Review Article
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Glecaprevir-pibrentasvir for chronic hepatitis C – a clinical review

Abstract

Hepatitis C virus (HCV) infection has a significant global burden with complications that include hepatocellular carcinoma, decompensated cirrhosis, and the need for liver transplantation to avoid death. Although many treatment options are available for treatment of HCV infections, treatment often requires at least 12 weeks of therapy, which may be complicated by HCV genotype, the need for addition of ribavirin, presence of advanced liver disease, end-stage kidney disease, prior treatment failure, and presence of resistance-associated substitutions. Glecaprevir-pibrentasvir is a pangenotypic, ribavirin-free treatment option approved for ages 3 years or older. This regimen can be used in patients with end-stage kidney disease, has a high-barrier to resistance, and has a shorter treatment duration of 8 weeks for most patients. The purpose of this review is to evaluate the safety and efficacy of this regimen in adults and children who are infected with HCV, which may be the only treatment option for certain patients.

Keywords: HCV, Hepatitis C, glecaprevir, ABT-493, pibrentasvir, ABT-530, Mavyret

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Abbreviations: EC, half-maximal effective concentration; P-pg, P-glycoprotein; AASLD, American Association for the Study of liver diseases; BCRP, breast cancer resistance protein; CI, confidence interval; CYP, cytochrome P450; DAA, direct-acting antiviral agent; GLE, glecaprevir; HBV, hepatitis B virus; HCV, hepatitis c virus; HIV, human immunodeficiency virus; IDSA, Infectious Diseases Society of America; OATP, organic anion-transporting Protein; PIB, pibrentasvir; RAS, resistance-associated substitution; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir; VOX, voxilaprevir

Introduction

Hepatitis C virus (HCV) carries a substantial disease burden and is a leading cause to many liver diseases in the western world.[1,2] The burdens are from serious complications with liver diseases such as chronic hepatitis, cirrhosis, liver cancer to being the primary indication for liver transplantation.[2-4] It is estimated as many as 71 to 178 million persons are infected with HCV worldwide, including approximately 3.5 to 4.7 million chronically infected individuals in the United States.[5,6] Patients who are acutely infected with HCV may spontaneously clear the virus or they may progress to chronic infection, which happens in the majority of infected patients.[7,8] Cirrhosis is developed in about 25% of chronically infected patients. Progression of cirrhosis seems to occur gradually over 2 to 3 decades, possibly sooner over a decade in those over 58 years of age.[9] Individuals who are coinfected with hepatitis B virus (HBV) and/or human immunodeficiency virus (HIV) are at higher risk to accelerate progression to cirrhosis.[10,11] Approximately 25% of patient with cirrhosis will develop decompensated liver disease, hepatocellular carcinoma, and eventually death without liver transplantation.[9] Annually, HCV-related complications accounted for about 350,000 deaths worldwide.[12]

HCV is an enveloped positive-sense single-stranded viral ribonucleic acid (RNA) belonging to Flaviviridae viral family.[13] Upon infection, the virus attacks the liver where it imposes the host's hepatocyte ribosomes to translate viral RNA into a polyprotein which is then processed into ten polypeptides each with a distinctive viral functions.[14] The end-product non-structural proteins include NS3/4A serine protease, NS5A, which is the regulator of replication and viral assembly, and NS5B RNA-dependent RNA polymerase.[15] Cellular proteases and viral NS3/4A protease cleave HCV polypeptide and release ten HCV proteins.[15] Due to the lack of proof-reading function in HCV replication machinery, viral mutations result in a high level of variation.[16] These variations lead to eight major HCV genotypes that are different primarily based on geographic origin.[17] In the United States, HCV genotype 1 accounts for about 75% of HCV infected individuals, which makes it the most prevalence genotype. Genotype 2 and 3 constitute the remaining of 25% of HCV infection, with genotype 3 being the second most prevalent.[19]

Sustained virologic response 12 weeks after the end of treatment (SVR), defined as undetectable HCV RNA serum levels, has been the primary efficacy surrogate endpoint of HCV clinical trials. Analyses of studies that used interferon-based treatment have shown that an SVR is associated with lower all-cause mortality, including both liver-related and non-liver-related mortality, in patients with chronic HCV monoinfection and advanced hepatic fibrosis and in patients with HIV-HCV coinfection.[20-23] Achieving SVR has also been associated with decrease in inflammation, reduction in the rate of liver fibrosis progression, reduction in the risk of hepatocellular carcinoma, reduction in risk of liver transplantation, higher complete remissions in patients with cryoglobulinemia vasculitis, higher objective response in patients with malignant B-cell lymphoproliferative diseases, and reduced insulin resistance at follow-up.[24-27] In recent years, interferon-free and ribavirin-free treatment options have become widely available due to high efficacy, safety and tolerability of currently available direct-acting agents, eliminating the intolerable adverse effects of interferon and ribavirin for most patients. While data with direct-acting agents (DAAs) are limited, achieving SVR by DAAs or interferon-based therapy in patients with type 2 diabetes seems to decrease risk of acute coronary syndrome, end-stage kidney disease, stroke, and retinopathy compared to patients without SVR.[28] Because of these benefits of treating chronic HCV, achieving SVR is the goal of therapy and treatment is indicated for the majority of patients.

The U.S. Preventive Services Task Force recommends screening adults aged 18 to 79 years for HCV infection.[29] Moreover, the 2020 CDC guidelines recommend screening for HCV at least once in a lifetime for all adults aged 18 years and older unless the HCV prevalence is <0.1%, given that 8-12 weeks of treatment is curative.[30] While disease association is largely similar across all HCV genotypes, treatment response varies.[15] Patients with cirrhosis and/or HCV genotype 3 are relatively difficult to treat compared to patients without cirrhosis or those with other HCV genotypes using currently available DAAs.[31] There are also fewer treatment options available for HCV genotype 3 compared to genotype 1. Other challenging clinical situations include patients who have undergone liver transplantation, patients at increased risk of rapid progression of liver fibrosis, people who inject drugs, and patients on hemodialysis. In this review, we summarize the evidence for use of glecaprevir/pibrentasvir and its place in treatment of hepatitis C.

Literature review

PubMed, EMBASE, and Google Scholar were searched through June 2021 using keyword terms glecaprevir, ABT-493, pibrentasvir, ABT-530, Mavyret, and hepatitis C. Phase 3 studies are included as well as studies related to pharmacology and pharmacokinetics of the drugs and studies related to clinical outcomes in patients with chronic hepatitis C published in the English language. References of selected articles were also screened to identify additional studies.

Results

Pharmacology and pharmacokinetics

The combination of glecaprevir and pibrentasvir (GLE/PIB), manufactured by AbbVie, was approved by the U.S. Food and Drug Administration on August 3, 2017 for use in adults. While the coformulation, Mavyret, is a once-daily regimen, it is divided into 3 tablets to maintain a reasonable pill size. Each pill contains 100 mg of glecaprevir and 40 mg of pibrentasvir. On April 30, 2019, it was approved for use in pediatric patients 12 years and older or weighing at least 45 kg.[32] On June 10, 2021, a new oral pellets formulation containing 50 mg of glecaprevir and 20 mg of pibrentasvir in each packet was approved for children 3 to less than 12years of age. Dosing for patients younger than 12years or weighing less than 45kg is based on body weight (3 packets for body weight less than 20kg, 4 packages for 20 to 30kg, and 5 packets for 30 to 45kg). The pharmacokinetic properties of the agents can be found in Table 1. Glecaprevir (ABT-493), a second-generation HCV NS3/4A protease inhibitor, is currently indicated, in combination with pibrentasvir, for the treatment of chronic HCV genotypes 1 through 6.[33] It possesses pangenotypic antiviral activity against HCV *in vitro*.[34,35] Pibrentasvir (ABT-530), a second-generation HCV NS5A inhibitor, is currently indicated, in combination with glecaprevir, for the treatment of HCV genotype 1 through 6.[32] It also possesses pangenotypic *in vitro* antiviral activity against HCV.[35,36] The combination of GLE/PIB should be taken with meals as food increases the absorption; although one study showed minimal effect of food on glecaprevir exposure [32,37]. The tablet formulation should not be crushed. A phase 1 study in healthy subjects suggested that cutting the tablet in half had minimal effect of ≤15% on glecaprevir and pibrentasvir exposure, while crushing or grinding the tablet resulted in lower glecaprevir exposure (27-61%) and higher pibrentasvir exposure (21-83%).[38]

Glecaprevir and pibrentasvir are substrates of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Glecaprevir is also a substrate of organic anion transporting polypeptide (OATP) 1B1/3. Coadministration of GLE/PIB with drugs that inhibit hepatic P-gp, BCRP, or OATP 1B1/3 may increase the plasma concentrations of glecaprevir and/or pibrentasvir. GLE/PIB is contraindicated in combination with atazanavir or rifampin, while coadministration with darunavir, lopinavir, ritonavir, and cyclosporine doses more than 100 mg per day is not recommended because they may significantly increase plasma concentrations of GLE/PIB.[32] Coadministration of GLE/PIB with drugs that induce P-gp and/or cytochrome P450 (CYP) 3A may decrease glecaprevir and pibrentasvir plasma concentrations. Therefore, coadministration of carbamazepine, efavirenz containing regimens, and St. John's wort with GLE/PIB is not recommended because they may significantly decrease plasma concentrations of GLE/PIB.

