[b]	3	0	3
HCV RNA ≥ 1 000 000 IU/mL, n (%)	39 (70)	102 (82)	141 (78)
HCV-treatment-experienced, n (%)[c]	10 (18)	12 (10)	22 (12)
Cirrhosis, n (%)	6 (11)	22 (18)	28 (15)
Fibrosis stage, n (%)			
F0-F1	40 (71)	83 (67)	123 (69)
F2	8 (14)	2 (2)	10 (6)
F3	2 (4)	16 (13)	18 (10)
F4	6 (11)	22 (18)	28 (16)
Missing[b]	0	2	2
Baseline polymorphisms, n (%)[d]			
NS3 only	23 (42)	0	23 (15)
NS5A only	3 (5)	57 (56)	60 (38)
NS3 and NS5A	4 (7)	3 (3)	7 (4)
None	25 (45)	41 (41)	66 (42)
Missing[b]	1	24	25
Treatment duration, n (%)			
8 wks	23 (41)	79 (63)	102 (56)
12 wks	33 (59)	46 (37)	79 (44)

Note: Sums of percentages may differ from 100% due to rounding.

Abbreviations: BMI, body mass index; HCV, hepatitis C virus; NS3, non-structural protein 3; NS5A, non-structural protein 5A; RNA, ribonucleic acid.

[a]All patients were subtype 5a.

[b]Missing not included in calculation of percentage.

[c]No patients with SOF-experience enrolled.

[d]Baseline polymorphisms assessed relative to a subtype-specific reference sequence at a 15% detection threshold in NS3 at amino acid positions 155, 156 and 168, and in NS5A at amino acid positions 24, 28, 30, 31, 58, 92 and 93 for patients with available data in both target sequences.

4 | DISCUSSION

In this integrated analysis, 8 or 12 weeks of treatment with the G/P regimen resulted in high rates of SVR12 in patients with chronic HCV GT5 or 6 infection without cirrhosis or with compensated cirrhosis. Efficacy was demonstrated in 15 of 16 HCV GT6 subtypes. In addition, 8-week treatment of patients with compensated cirrhosis achieved high SVR12 (100%, 10/10 patients). Treatment was well-tolerated, with mostly mild or moderate treatment-emergent adverse events.

This analysis further supports the use of G/P in treating patients with chronic HCV GT5 or 6 infection. The integrated data across phase 2 and 3 studies, to our knowledge, represent one of the largest evaluations of patients with HCV GT5 or 6 infection and the most diverse report of GT6 subtypes to date. Here, among 125 patients with GT6 infection, 16 different GT6 subtypes were identified