Table 1 Pharmacokinetic Properties of Glecaprevir-Pibrentasvir in Adults[32,34]

Agent	Glecaprevir (GLE)	Pibrentasvir (PIB)
Dosage	300 mg once daily with food (100 mg per tablet)	120 mg once daily with food (40 mg per tablet)
Half-life	6h	13h
Protein-binding	97.5%	>99%
Elimination	Feces	Feces
EC50	<5nM	<5pM
Pregnancy	Unknown	Unknown
Substrate	P-glycoprotein, BCRP, OATP, CYP3A	P-glycoprotein, BCRP
Inhibition	P-glycoprotein, BCRP, OATP	P-glycoprotein, BCRP, OATP

BCRP, breast cancer resistance protein; CYP, cytochrome P450; EC50, half-maximal effective concentration; OATP, organic anion-transporting polypeptides

Both glecaprevir and pibrentasvir are inhibitors of P-gp, BCRP, and OATP 1B1/3. Coadministration of drugs that are substrates of P-gp, BCRP, OATP1B1, or OATP1B3 with GLE/PIB may increase the plasma concentration of those drugs. Moreover, glecaprevir and pibrentasvir are weak inhibitors of CYP 3A, CYP 1A2, and uridine glucuronosyltransferase (UGT) 1A1. As a result, GLE/PIB may increase plasma concentrations of digoxin, dabigatran, pravastatin, rosuvastatin, fluvastatin, pitavastatin, atorvastatin, lovastatin, and

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simvastatin. While coadministration of GLE/PIB with atorvastatin, lovastatin, and simvastatin is not recommended, the interaction with the remaining drugs can be managed by dose adjustment. It is recommended to reduce digoxin dose by 50% and monitor digoxin plasma levels, reduce pravastatin dose by 50%, limit rosuvastatin dose to 10 mg, and use the lowest approved dose of fluvastatin 20 mg and pitavastatin 1 mg. Dabigatran co-administration with GLE/PIB should be avoided in patients with CrCl < 50 mL/min for the indication of prophylaxis or treatment of deep vein thrombosis or pulmonary embolism. However, a reduced dose of dabigatran 75 mg twice daily is recommended in patients with CrCl 30-50 mL/min with concomitant use of GLE/PIB for the indication of stroke prevention in non-valvular atrial fibrillation.[39] Limited data suggest that proton pump inhibitors (PPIs), particularly 40 mg of omeprazole, does not affect pibrentasvir exposures but reduces glecaprevir exposure by 51%. However, this reduction had no significant effect on efficacy.[40]

Furthermore, an analysis of 9 multicenter, phase 2 and 3 trials, evaluated the rate of SVR12 in 401 patients who reported taking acid-reducing agents, a PPI, an H2 blocker, or antacid. Of these patients, 263 patients took PPIs. The rate of SVR12 was 97.0% among patients who took acid-reducing agents and 97.5% among those not taking acid reducing agents (P=0.6). An SVR12 rate of 96.3% was achieved among patients taking a high-dose PPI (defined as daily dose greater than 20 mg omeprazole dose equivalent) and 97.4% taking a low-dose PPI, with no virologic failures among patients taking a high-dose PPI (P=0.7).[41] Lastly, no clinically significant drug interactions have been observed when GLE/PIB combination was coadministered with the following drugs: abacavir, amlodipine, buprenorphine, caffeine, dextromethorphan, dolutegravir, elvitegravir/cobicistat, emtricitabine, felodipine, lamivudine, lamotrigine, losartan, methadone, midazolam, naloxone, norethindrone or other progestin-only contraceptives, omeprazole, raltegravir, rilpivirine, sofosbuvir, tacrolimus, tenofovir alafenamide, tenofovir disoproxil fumarate, tolbutamide, and valsartan.[32,42]

Since this regimen is primarily eliminated via feces, it can be used for patients with kidney dysfunction such as those with a glomerular filtration rate < 30 mL/min/1.73 m^2 or with end-stage kidney disease, including patients who need intermittent hemodialysis. However, its use is contraindicated in patients with moderate hepatic impairment (Child-Pugh B), severe hepatic impairment (Child-Pugh C), or those with any history of prior hepatic decompensation.[32] Patients with moderate hepatic impairment may have 2-fold increase in glecaprevir AUC, whereas those with severe hepatic impairment may have 11- and 2-fold increase in glecaprevir and pibrentasvir AUC, respectively.[43] There is a risk of hepatic decompensation or failure in patients with evidence of advanced liver disease. GLE/PIB was generally well-tolerated in clinical studies, with headache and fatigue being the most commonly reported adverse effects.[32] As with all direct-acting antiviral agents, there is a black box warning for the risk of HBV reactivation in patients coinfected with HCV and HBV. Lastly, inadequate human data are available regarding the safety of GLE/PIB in pregnant patients.

Evidence for efficacy and safety

The efficacy and safety of GLE/PIB has been evaluated for the treatment of HCV genotypes 1 through 6 in several clinical trials. In phase 2 clinical trials, GLE/PIB was well tolerated. In treatment-naïve patients without cirrhosis, 12 weeks of treatment resulted in SVR rates of 100%, 96%, and 90-93% for genotype 1, 2, and 3, respectively, and 8 weeks of treatment resulted in SVR rates of 97%, 98%, and 97% for genotype 1, 2, and 3, respectively [44,45]. In treatment-naïve patients with compensated cirrhosis, 12 weeks of treatment resulted in SVR rates of 95% and 100% for genotype 1 and 3, respectively [46]. In treatment-experienced (prior interferon and ribavirin) patients without cirrhosis, 12 weeks of treatment resulted in SVR rates of 100%, 96%, and 93% for genotypes 1, 2, and 3, respectively, and 8 weeks of treatment resulted in SVR rates of 97%, and 98% for genotypes 1 and 2, respectively [44,47]. In patients without cirrhosis who had prior failure of DAA-containing therapy, 12 weeks of therapy resulted in SVR rate of 86% without addition of ribavirin and 95% with the addition of ribavirin.[47] In treatment-experienced patients with compensated cirrhosis, 12 weeks of treatment resulted in SVR rate of 100% and 75% for genotype 1 and 3, respectively, and 8 weeks of treatment resulted in SVR rates of 97% and 98% for genotype 1 and 2, respectively.[44,46] The addition of ribavirin to 12 weeks of GLE/PIB increased the SVR rate to 100% for genotype 3 in treatment-experienced patients with compensated cirrhosis.[46] As with most phase 2 clinical trials, these studies are limited by small sample sizes. Several phase 3 clinical trials have evaluated the safety and efficacy of GLE/PIB (Table 2).

Table 2 Phase 3 Clinical Trials Evaluating the Use of Glecaprevir-Pibrentasvir

Study	Patients	HCV genotype	Treatment duration	SVR12
EXPEDITION-1 (2017)[48]	Adult patients with compensated cirrhosis, 25% TE with IFN or SOF (N=146)	1 (60%), 2 (23%), 4 (11%), 5 (1%), or 6 (5%)	12 weeks	99% (145/146)
ENDURANCE-2 (2017)[49]	Adult patients without cirrhosis, 30% TE with IFN or SOF (N=302)	2	12 weeks	99.5% (201/202)
ENDURANCE-4 (2017)[49]	Adult patients without cirrhosis, 32% TE with IFN (N=121)	4 (63%), 5 (21%), or 6 (16%)	12 weeks	99% (120/121)
EXPEDITION-4 (2017)[51]	Adult patients with GFR < 30 mL/min/1.73 m^2, 82% on hemodialysis, 40% TE with IFN or SOF (N=104)	1 (50%), 2 (16%), 3 (11%), 4 (19%), 5 (1%), or 6 (1%)	12 weeks	98% (102/104)
CERTAIN-1 (2017)[70]	Adult patients, 17% with compensated cirrhosis, 28% TE with IFN (N=219)	1	8 weeks or 12 weeks if cirrhosis, or OMB/PTV/r 12 weeks	99.5% (218/219)
SURVEYOR-II Part 4 (2017)[49]	Adult patients without cirrhosis, 13% TE with IFN or SOF (N=203)	2 (71%), 4 (23%), 5 (1%), or 6 (5%)	8 weeks	98% (196/203)
SURVEYOR-II Part 3 (2018)[50]	Adult patients, 66% with compensated cirrhosis, 69% TE with IFN or SOF (N=131)	3	12 weeks or 16 weeks	95% (59/62) 96% (66/69)

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Table Continued...