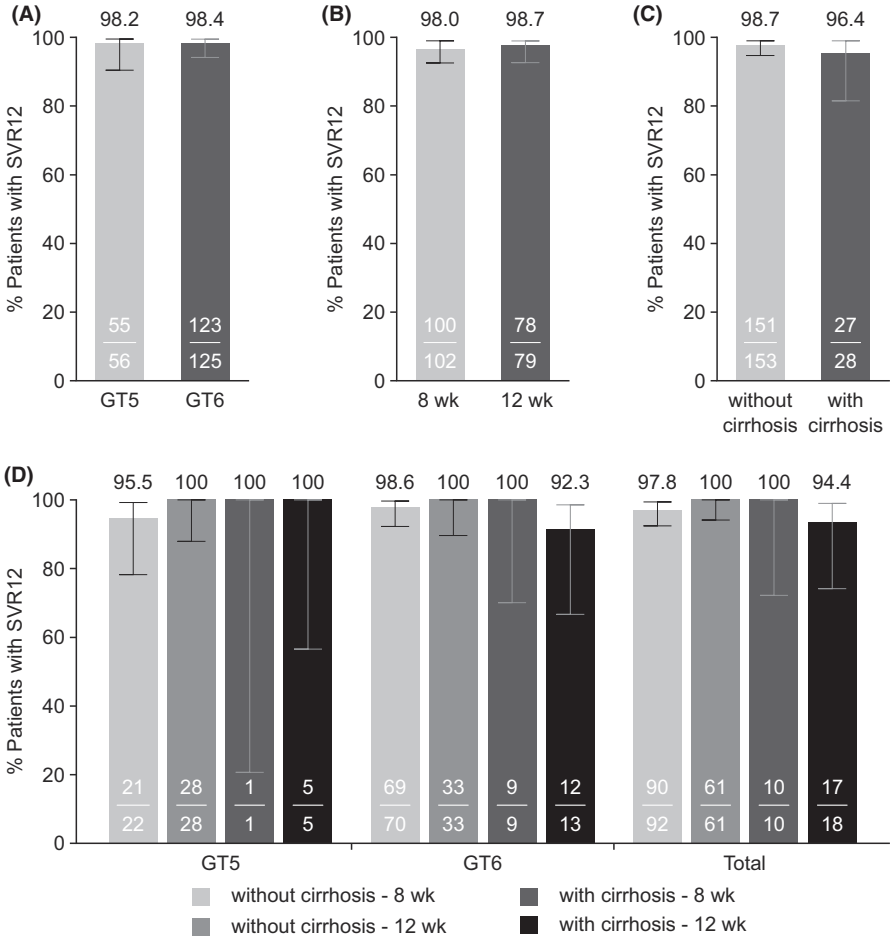

FIGURE 2 SVR12 in HCV GT5- and GT6-Infected Patients by A) Genotype, B) Treatment Duration, C) Cirrhosis Status, D) Genotype, Treatment Duration and Cirrhosis Status. GT, genotype; HCV, hepatitis C virus; SVR12, sustained virological response at post-treatment week 12

using a sequencing-based assay; SVR12 was achieved in 123 (98%) patients. Historically, the small number of recruited patients with GT5 or 6 infection in clinical trials has resulted in a limited amount of genotype-specific and subtype-specific data. In a study investigating the safety and efficacy of ledipasvir + SOF regimen for 12 weeks in patients with HCV infection in Myanmar, a low SVR rate of 64.1% (25/39) was achieved in GT6-infected patients.[25] One in vitro study explored the diversity of polymorphisms across GT6 genotypes at amino acid residues associated with DAA resistance and evaluated their impact on susceptibility to DAAs. HCV GT6 subtypes 6b, 6f and 6r contained polymorphisms in NS5A that conferred resistance to NS5A inhibitors daclatasvir, ledipasvir, ombitasvir and velpatasvir using an in vitro HCV replicon assay.[26]

Therefore, analysis of large cohorts of patients with HCV GT5 or 6 infection, including diverse GT6 subtypes is important for representation of less prevalent genotypes and for determination of optimal treatment.

The availability of pangenotypic DAA regimens is critical in achieving the World Health Organisation goal of HCV elimination by 2030.[27] Currently, HCV treatment guidelines established by EASL recommend 8 weeks of treatment with G/P for non-cirrhotic and 12 weeks of G/P treatment for cirrhotic patients with HCV GT5 or 6 infection.[4,28] American Association for the Study of Liver Disease (AASLD) recommends 8 weeks of treatment with G/P for non-cirrhotic patients and treatment-naïve cirrhotic patients and 12 weeks of G/P treatment for pegIFN/RBV-experienced patients with compensated cirrhosis.[4,28] Other regimens recommended by AASLD and European Association for the Study of the Liver for the treatment of HCV GT5 or 6 infection include 12-week pangenotypic SOF/velpatasvir and 12-week genotype-specific ledipasvir/SOF regimens.[4,28,29] AASLD also recommends 12 weeks of SOF/velpatasvir/voxilaprevir for treatment of DAA-experienced patients with HCV GT5 or 6 infection.[28] The European Commission has granted marketing authorization for G/P to shorten treatment duration from 12 to 8 weeks in chronic HCV GT1 – 6 infected, treatment-naïve patients with compensated cirrhosis. The United States Food and Drug Administration has approved the 8-week treatment duration with G/P in HCV GT1-6 infected, treatment-naïve patients with compensated cirrhosis.[30]

The sample size of patients with HCV GT5 or 6 infection included in this integrated analysis is large when compared with other clinical trials.[31-35] For example, 16 GT6 subtypes were represented in this analysis compared to seven GT6 subtypes evaluated in a previous study with the subtype distribution of 8 patients with GT6a, 6 with GT6e, 3 with GT6l, 2 with GT6m, 3 with GT6p, 2 with GT6q and 1 with GT6r.[35] However, one limitation of this study is the small sample size for many of the GT6 subtypes (Table 1). Furthermore, it should be noted that the studies included in this analysis were

TABLE 2 Characteristics of HCV GT5- and HCV GT6-infected patients with virological failure

Characteristic	Patient 1 (OTVF at TW12)	Patient 2 (Relapse at PTW12)	Patient 3[a] (Relapse at PTW24)
Sex	Male	Male	Male
Age, years	71	54	30
Race	White	White	Asian
Genotype/subtype	6f	5a	6k
Cirrhosis status	Compensated cirrhosis	No cirrhosis	No cirrhosis
Prior treatment experience	None	None	None
Baseline HCV RNA, IU/mL	625 000	10 800 000	244 000
DAA adherent[b]	Yes	Yes	Yes
NS3 baseline polymorphisms[c]	None	D168E	Data not available
NS5A baseline polymorphisms[c]	None	None	None
NS3 RAS at the time of failure[c]	A156M	None[d]	Data not available
NS5A RAS at the time of failure[c]	T93A	None	None

Abbreviations: DAA, direct-acting antiviral; HCV, hepatitis C virus; NS3, non-structural protein 3; NS5A, non-structural protein 5A; OTVF, on-treatment virological failure; PTW, post-treatment week; RAS, treatment-emergent resistance-associated substitution; RNA, ribonucleic acid; TW, treatment week.

[a]Patient achieved SVR12 but relapsed at post-treatment Week 24.

[b]Adherence measured by pill count. A patient is considered to have been compliant if the % of tablets taken relative to the total tablets expected to be taken is between 80% and 120%.

[c]Baseline polymorphisms and treatment-emergent resistance-associated substitutions were assessed in NS3 at amino acid positions 36, 43, 54, 55, 56, 80, 155, 156 and 168, and in NS5A at amino acid positions 24, 28, 29, 30, 31, 32, 58, 92 and 93.

[d]NS3 D168E was present at baseline and at the time of failure.

TABLE 3 Safety and tolerability of HCV GT5- and GT6-infected patients

Event, n (%)	Total N = 181
Any AE	105 (58)
Any AE with a Grade 3 or higher	6 (3)
Any G/P-related AE with a Grade 3 or higher	0
Any serious AE	7 (4)
Any G/P-related serious AE	0
Any AE leading to study discontinuation	2 (1)
Any G/P-related AE leading to study discontinuation	1 (1)
Any serious AE leading to study discontinuation	0
Death	0
AE's occurring in ≥ 10% total patients	
Fatigue	29 (16)
Headache	27 (15)
Laboratory Abnormalities[a]	
ALT, Grade ≥ 3 (>5 × ULN)	0
AST, Grade ≥ 3 (>5 × ULN)	0
Total Bilirubin, Grade ≥ 3 (>3 × ULN)	0

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; G/P, gelcaprevir/pibrentasvir; ULN, upper limit of normal.

[a]Grade must have been more extreme than the baseline grade.

mostly conducted in Western countries, whereas GT5 and GT6 are most prevalent in South Africa and Southeast Asia respectively[10,11]; therefore there may be some differences to the study population in terms of host factors (genetic background, racial factors and comorbidities), and viral factors (regional HCV subtypes).

In conclusion, this integrated analysis shows treatment with G/P of patients with chronic HCV GT5 or 6 infection results in a high SVR12 rate. Efficacy was demonstrated in diverse GT6 subtypes. The regimen was well-tolerated, and the safety profile was consistent with previous reports and real-world data.[20,24,36,37] This integrated analysis represents one of the largest evaluations of patients with HCV GT5 or 6 infection and the most diverse report of GT6 subtypes to date, supporting G/P as a true pangenotypic regimen.

ACKNOWLEDGEMENTS

The authors thank the patients, trial investigators, coordinators and study staff who made this study possible. Glecaprevir was identified by AbbVie and Enanta. Medical writing support, under the guidance of the authors, was provided by Salil Sharma, PhD, of AbbVie, and funded by AbbVie.

CONFLICT OF INTEREST

T Asselah has served as a clinical investigator, speaker, and consultant for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp & Dohme, and Roche. **K Kowdley** has received grant/research Funding: AbbVie,