Study	Patients	HCV genotype	Treatment duration	SVR12
CERTAIN-2 (2018)[71]	Adult patients without cirrhosis, 17% TE with IFN (N=136)	2	8 weeks or SOF+RBV 12 weeks	97.8% (88/90) 93.5% (43/46)
ENDURANCE-1 (2018)[53]	Adult patients without cirrhosis, 5% HIV, 38% TE with IFN or SOF (N=703)	1	8 weeks or 12 weeks	99.1% (348/351) 99.7% (351/352)
ENDURANCE-3 (2018)[53]	Adult TN patients without cirrhosis (N=505)	3	8 weeks or 12 weeks or SOF+DCV 12 weeks	95% (149/157) 95% (222/233) 97% (111/115)
EXPEDITION-2 (2018)[60]	Adult patients with HIV, 10% with compensated cirrhosis, 18% TE with IFN or SOF (N=153)	1 (63%), 2 (7%), 3 (17%), 4 (11%), or 6 (2%)	8 weeks or 12 weeks if cirrhosis	98% (150/153)
MAGELLAN-1 Part 2 (2018)[62]	Adult TE patients with NS3/4 protease inhibitor and/or NS5A inhibitor-based regimen, 30% with compensated cirrhosis (N=91)	1 (96%) or 4 (4%)	12 weeks or 16 weeks	89% (39/44) 91% (43/47)
MAGELLAN-2 (2018)[63]	Adult patients without cirrhosis who had received primary liver (80%) or kidney (20%) transplant, 34% TE with IFN (N=100)	1 (57%), 2 (13%), 3 (24%), 4 (4%), or 6 (2%)	12 weeks	98% (98/100)
ENDURANCE-5,6 (2019)[57]	Adult patients, 11% with compensated cirrhosis, 10% TE with IFN (N=84)	5 (27%) or 6 (73%)	8 weeks or 12 weeks if cirrhosis	98% (82/84)
Fontana et al (2019)[54]	Adult TN patients with APRI≤ 1 and no prior evidence of cirrhosis, 4% HIV (N=230)	1 (66%), 2 (14%), 3 (15%), 4 (4%), or 6 (1%)	8 weeks	97% (222/230)
EXPEDITION-8 (2019)[59]	Adult TN patients with compensated cirrhosis (N=343)	1 (67%), 2 (8%), 3 (18%), 4 (4%), 5 (<1%), or 6 (3%)	8 weeks	98% (335/343)
EXPEDITION-5 (2019)[61]	Adult patients, 14% with compensated cirrhosis, 20% TE (N=101)	1 (55%), 2 (27%), 3 (15%), or 4 (4%)	8 weeks or 12 weeks if cirrhosis or 16 weeks if TE GT3	97% (98/101)
HCV-TARGET (2019)[64]	Adult patients, 28% with compensated cirrhosis (N=177)	1	12 weeks if no cirrhosis, or 12 weeks with RBV or 16 weeks if cirrhosis	91.5% (162/177)
MAGELLAN-3 (2019)[65]	Adult TE patients who failed GLE/PIB, 30% with compensated cirrhosis (N=23)	1 (30%), 2 (9%), or 3 (61%)	GLE/PIB + SOF + RBV 12 weeks or 16 weeks if GT3, cirrhosis, or prior NS5A or NS3 inhibitor	96% (22/23)
VOYAGE-1 (2020)[73]	Adult patients without cirrhosis, 20% TE with IFN or SOF (N=545)	1 (49%), 2 (39%), 3 (6%), or 6 (6%)	8 weeks or 16 weeks if TE with GT 3	97.2% (352/362)
VOYAGE-2 (2020)[73]	Adult patients with compensated cirrhosis, 31% TE with IFN or SOF (N=160)	1 (53%), 2 (33%), 3 (9%), 4 (1%), or 6 (4%)	12 weeks or 16 weeks if TE with GT 3	99.4% (159/160)
TARGET 3D Cohort 2 (2020)[66]	Adult TN patients within 12 months of HCV infection, without cirrhosis, 77% HIV (N=30)	1 (83%), 3 (7%), or 4 (10%)	6 weeks	90% (27/30)
MYTHIC (2020)[67]	Adult HCV-noninfected patients receiving a kidney transplant from HCV-positive deceased donors (N=30)	1, 2, or 4 (only 15 donors had genotype data available)	8weeks	100% (30/30)
DORA Part 1 (2020)[68]	Adolescent patients 12-17 years of age without cirrhosis, 23% TE with IFN (N=48)	1 (28%), 2 (6%), 3 (9%), and 4 (6%)	Mostly 8 weeks, 16 weeks in 3 patients	100% (47/47)
DORA Part 2 (2021)[69]	Children 3-11 years of age without cirrhosis, 2% TE with IFN (N=81)	1 (72%), 2 (3%), 3 (23%), and 4 (3%)	Mostly 8 weeks, 12-16 weeks in 2 patients	96% (77/80)
EXPEDITOIN-3 (2021)[58]	Adult TN patients, 26% with compensated cirrhosis (N=100)	1 (56%), 2 (5%), or 3 (39%)	8 weeks or 12 weeks if cirrhosis	98% (98/100)

DCV, daclatasvir; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; GT, genotype; IFN, interferon; OMB/PTV/r, ombitasvir/paritaprevir/ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-naive; TN, treatment-experienced

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EXPEDITION-1 (2017) was an open-label, single-arm, multicenter phase 3 trial in the United States, Europe, and South Africa.[48] The study enrolled 146 adult patients with compensated cirrhosis who were infected with HCV genotype 1 (60%), 2 (23%), 4 (11%), 5 (1%), or 6 (5%). About 75% of patients were treatment-naïve and of the remaining 25%, 69% had failed a prior interferon-based regimen and 31% had failed a prior sofosbuvir-based regimen. About 10% of patients were Black. All patients received oral glecaprevir (300 mg) coformulated with pibrentasvir (120 mg) once daily for 12 weeks. Patients with creatinine clearance < 50 mL/min as calculated by the Cockcroft-Gault equation and those with decompensated cirrhosis, current or past Child-Pugh B or C classification, were excluded. SVR12 was achieved in 145/146 (99%; 95% CI, 98-100) of all patients with 1 relapse. The SVR rate was 99% (88/87) in patients with genotype 1 and 100% in patients with genotype 2, 4, 5, or 6. Viral sequencing data were available for 133 patients. While 57 of these patients had baseline polymorphism in NS3 or NS5A, only 1 of them had virologic failure. One patient with HCV genotype 1a who had failed prior treatment with interferon plus ribavirin relapsed GLE/PIB at treatment week 8. This patient had no baseline or treatment-emergent substitutions in NS3, but there was a Q30R-H58D polymorphism in NS5A at the time of failure and Y93N substitution was present at baseline and at the time of failure. The treatment was well-tolerated, with no patient discontinuing GLE/PIB due to adverse events. Although 69% of patients reported adverse events, 64% were mild. Common adverse events included fatigue (19%), headache (14%), pruritus (10%), nausea (9%), diarrhea (8%), and urinary tract infection (6%). The results of EXPEDITION-1 suggest that treatment with GLE/PIB for 12 weeks is safe and effective in both treatment-naïve and treatment-experienced (interferon or sofosbuvir-regimens) patients with compensated cirrhosis who are infected with HCV genotype 1, 2, 4, 5, or 6.

ENDURANCE-2 (2017) was a randomized, double blind, placebo-controlled, multicenter, phase 3 trial in Canada, Europe, and South Africa.[49] The study enrolled 302 adult patients without cirrhosis and with creatinine clearance above 50 mL/min who were infected with chronic HCV genotype 2. Patients with HIV or HBV coinfections were excluded. About 30% of patients were treatment-experienced, including 27% with a prior interferon-based regimen and 3% with a prior sofosbuvir-based regimen. About 33% of patients were Asian and 5% of patients were Black. Patients were randomized in a 2:1 ratio to receive three coformulated tablets, each containing 100 mg of glecaprevir and 40 mg of pibrentasvir by mouth once daily (total daily dose of 300 mg of glecaprevir and 120 mg of pibrentasvir) or placebo for 12 weeks. Baseline characteristics were similar between the two groups. SVR12 was achieved in 201/202 (99.5%; 95% CI, 99-100) of all patients, with no virologic failures. All 6 patients with prior sofosbuvir-regimen treatment achieved SVR12. The treatment was well-tolerated as there was no discontinuation due to adverse events. Common adverse events included fatigue (13%), headache (12%), and nausea (11%). Elevation of liver enzymes occurred in 1 patient receiving treatment and 2 patients receiving placebo. The results of ENDURANCE-2 suggest that treatment with GLE/PIB for 12 weeks is safe and effect in both treatment-naïve and treatment-experienced (interferon regimens) patients without cirrhosis infected with HCV genotype 2.

SURVEYOR-II Part 3 (2018) was a partially-randomized, open-label, four-arm, multicenter phase 3 trial in Australia, Canada, France, New Zealand, the U.K., and the U.S. [50]. The study enrolled 131 adult patients without cirrhosis (34%) or with compensated cirrhosis (66%) infected with chronic HCV genotype 3. Patients with HIV or HBV coinfections and those with creatinine clearance below 50 mL/min were excluded. About 31% of patients were treatment-naïve, all with compensated cirrhosis. The remaining 69% were treatment-experienced, including 37% with a prior interferon-based regimen and 32% with a prior sofosbuvir-based regimen. Treatment-experienced noncirrhotic patients were randomized in a 1:1 ratio to receive either 12 of 16 weeks of treatment with GLE/PIB (total daily dose of 300 mg of glecaprevir and 120 mg of pibrentasvir). Treatment-naïve patients, all of whom had cirrhosis, received 12 weeks of treatment, and treatment-experienced patients with cirrhosis received 16weeks of treatment. Overall, SVR12 was achieved in 59/62 (95%; 95% CI, 87-98) of all patients who received 12 weeks of treatment and in 66/69 (96%; 95% CI, 88-99) of all patients who received 16 weeks of treatment. In treatment-naïve patients without cirrhosis, SVR12 was 98% (39/40) after 12 weeks of treatment with no virologic failure or relapse (1 patient had missing data). In treatment-experienced patients with cirrhosis, SVR12 was 96% (45/47) after 16 weeks of treatment with 1 virologic breakthrough and 1 relapse. For treatment-experienced patients without cirrhosis, SVR12 was 91% (20/22) for those randomized to 12 weeks of treatment with 2 relapses and no virologic failure, and 95% (21/22) for those randomized to 16 weeks of treatment with 1 relapse and no virologic failure. All patients with virologic failure had treatment-emergent substitutions in NS3 (Y56H, A156G, or Q168R) and NS5A (A30K, L31F, or Y93H). Patients with a baseline NS3 polymorphism had a SVR12 rate of 95% (18/19) and those with baseline NS5A polymorphism had a SVR12 rate of 100% (15/15). Given the small sample size, it was difficult to evaluate the impact of baseline polymorphisms on treatment outcome. The treatment was well-tolerated as there was no discontinuation due to adverse events. Common adverse events included fatigue (22%) and headache (19%). There was no clinically significant elevation of liver enzymes. The results of SURVEYOR-II Part 3 suggest that treatment with GLE/PIB for 12 weeks in treatment-naïve cirrhotic patients and treatment-experienced noncirrhotic patients and 16 weeks in treatment-experienced cirrhotic patients is safe and effect in patients infected with HCV genotype 3.