Gilead, Merck; Consultant/Advisor: AbbVie, Gilead, Merck, Trio Health Advisory Group. **P Kwo** has received a grant from AbbVie, Bristol Myers Squibb, Gilead, Allergan, La Jolla Pharmaceuticals, Assembly Biosciences, and served as a consultant for AbbVie, Bristol Myers Squibb, Gilead, Janssen, Merck, Quest, Durect, Surrozen, Ferring, DSMB, Janssen, Durect; Other: Merck. **F Poordad** has received grant/research support from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Intercept Pharmaceuticals, Merck, Salix; Served as a speaker for AbbVie, Gilead, Merck, Salix and a consultant/advisor for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Intercept Pharmaceuticals, Merck. **K Nguyen** has served as a clinical investigator for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, Roche, Janssen Pharmaceuticals. **SS Lee** provides research support and is a consultant for AbbVie Inc, Gilead Sciences, Janssen Pharmaceuticals Inc, Merck & Co, and Pendopharm, and is a speaker for Abbvie, Gilead and Merck. **C George:** None. **F Wong** has received grant/research support from Gilead, Abbvie. **E Gane** has served as a clinical investigator for AbbVie, BMS, Gilead Sciences, Janssen Pharmaceuticals, ARBUTUS, ALIGOS, Merck, Dicerna and Roche and on an advisory committee for AbbVie, ALIGOS, Janssen Pharmaceuticals, Mylan and Roche; Speaker: AbbVie, Gilead Sciences and Mylan. **A Abergel** has served as a clinical investigator, speaker and consultant for AbbVie, Gilead Sciences, Merck Sharp & Dohme. **C W Spearman** has served as a clinical investigator for AbbVie and Merck Sharp & Dohme. Grant/Research Funding: Gilead Sciences and Bristol-Myers Squibb. **T Nguyen** has received grant/research support from Abbvie, Bristol Myers Squibb, Gilead, Assembly Biosciences. **H Le** has served as a clinical investigator for Abbvie, Gilead Sciences, Merck Sharp & Dohme. **T Pham:** None. **B Yao, L Fredrick, G Schnell and F Mensa** are employees of AbbVie and may hold AbbVie stock or options.

ETHICS APPROVAL STATEMENT

All patients signed informed consent for their respective trial, and the original studies were conducted in accordance with the International Conference on Harmonization guidelines and the ethics set forth by the Declaration of Helsinki.

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REFERENCES

1. Sebag J. Vitreous: the resplendent enigma. *Br J Ophthalmol*. 2009;93:989-991.
2. Blach S, Zeuzem S, Manns M, et al. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol*. 2017;2(3):161-176.
3. Razavi H, Robbins S, Zeuzem S, et al. Hepatitis C virus prevalence and level of intervention required to achieve the WHO targets for elimination in the European Union by 2030: a modelling study. *Lancet Gastroenterol Hepatol*. 2017;2:325-336.
4. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. *J Hepatol*. 2018;69:461-511.
5. European Association for Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol*. 2014;60:392-420.
6. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology*. 2015;61:77-87.
7. Kershenobich D, Razavi HA, Sánchez-Avila JF, et al. Trends and projections of hepatitis C virus epidemiology in Latin America. *Liver Int*. 2011;31(Suppl 2):18-29.
8. Sievert W, Altraif I, Razavi HA, et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. *Liver Int*. 2011;31(Suppl 2):61-80.
9. Manos MM, Shvachko VA, Murphy RC, Arduino JM, Shire NJ. Distribution of hepatitis C virus genotypes in a diverse US integrated health care population. *J Med Virol*. 2012;84:1744-1750.
10. Smith DB, Bukh J, Kuiken C, et al. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource. *Hepatology*. 2014;59:318-327.
11. Mettikanont P, Bunchorntavakul C, Reddy KR. Systematic review: epidemiology and response to direct-acting antiviral therapy in genotype 6 chronic hepatitis C virus infection. *Aliment Pharmacol Ther*. 2019;49:492-505.
12. Asselah T, Hassanein T, Waked I, Mansouri A, Dusheiko G, Gane E. Eliminating hepatitis C within low-income countries - The need to cure genotypes 4, 5, 6. *J Hepatol*. 2018;68(4):814-826.
13. Boyd SD, Harrington P, Komatsu TE, et al. HCV genotype 4, 5 and 6: Distribution of viral subtypes and sustained virologic response rates in clinical trials of approved direct-acting antiviral regimens. *J Viral Hepat*. 2018;25:969-975.
14. Asselah T, Boyer N, Saadoun D, Martinot-Peignoux M, Marcellin P. Direct-acting antivirals for the treatment of hepatitis C virus infection: optimizing current IFN-free treatment and future perspectives. *Liver Int*. 2016;36(Suppl 1):47-57.
15. Schinazi R, Halfon P, Marcellin P, Asselah T. HCV direct-acting antiviral agents: the best interferon-free combinations. *Liver Int*. 2014;34(Suppl 1):69-78.
16. Schinazi RF, Asselah T. From HCV to HBV Cure. *Liver Int*. 2017;37(Suppl 1):73-80.
17. Forns 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;17:1062-1068.
18. Reau N, Kwo PY, Rhee S, et al. Glecaprevir/pibrentasvir treatment in liver or kidney transplant patients with hepatitis C virus infection. *Hepatology*. 2018;68:1298-1307.
19. Rockstroh JK, Lacombe K, Viani RM, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients coinfected with hepatitis C virus and human immunodeficiency virus type 1: the EXPEDITION-2 study. *Clin Infect Dis*. 2018;67:1010-1017.
20. Asselah T, Kowdley KV, Zadeikis N, et al. Efficacy of glecaprevir/pibrentasvir for 8 or 12 weeks in patients with hepatitis C virus GENOTYPE 2, 4, 5, or 6 infection without cirrhosis. *Clin Gastroenterol Hepatol*. 2018;16:417-426.
21. Gane E, Lawitz E, Pugatch D, et al. Glecaprevir and pibrentasvir in patients with HCV and severe renal impairment. *N Engl J Med*. 2017;377:1448-1455.
22. Puoti M, Foster GR, Wang S, et al. High SVR12 with 8-week and 12-week glecaprevir/pibrentasvir therapy: an integrated analysis of HCV genotype 1–6 patients without cirrhosis. *J Hepatol*. 2018;69:293-300.