ENDURANCE-4 (2017) was an open-label, single-arm, multicenter phase 3 trial in Canada, Europe, and South Africa.[49] The study enrolled 121 adult patients without cirrhosis and with creatinine clearance above 50 mL/min. Patients were infected with chronic HCV genotype 4 (63%), 5 (21%), or 6 (16%). Patients with HIV or HBV coinfections were excluded. About 32% of patients were treatment-experienced, all with a prior interferon-based regimen and none with a prior sofosbuvir-based regimen. About 20% of patients were Asian and 8% of patients were Black. All patients received three coformulated tablets, each containing 100 mg of glecaprevir and 40 mg of pibrentasvir by mouth once daily (total daily dose of 300 mg of glecaprevir and 120 mg of pibrentasvir) for 12 weeks. SVR12 was achieved in 120/121 (99%; 95% CI, 98-100) of all patients, with no virologic failures, and in 99% (75/76) with GT 4, 100% (26/26) with GT 5, and 100% (19/19) with GT 6. Overall, the treatment was well-tolerated. Discontinuation due to adverse events occurred in 3 patients, including 1 patient with transient ischemic attach that was deemed related to treatment. The other 2 patients discontinued treatment because of anxiety and dyspepsia. Common adverse events included headache (21%), fatigue (17%), and nausea (10%). There was no significant elevation of liver enzymes. The results of ENDURANCE-4 suggest that treatment with GLE/PIB for 12 weeks is safe and effect in both treatment-naïve and interferon-experienced patients without cirrhosis infected with HCV genotype 4, 5, or 6.

EXPEDITION-4 (2017) was an open-label, single-group, multicenter phase 3 trial in the United States, Canada, Europe, Australia, and New Zealand.[51] The study enrolled 104 adult patients with an estimated glomerular filtration rates (eGFR) at screening of less than 30mL/min/1.73m^2 as calculated by the MDRD method, 82% of which were undergoing hemodialysis at baseline. Patients were infected with HCV genotype 1 (50%), 2 (16%), 3 (11%), 4 (19%), 5 (1%), or 6 (1%). While majority of the patients did not have cirrhosis, about 19% had compensated cirrhosis. About 58% of patients were treatment-naïve, 40% had failed a prior interferon-based regimen, and 2% had failed a prior sofosbuvir-based regimen. About 24% of patients were Black and 9% of patients were Asian. All patients received three coformulated tablets, each containing 100 mg of glecaprevir and 40 mg of pibrentasvir by mouth once daily (total daily dose of 300 mg of glecaprevir and 120 mg of pibrentasvir) for 12 weeks. Patients with decompensated cirrhosis and patients who had both HCV genotype 3 infection and previous treatment for HCV were excluded (i.e., all patients with HCV genotype 3 were treatment-naïve). SVR12 was achieved in 102/104 (98%; 95% CI, 95-100) of all patients. Of the 2 patients who did not achieve SVR, 1 patient who was undergoing hemodialysis and had compensated cirrhosis died after posttreatment week 2 due to cerebral hemorrhage, which was deemed unrelated to GLE/PIB. The other patient had discontinued the trial treatment prematurely because of a non-serious diarrhea, which was possibly related to GLE/PIB. Viral sequencing data were available for 96 patients. While 28 of these patients had baseline polymorphism in NS3 or NS5A, none of them had virologic failure. Overall, the treatment was well-tolerated as none of the serious adverse events (24%) were considered to be drug-related. However, 72% of patient who were undergoing hemodialysis at baseline and 68% of patients who were not undergoing hemodialysis experienced adverse events. Common adverse events included pruritus (20%), fatigue (14%), and nausea (12%). Pharmacokinetic analysis in a subgroup of 6 patients revealed that glecaprevir and pibrentasvir were not removed from plasma by hemodialysis. These results are consistent with the results of a phase 1 study that evaluated the effects of kidney impairment, including hemodialysis, on the pharmacokinetics and safety of GLE/PIB.[52] The results of EXPEDITION-4 suggest that treatment with GLE/PIB for 12 weeks is safe and effect in both treatment-naïve and treatment-experienced (interferon regimens) patients without cirrhosis or with compensated cirrhosis who have end-stage kidney disease, including those undergoing hemodialysis, and are infected with HCV genotype 1, 2, 3, 4, 5, or 6.

ENDURANCE-1 (2018) was a randomized, open-label, multicenter, phase 3 trial.[53] The study enrolled 703 adult patients without cirrhosis and with creatinine clearance above 50mL/min who were infected with chronic HCV genotype 1. About 38% of patients were treatment-experienced, almost exclusively with a prior interferon-based regimen and only 3 patients with a prior sofosbuvir-based regimen. About 4% of patients were Black and 5% of patients were coinfected with HIV-1. Patients were randomized in a 1:1 ratio to receive three coformulated tablets, each containing 100 mg of glecaprevir and 40 mg of pibrentasvir by mouth once daily (total daily dose of 300 mg of glecaprevir and 120 mg of pibrentasvir) for 8 or 12 weeks. Baseline characteristics were mostly similar between the two groups. SVR12 was achieved in 348/351 (99.1%; 95% CI, 98-100) of patients receiving 8 weeks of treatment and in 351/352 (99.7%; 95% CI, 99-100) of those receiving 12 weeks of treatment, meeting the non-inferiority threshold of 5%. There was no relapse in either group. SVR12 was achieved in all patients with HIV coinfection. The treatment was well-tolerated with only 1 discontinuation due to adverse events. Common adverse events included headache (18%), fatigue (11%), and nausea (7%). Elevation of liver enzymes occurred in only 1 patient receiving treatment. The results of ENDURANCE-1 suggest that treatment with GLE/PIB for 8 weeks is safe and as effect as 12 weeks of treatment in both treatment-naïve and treatment-experienced (interferon regimens) patients without cirrhosis infected with HCV genotype 1.

A single-arm, open-label, multicenter phase 3 trial (2019) was conducted in Bulgaria, Canada, France, Germany, Poland, Puerto Rico, Russia, Spain, the U.K., and the U.S.[54] The study enrolled 230 adult treatment-naïve patients with APRI$\leq$1 and no prior evidence of cirrhosis and with creatinine clearance above 30mL/min to receive 8 weeks of daily GLE-PIB 300 mg/120 mg with food. Patients were infected with chronic HCV genotype 1 (66%), 2 (14%), 3 (15%), 4 (4%), or 6 (1%). About 6% of patients were Black, 4% Asian, and 4% were coinfected with HIV. SVR12 was achieved in 222/230 (97%; 95% CI, 94-99) of all patients, with no virologic failures. Of the 8 patients no achieving SVR12, 5 patients had missing data and 3 patients discontinued treatment prematurely. The treatment was well-tolerated with only 2 discontinuations due to adverse events related to treatment. These 2 patients experienced angioedema. However, both patients were Black and were taking an angiotensin-converting enzyme (ACE) inhibitor. Common adverse events included headache (13%) and fatigue (7%). There was no significant elevation of liver enzymes. The results of this trial suggest that treatment with GLE/PIB for 8 weeks is safe and effect in treatment-naïve patients without cirrhosis infected with HCV genotype 1, 2, 3, 4, or 6, using APRI score $\leq$1 to rule out cirrhotic patients.

SURVEYOR-II Part 4 (2017) was an open-label, single-arm, multicenter phase 3 trial in Canada, Europe, and South Africa.[49] The study enrolled 203 adult patients without cirrhosis and with creatinine clearance above 50mL/min. Patients were infected with chronic HCV genotype 2 (71%), 4 (23%), 5 (1%), or 6 (5%). Patients with HIV or HBV coinfections were excluded. About 13% of patients were treatment-experienced, including 10% with a prior interferon-based regimen and 3% with a prior sofosbuvir-based regimen. About 11% of patients were Asian and 10% of patients were Black. All patients received three coformulated tablets, each containing 100 mg of glecaprevir and 40 mg of pibrentasvir by mouth once daily (total daily dose of 300 mg of glecaprevir and 120 mg of pibrentasvir) for 8 weeks. SVR12 was achieved in 196/203 (98%; 95% CI, 95-100) of all patients. For patients with HCV GT2, SVR12 was 98% (142/145) with 2 virologic relapses. In sofosbuvir-experienced patients with GT2, SVR12 was achieved in 5/6 patients, with 1 relapse. In patients with GT 4, 5, and 6, SVR12 was achieved in 54/58 (93%; 95% CI, 84-97), with no treatment failures. There were no treatment-emergent substitutions in patients with relapses, but both had M31 polymorphism in NS5A at baseline. M31 polymorphism has been shown to confer resistance to other NS5A inhibitors such as ledipasvir and daclatasvir.[55,56] However, there were 21 patients in this study with HCV GT 2 having this polymorphism at baseline and SVR12 was achieved in 90% of them. The treatment was well-tolerated as there was no discontinuation due to adverse events. Common adverse events included headache (21%), fatigue (17%), and nausea (11%). There was no significant elevation of liver enzymes. The results of SURVEYOR-II Part 4 suggest that treatment with GLE/PIB for 8 weeks is safe and effect in both treatment-naïve and treatment-experienced (interferon regimens) patients without cirrhosis infected with HCV genotype 2, 4, 5, or 6.

ENDURANCE-3 (2018) was a partially randomized, open-label, active-controlled, multicenter, phase 3 trial [53]. The study enrolled

505 adult patients without cirrhosis and with creatinine clearance above 50 mL/min who were infected with chronic HCV genotype 3. All patients were treatment-naïve. About 2% of patients were Black. Patients coinfected with HIV or HBV were excluded. Patients were randomized in a 2:1 ratio to receive three coformulated tablets, each containing 100 mg of glecaprevir and 40 mg of pibrentasvir by mouth once daily (total daily dose of 300 mg of glecaprevir and 120 mg of pibrentasvir) or sofosbuvir 400 mg plus daclatasvir 60 mg for 12 weeks. Baseline characteristics were mostly similar between the two groups. A third group of patients were non-randomly assigned to receive 8 weeks of treatment with GLE/PIB. SVR12 was achieved in 222/233 (95%; 95% CI, 93-98) of patients receiving 12 weeks of GLE/PIB and in 111/115 (97%; 95% CI, 93-99.9) of those receiving 12 weeks of sofosbuvir plus daclatasvir, meeting the non-inferiority threshold of 6%. Only 1% of patients had relapse in either group. SVR12 was achieved in 149/157 (95% CI, 91-98) of patients receiving 8 weeks of GLE/PIB, meeting the non-inferiority margin of 6% when compared to 12 weeks of GLE/PIB. About 3% of patients had relapse with 8 weeks of treatment. In patients with baseline GT3 Y93H variant, SVR12 was achieved in 5/5 (100%) and 10/11 (91%) in the 8-week and 12-week GLE-PIB groups, and in 7/8 (88%) in the 12-week sofosbuvir plus daclatasvir group. In patients with baseline GT3 A30K variant, SVR12 was achieved in 12/16 (75%) and 9/10 (90%) in the 8-week and 12-week GLE-PIB groups, and in 5/5 (100%) in the 12-week sofosbuvir plus daclatasvir group. The treatment was well-tolerated with only 1 discontinuation due to adverse events of GLE-PIB because of abdominal pain, headache, and malaise. Common adverse events included headache (23%), fatigue (16%), and nausea (13%). Elevation of liver enzymes occurred in only 1 patient receiving GLE/PIB. The results of ENDURANCE-3 suggest that treatment with GLE/PIB for 8 weeks is safe and as effective as 12 weeks of treatment in treatment-naïve patients without cirrhosis infected with HCV genotype 3.

ENDURANCE-5,6 (2019) was an open-label, single-arm, multicenter, phase 3 trial in Belgium, France, Australia, New Zealand, Canada, USA, South Africa, Singapore, and Vietnam.[57] The study enrolled 84 adult patients without cirrhosis (89%) or with compensated cirrhosis (11%) who were infected with chronic HCV genotype 5 (27%) or 6 (73%). About 10% of patients were treatment-experienced with a prior interferon-based regimen. While it was allowed, no patient was previously treated with a sofosbuvir-based regimen. Patients coinfected with HBV or HIV were excluded. Patients received three coformulated tablets, each containing 100 mg of glecaprevir and 40 mg of pibrentasvir by mouth once daily (total daily dose of 300 mg of glecaprevir and 120 mg of pibrentasvir) for 8 weeks if they did not have cirrhosis or 12 weeks if they had cirrhosis. SVR12 was achieved in 82/84 (98%; 95% CI, 94-100) of all patients, in 22/23 (96%; 95% CI, 87-100) of those with genotype 5, and in 60/61 (98%; 95% CI, 95-100) of those with genotype 6. There were 2 relapses, 1 in a cirrhotic patient with genotype 6 and 1 in a non-cirrhotic patient with genotype 5. Baseline polymorphism in NS3 or NS5A did not affect treatment outcomes. The treatment was well-tolerated with no discontinuation due to adverse events. Common adverse events included headache (13%) and fatigue (13%). No significant elevation of liver enzymes occurred. The results of ENDURANCE-5,6 suggest that treatment with GLE/PIB for 8 weeks (if no cirrhosis) or 12 weeks (if cirrhosis) is safe and effective in both treatment-naïve and interferon-experienced patients infected with HCV genotype 5 or 6.

EXPEDITOIN-3 (2021) was an open-label, non-randomized, multicenter, phase 3 trial in Brazil.[58] The study enrolled 100 adult patients without cirrhosis (74%) or with compensated cirrhosis (26%) who had chronic HCV genotype 1 (56%), 2 (5%), or 3 (39%). All patients were treatment-naïve. About 26% of patients were Black and 2% Asian. Patients coinfected with HBV, and those with decompensated cirrhosis were excluded. Patients received 300 mg of glecaprevir and 120 mg of pibrentasvir once daily for 8 weeks if no cirrhosis and 12 weeks if cirrhotic. SVR12 was achieved in 98/100 (98%; 95% CI, 93-99.4) of all patients, with one relapse (noncirrhotic patient with HCV genotype 3a) and one missing data. Baseline NS5A polymorphisms were detected in 26% of patients, but NS3 polymorphism was detected in only one patient. While the patient who relapsed had no baseline NS3 polymorphisms, there were baseline and treatment-emergent polymorphisms in NS5A. Overall, baseline polymorphisms in NS3 or NS5A did not seem to impact outcomes. The treatment was well-tolerated with no severe adverse events leading to treatment discontinuation. No severe adverse events were related to treatment. Common adverse events included headache (18%), pruritus (7%), nausea (6%), and fatigue (5%). Significant elevation of liver enzymes did not occur. The results of EXPEDITION-3 suggest that treatment with GLE/PIB for 8 weeks is safe and effective treatment-naïve patients without cirrhosis and 12 weeks in patients with compensated cirrhosis who are infected with HCV genotype 1-3.

EXPEDITION-8 (2019) was an open-label, single-arm, multicenter, phase 3b trial in Bulgaria, Canada, the Czech Republic, France, Greece, Hungary, Ireland, Israel, Italy, Poland, Portugal, Romania, Russia, Spain, Taiwan, the U.K., the U.S..[59] and Puerto Rico, and Vietnam. The study enrolled 343 adult treatment-naïve patients with compensated cirrhosis who had chronic HCV genotype 1 (67%), 2 (8%), 3 (18%), 4 (4%), 5 (<1%), or 6 (3%). About 8% of patients were Black. Patients coinfected with HBV or HIV and those with creatinine clearance below 50mL/min were excluded. Patients received total daily dose of 300 mg of glecaprevir and 120 mg of pibrentasvir with food for 8 weeks. SVR12 was achieved in 335/343 (98%; 95% CI, 96-99) of all patients, with no on-treatment virologic failures and 1 relapse. Six patients had missing SVR12 data and 1 patient prematurely discontinued treatment. SVR12 was achieved in 60/61 (98%; 95% CI, 91-99.7%) of patients with HCV genotype 3. All patients with documented baseline polymorphisms achieved SVR12. The patient who relapsed had genotype 3a with treatment-emergent A30K and Y93H in NS5A with no treatment-emergent RASs in NS3. Baseline NS3 or NS5A polymorphisms did not affect SVR12 rates. The treatment was well-tolerated with no discontinuation due to adverse events. Common adverse events included fatigue (9%), headache (8%), pruritus (8%), and nausea (6%). Significant elevation of liver enzymes occurred in only 1 patient. The results of EXPEDITION-8 suggest that treatment with GLE/PIB for 8 weeks is safe and effective in treatment-naïve patients with compensated cirrhosis who infected with HCV.

EXPEDITION-2 (2018) was an open-label, single-arm, multicenter, phase 3 trial in Australia, Belarus, France, Germany, Poland, Puerto Rico, Russia, the U.K., and the U.S.[60] The study enrolled 153 adult patients without cirrhosis (90%) or with compensated cirrhosis (10%) who were coinfected with HIV-1 and chronic HCV genotype 1 (63%), 2 (7%), 3 (17%), 4 (11%), or 6 (2%). While it was allowed, no patient was infected with genotype 5. About 18% of patients were treatment-experienced with a prior interferon- (16%) or sofosbuvir-based (2%) regimen. About 16% of patients were Black. All patients with genotype 3 were treatment-naïve. Patients coinfected with HBV and those with creatinine clearance below 50 mL/min were excluded. Patients received three coformulated tablets, each containing 100 mg of glecaprevir and 40 mg of pibrentasvir by mouth once daily

(total daily dose of 300 mg of glecaprevir and 120 mg of pibrentasvir) for 8 weeks if they did not have cirrhosis or 12 weeks if they had cirrhosis. Coadministration of GLE/PIB with HIV regimens that induce P-glycoprotein and cytochrome P450 (e.g., efavirenz) were not allowed due to drug interactions. SVR12 was achieved in 150/153 (98%; 95% CI, 96-100) of all patients, with no relapses. Baseline polymorphism in NS3 or NS5A did not affect SVR12. The treatment was well-tolerated with no discontinuation due to adverse events. Common adverse events included fatigue (12%), nausea (8%), and headache (8%). No significant elevation of liver enzymes occurred. The results of EXPEDITION-2 suggest that treatment with GLE/PIB for 8 weeks (if no cirrhosis) or 12 weeks (if cirrhosis) is safe and effective in both treatment-naïve and treatment-experienced (interferon regimens) patients coinfected with HCV and HIV-1.

EXPEDITION-5 (2019) was an open-label, non-randomized, multicenter, phase 3b trial in Canada, Germany, Greece, Italy, Poland, Puerto Rico, South Korea, Spain, Sweden, and the U.S..[61] The study enrolled 101 adult patients without cirrhosis (86%) or with compensated cirrhosis (14%) who had chronic HCV genotype 1 (55%), 2 (27%), 3 (15%), or 4 (4%). Both treatment-naïve (80%) and interferon-experienced (20%) patients were included. About 14% of patients were Black and 13% Asian. All patients were required to have an estimated GFR, as calculated by the MDRD method, of less than 45 mL/min/1.73 m^2. About 76% of patients were on dialysis, including hemodialysis (72%) and peritoneal dialysis (4%). Patients coinfected with HBV or HIV were excluded. Patients received 300 mg of glecaprevir and 120 mg of pibrentasvir once daily for 8 weeks if treatment-naïve and no cirrhosis, 12 weeks if treatment naïve with cirrhosis or treatment-experienced with cirrhosis except genotype 3, and 16 weeks if treatment experienced with genotype 3. SVR12 was achieved in 98/101 (97%; 95% CI, 92-99) of all patients, with no on-treatment virologic failure or relapse. One patient was lost to follow-up while 2 patients discontinued treatment. There were no baseline polymorphisms in NS3, but NS5A polymorphisms were detected in 45% of patients. However, baseline polymorphisms had no impact on outcomes. The treatment was well-tolerated. Although 12% of patients reported severe adverse events, none were related to treatment. Common adverse events included pruritus (16%), hypertension (6%), generalized pruritus (6%), and bronchitis (6%). One of the 2 patients who discontinued treatment had ileus and the other discontinued due to pruritus. Hypertension was not considered related to treatment as those patients had baseline hypertension. Significant elevation of liver enzymes did not occur. The results of EXPEDITION-5 suggest that treatment with GLE/PIB is safe and effective in treatment-naïve and interferon-experienced patients with advanced renal impairment with or without compensated cirrhosis who are infected with HCV.