23. Kwo PY, Poordad F, Asatryan A, et al. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1–6 without cirrhosis. *J Hepatol*. 2017;67:263-271.
24. Asselah T, Lee SS, Yao BB, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients with chronic hepatitis C virus genotype 5 or 6 infection (ENDURANCE-5,6): an open-label, multicentre, phase 3b trial. *Lancet Gastroenterol Hepatol*. 2019;4:45-51.
25. Hlaing NKT, Mitrani RA, Aung ST, et al. Safety and efficacy of sofosbuvir-based direct-acting antiviral regimens for hepatitis C virus genotypes 1–4 and 6 in Myanmar: Real-world experience. *J Viral Hepat*. 2017;24:927-935.
26. McPhee F, Ueland J, Vellucci V, Bowden S, Sievert W, Zhou N. Impact of preexisting hepatitis C virus genotype 6 NS3, NS5A, and NS5B polymorphisms on the in vitro potency of direct-acting antiviral agents. *Antimicrob Agents Chemother*. 2019;63(4):.e02205–e02218.
27. Kyama CM, Overbergh L, Mihalyi A, et al. Endometrial and peritoneal expression of aromatase, cytokines, and adhesion factors in women with endometriosis. *Fertil Steril*. 2008;89:301-310.
28. Hudelist G, Czerwenka K, Keckstein J, et al. Expression of aromatase and estrogen sulfotransferase in eutopic and ectopic endometrium: evidence for unbalanced estradiol production in endometriosis. *Reprod Sci*. 2007;14:798-805.
29. Nguyen E, Trinh S, Trinh H, et al. Sustained virologic response rates in patients with chronic hepatitis C genotype 6 treated with ledipasvir+sofosbuvir or sofosbuvir+velpatasvir. *Aliment Pharmacol Ther*. 2019;49:99-106.
30. AbbVie. MAVIRET (SmPC); AbbVie 2019/Mavyret (US package insert). 2019.
31. George J, Burnevich E, Sheen I-S, et al. Elbasvir/grazoprevir in Asia-Pacific/Russian participants with chronic hepatitis C virus genotype 1, 4, or 6 infection. *Hepatol Commun*. 2018;2:595-606.
32. Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med*. 2015;373:2599-2607.
33. Abergel A, Asselah T, Metivier S, et al. Ledipasvir-sofosbuvir in patients with hepatitis C virus genotype 5 infection: an open-label, multicentre, single-arm, phase 2 study. *Lancet Infect Dis*. 2016;16:459-464.
34. Gane EJ, Hyland RH, An D, et al. Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV genotype 3 or 6 infection. *Gastroenterology*. 2015;149:1454-1461.
35. Jacobson IM, Lawitz E, Gane EJ, et al. Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials. *Gastroenterology*. 2017;153:113-122.
36. D'Ambrosio R, Pasulo L, Puoti M, et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir in 723 patients with chronic hepatitis C. *J Hepatol*. 2019;70:379-387.
37. Berg T, Naumann U, Stoehr A, et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of chronic hepatitis C infection: data from the German Hepatitis C-Registry. *Aliment Pharmacol Ther*. 2019;49:1052-1059.

How to cite this article: Yao BB, Fredrick LM, Schnell G, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients with HCV genotype 5/6: An integrated analysis of phase 2/3 studies. *Liver Int*. 2020;40:2385–2393. https://doi.org/10.1111/liv.14535