MAGELLAN-1 Part 2 (2018) was an open-label, randomized, multicenter phase 3 trial in the United States, Europe, and Australia.[62] The study enrolled 91 adult patients with either no cirrhosis (70%) or with compensated cirrhosis (30%) who were infected with either HCV genotype 1 (96%) or 4 (4%) and had past failure on at least one NS3/4 protease inhibitor and/or NS5A inhibitor-based regimen (all patients were treatment-experienced). About 22% of patients were Black. The study randomly assigned 44 patients to received 3 pills of coformulated GLE/PIB (100 mg/40 mg each; total dose of 300 mg/120 mg) by mouth once daily for 12 weeks and assigned 47 patients to receive the same regimen for 16 weeks. Patients with creatinine clearance < 50mL/min and those with decompensated cirrhosis were excluded. Baseline characteristics were mostly similar between the two groups. More patients in the 12-week group had compensated cirrhosis. SVR12 was achieved in 39/44 (89%; 95% CI, 76-95) of patients in the 12-week treatment group and 43/47 (91%; 95% CI, 80-97) of patients in the 16-week treatment group. All 4 patients with genotype 4 achieved SVR. Out of the 87 patients with genotype 1, 4 had relapses in the 12-week group and none in the 16-week group. Out of 5 patients with genotype 1 who had on-treatment failures, 1 was in the 12-week group in 4 were in the 16-week group. All of these patients had prior experience with an NS5A-based regimen. Patients who had prior experience with only NS3/4A protease inhibitors (i.e., NS5A inhibitor-naïve patients) had an SVR rate of 100%. Patients who had prior experience with only NS5A inhibitors had an SVR rate of 88% (95% CI, 64-97) in the 12-week group and 94% (95% CI, 74-99) in the 16-week group. Patients who had prior experience with both NS3/4A protease inhibitors and NS5A inhibitors had an SVR rate of 79% (95% CI, 52-92) in the 12-week group and 81% (95% CI, 57-93) in the 16-week group. Viral sequencing data were available for 88 patients, 44 patients in each group. The SVR rate was 100% in patients with no baseline substitutions in either NS3 or NS5A, or with substitutions in NS3 alone. The SVR rate in patients with baseline substitutions in NS5A alone was 83% (95% CI, 64-93) in the 12-week group (2 out of 24 patients had failure) and 96% (95% CI, 79-99) in the 16-week group (1 out of 23 patients had failure). The treatment was well-tolerated, with no patient discontinuing GLE/PIB due to adverse events. Although 71% of patients reported adverse events, 65% were mild. No serious adverse events were related to study drugs. The most common adverse event was headache in 14% of patients in the 12-week group and 23% of patients in the 16-week group. There were no laboratory abnormalities in either group. An important limitation of this study is the lack of patients with prior experience with elbasvir/grazoprevir and sofosbuvir/velpatasvir, which were not available at the time of this study. The results of MAGELLAN-1 Part 2 suggest that treatment of HCV genotype 1 with GLE/PIB for 12 weeks is safe and effective in patients with only NS3/4A inhibitor prior experience. However, in patients with NS5A inhibitor prior experience (or patients with both NS3/4A protease and NS5A inhibitor prior experience), 12 weeks of treatment is effective in those without a baseline substitution in NS5A, whereas those who have a baseline substitution in NS5A would benefit from 16 weeks of ribavirin-free GLE/PIB treatment.

MAGELLAN-2 (2018) was an open-label, single-arm, multicenter, phase 3 trial in Australia, Canada, Italy, New Zealand, Puerto Rico, Spain, Taiwan, the U.K., and the U.S.[63] The study enrolled 100 adult patients without cirrhosis who had received primary liver (80%) or kidney (20%) transplant and had chronic HCV genotype 1 (57%), 2 (13%), 3 (24%), 4 (4%), or 6 (2%). While it was allowed, no patient was infected with genotype 5. About 34% of patients were treatment-experienced almost all with a prior interferon-based regimen (32%). All patients with genotype 3 were treatment-naïve. Patients coinfected with HBV or HIV and those with creatinine clearance below 30 mL/min were excluded. Patients received three coformulated tablets, each containing 100 mg of glecaprevir and 40 mg of pibrentasvir by mouth once daily (total daily dose of 300 mg of glecaprevir and 120 mg of pibrentasvir) for 12 weeks. The most commonly used immunosuppressive agent was tacrolimus (68%). SVR12 was achieved in 98/100 (98%; 95% CI, 95-100) of all patients, with 1 relapse and 1 on-treatment virologic failure. While baseline polymorphisms were not detected in NS3, they were detected in NS5A, including Y93H in GT3. The patient who had relapse had baseline Y93H polymorphism in NS5A and treatment-emergent Y56H in NS3. Overall, baseline polymorphism in NS3 or NS5A did not affect SVR12, although only 3 patients had GT3 Y93H in NS5A. The treatment was well-tolerated with 1 discontinuation unrelated to treatment. Common adverse events included fatigue (22%), headache

(22%), nausea (12%), pruritus (12%), and diarrhea (10%). Significant elevation of liver enzymes occurred in only 1 patient. Unrelated to GLE/PIB, 1 patient had elevation of total bilirubin and creatinine likely due to drug interaction between clarithromycin and tacrolimus. The results of MAGELLAN-2 suggest that treatment with GLE/PIB for 12 weeks is safe and effective in both treatment-naïve and treatment-experienced noncirrhotic patients who have received liver or kidney transplant and are infected with HCV.

HCV-TARGET (2019) was an open-label, randomized, multicenter, pragmatic phase 3b trial in the U.S.[64] The study enrolled 177 adult patients without cirrhosis (72%) or with compensated cirrhosis (28%) who had chronic HCV genotype 1 and had failed previous treatment with sofosbuvir plus either ledipasvir (94%), velpatasvir (6%), or dacltatasvir (<1%). Only 5% of patient shad prior NS3 inhibitor exposure. About 44% of patients were Black, 8% had received liver transplantation (with no cirrhosis), and 5% had HIV coninfection. Patients previous treated concurrently with NS3 and NS5A inhibitors, coinfected with HBV, and those with decompensated cirrhosis were excluded. Patients received 300 mg of glecaprevir and 120 mg of pibrentasvir once daily. Noncirrhotic patients received either 12 weeks of 16 weeks of treatment. Cirrhotic patients received either 12 weeks of treatment (with the addition of ribavirin) or 16 weeks of treatment. All patients with prior NS3 inhibitor exposure received 16 weeks of treatment. Overall, SVR12 was achieved in 162/177 (91.5%) of all patients, including in 88/99 (89%) of patients receiving 12 weeks and in 74/78 (95%) of patients receiving 16 weeks of treatment. One patient died from HCC. Of the 14 patients who failed treatment, 9 had relapse, 4 had breakthrough virologic failure, and 1 had reinfection. For noncirrhotic patients, SVR12 was achieved in 70/78 (90%; 95% CI, 81-95) of patients receiving 12 weeks and in 46/49 (94%; 95% CI, 83-98) of patients receiving 16 weeks of treatment. For cirrhotic patients, SVR12 was achieved in 18/21 (86%; 95% CI, 65-95) of patients receiving 12 weeks and in 28/29 (97%; 95% CI, 83-99) of patients receiving 16 weeks of treatment. The addition of ribavirin did not seem to improve outcomes. All patients with prior NS3 inhibitor exposure achieved SVR12. About half of the patients had baseline polymorphisms in NS3 and about three quarter had baseline NS5A polymorphisms. While baseline NS3 polymorphisms had no impact on outcomes, baseline NS5A polymorphisms were present in 12 out of 14 patients with virologic failure. The treatment was well-tolerated with no severe adverse events leading to treatment discontinuation. No severe adverse events were related to treatment. Common adverse events included fatigue (23%), headache (21%), and nausea (10%). Significant elevation of liver enzymes did not occur, except in one patient who had new diagnosis of advanced HCC. The results of HCV-TARGET suggest that treatment with GLE/PIB for 16 weeks is safe and effective in sofosbuvir and NS5A inhibitor-experienced patients with or without compensated cirrhosis who are infected with HCV genotype 1.

MAGELLAN-3 (2019) is an ongoing open-label, non-randomized, multicenter, phase 3b trial.[65] The study enrolled patients (23 patients as of this publication) who failed GLE/PIB treatment in a parent study to receive GLE/PIB plus SOF plus ribavirin. About 30% of patients had compensated cirrhosis, 61% had HCV genotype 3, 30% genotype 1, and 9% genotype 2. About 9% of patients were Asian and 4% Black. Patients with genotype 3, compensated cirrhosis, and/or prior NS5A or NS3 inhibitor received 16 weeks of treatment. Everyone else received 12 weeks of treatment. SVR12 was achieved in 22/23 (96%; 95% CI, 79-99), with only 1 relapse (genotype 1a) and no on-treatment virologic failure. Baseline NS3 and NS5A polymorphisms were present in 22% and 91% of patients, respective, and 61% had polymorphisms in both NS3 and NS5A. While there were no baseline NS3 polymorphisms identified in the patient who relapsed, NS5A polymorphisms (Q30K and Y93H) were identified at baseline and at the time of failure. The treatment was well-tolerated with no severe adverse events leading to treatment discontinuation. Common adverse events included headache (26%), pruritus (22%), dizziness (17%), irritability (17%), fatigue (13%), insomnia (13%), and upper respiratory tract infection (13%). Significant elevation of liver enzymes occurred in only 1 patient. No patient developed hemoglobin level reduction to less than 8 g/dL. The results of MAGELLAN-3 suggest that treatment with GLE/PIB plus SOF plus RBV for 12 or 16 weeks is safe and effective in GLE/PIB-experienced patients with or without compensated cirrhosis who are infected with HCV genotype 1, 2, or 3.

TARGET 3D Cohort 2 (2020) was an open-label, single-arm, multicenter trial in Australia, England, and New Zealand.[66] The study enrolled 30 treatment-naïve adult patients without cirrhosis who had recent HCV genotype 1 (83%), 3 (7%), or 4 (10%) infection within 12months. About 13% of patients were Asian and 77% of patients were coinfected with HIV. Patients with chronic liver disease, HCC, HBV coinfection, or those with creatinine clearance <50 mL/min were excluded. Patients received 300 mg of glecaprevir and 120 mg of pibrentasvir once daily for 6 weeks. SVR12 was achieved in 27/30 (90%; 95% CI, 73-98) of all patients, with 1 relapse (genotype 1a), 1 patient died due to illicit drug overdose, and 1 patient lost to follow-up. Among patients with HIV, SVR12 was achieved in 20/23 (87%; 95% CI, 66-97). NS3 or NS5A polymorphisms were not detected at baseline or posttreatment week 12 in the patient with relapse. The treatment was well-tolerated with no severe adverse events leading to treatment discontinuation. No severe adverse events were related to treatment. Common adverse events included fatigue (10%), diarrhea (7%), nasopharyngitis (7%), rash (7%), and rhinitis (7%). The results of TARGET 3D Cohort 2 suggest that treatment with GLE/PIB for 6 weeks is safe and effective in noncirrhotic patients recently infected with HCV genotype 1, 3, or 4 within the past 12months.

MYTHIC (2020) was an open-label, single-arm, multicenter trial the U.S.[67] The study enrolled 30 adult HCV-noninfected patients without cirrhosis who had an eGFR <15 mL/min/1.73 m2 (based on MDRD equation) or were on dialysis and were receiving a kidney transplant from HCV-positive deceased donors. About 30% of patients were Black. Only 15 donors had genotype data available, which included genotype 1, 2, or 4. Patients with chronic liver disease and those with HIV or HBV coinfection were excluded. Patients received 300 mg of glecaprevir and 120 mg of pibrentasvir once daily for 8 weeks, starting as early as post-operative day 2-5. At the beginning of treatment, 23/29 (79%) patients tested had detectable HVC RNA. SVR12 was achieved in 30/30 (100%) of all patients. The treatment was well-tolerated in the post-transplant period. No severe adverse events were related to treatment. Common adverse events included dizziness (23%), hypertension (23%), hyperglycemia (17%), hyperkalemia (17%), hypotension (17%), nausea (17%), and vomiting (17%). The results of MYTHIC suggest that post-kidney transplant treatment with GLE/PIB for 8 weeks is safe and effective in noncirrhotic patients receiving kidney transplantation from HCV-positive deceased donors.

DORA Part 1 (2020) was an open-label, non-randomized, multicenter, phase 2/3 trial.[68] The study enrolled 48 adolescent patients 12-17 years of age without cirrhosis who had chronic HCV genotype 1 (28%), 2 (6%), 3 (9%), and 4 (6%). Both treatment-naïve (77%), and treatment-experienced (23%), all with prior interferon-regimen exposure, patients were included. About 13% of patients were Asian

and 9% Black. While it was allowed, no patient had cirrhosis and no HIV coinfection. Patients coinfected with HBV, and those with decompensated cirrhosis were excluded. Patients received 300 mg of glecaprevir and 120 mg of pibrentasvir once daily with food. Most patients received treatment for 8 weeks while 3 treatment-experienced patients with genotype 3 received treatment for 16 weeks. SVR12 was achieved in 47/47 (100%; 95% CI, 92-100) of all patients, with no virologic failures. Baseline NS5A polymorphisms were detected in 25% of patients, but NS3 polymorphism was detected in none of the patients. Baseline polymorphisms had no impact on outcomes. The treatment was well-tolerated with no severe adverse events leading to treatment discontinuation. No severe adverse events were related to treatment. Common adverse events included nasopharyngitis (26%), upper respiratory tract infection (19%), headache (17%), fatigue (11%), oropharyngeal pain (11%), and pyrexia (11%). Significant elevation of liver enzymes did not occur. The results of DORA Part 1 suggest that treatment with GLE/PIB for 8 weeks is safe and effective in treatment-naïve and treatment-experienced (interferon regimens) adolescent patients without cirrhosis who are infected with HCV genotype 1-4.

DORA Part 2 (2021) was an open-label, non-randomized, multicenter, phase 2/3 trial [69]. The study enrolled 81 children 3-11 years of age without cirrhosis who had chronic HCV genotype 1 (72%), 2 (3%), 3 (23%), and 4 (3%). Most patients were treatment-naïve (98%) with only 2 treatment-experienced patients, both with prior interferon-regimen exposure. About 18% of patients were Asian and 4% Black. While it was allowed, no patient had cirrhosis and only 1 patient had HIV coinfection. Patients coinfected with HBV, and those with decompensated cirrhosis were excluded. There were 3 cohorts in the study. Patients in cohort 2 (aged 9 to 11years or weighing 20-44kg) received 250 mg of glecaprevir and 100 mg of pibrentasvir once daily with food. Patients in cohort 3 (aged 6 to 8 years or weighing 20-29kg) received 200 mg of glecaprevir and 80 mg of pibrentasvir once daily with food. Patients in cohort 4 (aged 3 to 5years or weighing 12-19kg) received 150 mg of glecaprevir and 60 mg of pibrentasvir once daily with food. Most patients received treatment for 8 weeks while 2 patients with genotype 3 received treatment for 12-16 weeks. SVR12 was achieved in 77/80 (96%; 95% CI, 90-99) of all patients, with 1 virologic failure. There was no virologic failure on the final GLE/PIB dose ratio of 50 mg/20 mg. The one patient with relapse received the initial dose ratio of GLE/PIB 40 mg/15 mg for 8 weeks and had baseline NS5A K30R and V31M polymorphism as well as treatment-emergent NS5A Y93H. Although the taste of the formulation was disliked by 82% of participants, there were only 2 premature discontinuations. The treatment was well-tolerated with no severe adverse events leading to treatment discontinuation. Only one patient discontinued treatment due to drug-related rash, which was nonsevere. No severe adverse events were related to treatment. Common adverse events included vomiting (14%), headache (14%), and diarrhea (10%). Significant elevation of liver enzymes did not occur. The results of DORA Part 2 suggest that treatment with GLE/PIB at a dose ratio of 50 mg/20 mg is safe and effective in treatment-naïve and treatment-experienced (interferon regimens) adolescent patients without cirrhosis who are infected with HCV genotype 1-4.

Lastly, GLE/PIB has been extensively evaluated in Asian HCV patient population. In a phase 1 trial consisting of healthy white, Chinese, and Japanese adult subjects, it was shown that race or ethnicity has no clinically meaningful impact on GLE/PIB exposures, safety, or tolerability.[37] CERTAIN-1 (2017) was an open-label, multicenter phase 3 trial that enrolled 219 Japanese adult patients without cirrhosis (83%) or with compensated cirrhosis (17%) who were infected with HCV genotype 1 to receive treatment with GLE/PIB or ombitasvir/paritaprevir/ritonavir.[70] About 28% of patients were treatment-experienced, all with interferon regimens. SVR12 was achieved in 218/219 (99.5%) of all patients. Cirrhotic patients received 12 weeks of treatment with 100% SVR12 rate. Patients treated with ombitasvir/paritaprevir/ritonavir also received 12 weeks of treatment with 100% SVR12 rate. The remaining patients received 8 weeks of GLE/PIB with SVR12 rate of 99.2% (128/129), with one patient being lost to follow up. GLE/PIB was well tolerated with no adverse events leading to discontinuation of treatment and no significant elevation of liver enzymes. CERTAIN-1 Substudy 2 enrolled 18 Japanese adult patients with compensated cirrhosis infected with HCV genotype 2 to receive 12 weeks of GLE/PIB.[71] SVR12 was achieved in all patients and was well tolerated. Reported separately, CERTAIN-1 Substudy 2[72] also enrolled patients with HCV genotype 3 (N=12), severe kidney disease (N=12), or prior DAA-failure (N=33). Noncirrhotic patients with severe kidney disease infected with genotype 1 or 2 received 8 weeks of treatment. Everybody else received 12 weeks of treatment. SVR12 was achieved in 31/33 (93.9%) of patients with prior DAA-failure with one relapse and one on-treatment virologic failure, 12/12 (100%) of patients with severe kidney disease, and 10/12 (83.3%) of patients with genotype 3 with 2 relapses.

CERTAIN-2 (2018) was an open-label, multicenter phase 3 trial that enrolled 136 Japanese adult patients without cirrhosis who were infected with HCV genotype 2 to receive treatment with GLE/PIB for 8 weeks or sofosbuvir plus ribavirin for 12 weeks.[71] About 17% of patients were treatment-experienced, with interferon regimens. SVR12 was achieved in 88/90 (97.8%) of patients receiving GLE/PIB, with one patient lost to follow-up and one patient prematurely discontinuing treatment due to grade 2 nausea and vomiting. SVR12 was achieved in 43/46 (93.5%) of patients receiving sofosbuvir plus ribavirin, with 2 relapses and one patient prematurely discontinuing treatment due to grade 1 malaise. Overall, GLE/PIB was well tolerated with no significant elevation of liver enzymes and only 1 patient discontinuing treatment due to non-serious adverse events. Again, GLE/PIB was well tolerated with no serious adverse events and no significant elevation of liver enzymes.

VOYAGE-1 (2020) genotype 1-6 without cirrhosis was a randomized, double-blind, placebo-controlled, multicenter study in China, South Korea, and Singapore.[73] The study enrolled 545 adult Asian patients without cirrhosis and with estimated GFR above 50 mL/min (as calculated using a modified MDRD equation for Asian populations) who were infected with chronic HCV genotype 1 (49%), 2 (39%), 3 (6%), or 6 (6%). Patients with HIV-2 or HBV coinfections were excluded. About 20% of patients were treatment-experienced, including 19% with a prior interferon-based regimen and 1% with a prior sofosbuvir-based regimen. Patients were randomized in a 2:1 ratio to receive GLE/PIB 100 mg/40 mg once daily with food or placebo for 8 weeks or 16 weeks if treatment-experienced with genotype 3. Baseline characteristics were mostly similar between the two groups, with more treatment-experienced patients in the intervention group. SVR12 was achieved in 352/362 (97.2%; 95% CI, 95.5-98.9) of all patients who received treatment, with 6 relapses, 2 on-treatment virologic failures, 1 premature discontinuation, and 1 missing data. Baseline NS3 polymorphisms were not present in any of the 8 patients with virologic failure, but 3 of them had treatment-emergent substitutions in NS3. Baseline NS5A polymorphisms were present in 5 of the 8 patients, with 6 having treatment-emergent substitutions in NS5A. Five of the 8 patients had HCV genotype 3b with 4 having

NS5A-Y93H variant at the time of failure. Overall, SVR12 rate was numerically lower in genotype 3b compared to genotype 3a. However, sample sizes were small and further evaluation is warranted. The treatment was well-tolerated with no discontinuation due to adverse events. One patient receiving treatment had significant elevation of liver enzymes compared to several patients who received placebo. The results of VOYAGE-1 suggest that treatment with GLE/PIB is safe and effect in both treatment-naïve and treatment-experienced (interferon regimens) Asian patients without cirrhosis infected with HCV.

VOYAGE-2 (2020) was an open-label, single-arm, multicenter study in China and South Korea.[73] The study enrolled 160 adult Asian patients with compensated cirrhosis and with estimated GFR above 50mL/min (as calculated using a modified MDRD equation for Asian populations) who were infected with chronic HCV genotype 1 (53%), 2 (33%), 3 (9%), 4 (1%), or 6 (4%). Patients with HIV-2 or HBV coinfections were excluded. About 31% of patients were treatment-experienced, including 30% with a prior interferon-based regimen and 1% with a prior sofosbuvir-based regimen. Patients receive GLE/PIB 100 mg/40 mg once daily with food or placebo for 12 weeks (16 weeks if treatment-experienced with genotype 3). SVR12 was achieved in 159/160 (99.4%; 95% CI, 98-100) of all patients, with 1 relapse. Baseline polymorphisms did not affect outcomes. However, there was only 1 virologic failure in this study. The treatment was well-tolerated with only 1 discontinuation due to adverse events. Only one patient receiving treatment had significant elevation of liver enzymes. The results of VOYAGE-2 suggest that treatment with GLE/PIB is safe and effect in both treatment-naïve and treatment-experienced (interferon regimens) Asian patients with compensated cirrhosis infected with HCV.

Collectively, these clinical trials show that treatment with GLE/PIB is very effective and safe. An integrated analysis of 9 phase 2 and 3 trials including 2041 patients without cirrhosis infected with HCV genotype 1-6 found an SVR12 rate of 98%, including a cure rate of 99% with 12 weeks and 98% with 8 weeks of GLE/PIB treatment.[74] The results were similar for treatment-naïve, treatment-experienced, and HIV-coinfected patients. For patient infected with HCV genotype 3 specifically, an integrated analysis of 5 phase 2 or 3 trials including 693 patients found an SVR12 rate of 95% in treatment-naïve patients without cirrhosis receiving 8 weeks of GLE/PIB, 97% in treatment naïve patients with cirrhosis receiving treatment for 12 weeks, 90% in treatment-experienced, noncirrhotic patients receiving 12 weeks of treatment, 95% in treatment-experienced, noncirrhotic patients receiving 16 weeks of treatment, and 94% in treatment-experienced patients with compensated cirrhosis receiving 16 weeks of treatment.[75] For patients with compensated cirrhosis specifically, an integrated analysis of 9 phase 2 and 3 trials including 308 patients infected with HCV genotype 1-6 found an SVR12 rate of 96% [76]. For elderly patients aged 65 years or older, an integrated analysis of 9 phase 2 and 3 trials including 328 elderly patients infected with HCV genotype 1-6, including treatment-naïve (60%), treatment-experienced (40%), and those with compensated cirrhosis (20%), found an SVR12 rate of 98% with 8-16 weeks of treatment.[77] For patients with psychiatric disorders (64% depression, 27% anxiety disorders), an integrated analysis of phase 2 and 3 trials including 789 patients with HCV genotype 1-6, with or without compensated cirrhosis, found an SVR12 rate of 97%.[78] Moreover, for patients with HCV genotype 1-6 receiving opioid substitution therapy, an integrated analysis of phase 2 and 3 trials including 157 patients found an SVR12 rate of 96%.[79] Likewise, an integrated analysis of 7 phase 3 trials including 98 recent and 610 former drug users, found an SVR12 rate of 93% among recent users and 97% among former drug users.[80]

Furthermore, a systematic review and meta-analysis of 13 phase 2 and 3 trials including 3082 patients with chronic HCV genotype 1-6 found an SVR12 rate of 98%, including 97% in treatment-naïve and 98% in treatment-experienced patients.[81] The rates were similar for patients without cirrhosis and those with compensated cirrhosis, for patients without kidney disease and those with severe kidney disease, as wells as for patients coinfected with HIV, all at 99% with 8-12 weeks of treatment. These results were confirmed in another systematic review and meta-analysis of 21 phase 3 clinical trials including 4817 patients with HCV genotype 1-6, which found an SVR12 rate of 97%.[82] Moreover, real-world data from Italy,[83-86] Germany,[87] Scotland,[88] Austria,[86] Belgium,[86] France,[86] Greece,[86] Poland,[86] Portugal,[86] Switzerland,[86] Israel,[86] Taiwan,[89,90] Japan,[91-100] and the U.S.[88,101] confirm the efficacy and safety of GLE/PIB in patients with chronic HCV genotype 1-6, including those on hemodialysis[90,92,97,98] and recipients of liver transplantation.[93] Although there have been a few case reports of acute liver injury, including a case of elevated liver enzymes in a non-cirrhotic patient,[102] a case report of severe hyperbilirubinemia and jaundice in a patient with compensated cirrhosis,[103] and a case of jaundice and fatigue,[104] it is difficult to attribute these to GLE/PIB treatment given the pathology of HCV infection itself. There has also been a case report of angioedema,[105] possibly due to drug-drug interaction with sitagliptin. Overall, 8-16 weeks of GLE/PIB is very safe and well tolerated with a high rate of adherence of about 97%.[106] There are even beneficial effects, including reduced triglyceride and plasma glucose,[107] and improved anemia (increased hemoglobin) in patients undergoing intermittent hemodialysis.[97]

Resistance

Glecaprevir is a second-generation HCV NS3/4A protease inhibitor with a high barrier to resistance. Mutations in NS3 generally result in poor fitness and eventually return to low or undetectable levels with time.[108] *In vitro* resistance profile of glecaprevir demonstrated selection of A156T/V in genotypes 1a, 1b, 2a, 2b, 3a, and 4a, and mutation at D168 in genotypes 3a, 5a, and 6a [34]. Polymorphisms at A156 can cause >100-fold reduction in susceptibility to glecaprevir in most genotypes, whereas polymorphisms at D168 can cause >30-fold reduction in susceptibility to glecaprevir.[34] While A156T and A156V in NS3 reduced *in vitro* susceptibility to glecaprevir, it was at the cost of low replication efficiency.[34] Therefore, they may have insignificant effect on treatment outcomes. In EXPEDITION-1, only 1 patient had a relapse and this patient had no baseline or treatment-emergent substitutions in NS3.[48] In SURVEYOR-II Part 3, all 3 patients with virologic failure had treatment-emergent substitutions in NS3 (Y56H, A156G, or Q168R) and NS5A (A30K, L31F, or Y93H); patients with a baseline NS3 polymorphism had a SVR12 rate of 95% (18/19).[50] Given the small sample size, it was difficult to evaluate the impact of baseline polymorphisms on treatment outcome. In EXPEDITION-4, viral sequencing data were available for 96 patients and while 28 of these patients had baseline polymorphism in NS3 or NS5A, none of them had virologic failure.[51] In SURVEYOR-II Part 4, there were 2 relapses but there were no baseline or treatment-emergent substitutions in NS3.[49] In ENDURANCE-3, baseline NS3 polymorphisms were present in 11% of patients with sequence data available but was not associated with worse outcomes.[53] In ENDURANCE-5,6, baseline polymorphism in NS3 or NS5A did not affect treatment outcomes.[57] In EXPEDITOIN-3, baseline NS3 polymorphisms were detected in only one patient and it was not detected in the only patient who had a relapse.[58] In EXPEDITION-8, one patient relapsed but did not have baseline or treatment-emergent RAS in NS3.[59] In EXPEDITION-2, there were no relapses and baseline NS3 polymorphism did not affect SVR12.[60] In EXPEDITION-5, there were no relapses and no baseline NS3 polymorphisms.[61] In MAGELLAN-1 Part 2, the SVR12 rate

was 100% in patients with no baseline substitutions in either NS3 or NS5A, or with substitutions in NS3 alone.[62] In MAGELLAN-2, 1 patient had a relapse and 1 had on-treatment virologic failure, but there were no baseline NS3 polymorphisms in any patients.[63] However, the patient with relapse had treatment-emergent Y56H in NS3. In HCV-TARGET, about half of the patients had baseline polymorphisms in NS3 but had no impact on outcomes.[64] In MAGELLAN-3, baseline NS3 polymorphisms were present in 22% of patients and 61% of patients had polymorphisms in both NS3 and NS5A.[65] However, there was no baseline NS3 polymorphisms identified in the only patient who relapsed. In TARGET 3D Cohort 2, NS3 polymorphisms were not detected at baseline or posttreatment week 12 in the patient with relapse.[66] In DORA Part 1, none of the patients had baseline NS3 polymorphis. [68] In a pooled resistance analysis of 8 phase 2 and 3 trials, baseline polymorphisms (e.g., Q168R, Q80R, Q80K) in NS3 did not impact treatment outcomes in patients infected with genotype 1-6, except for treatment-experienced patients with genotype 3 who benefited from a 16-week regimen compared to a 12 week regimen.[109] Of note, A156, D168, and Q80R in GT3 were not detected at baseline in any patients and Q168R was rarely detected in 0.7% of patients. In this analysis, half of the GT3a-infected patients with virologic failure had treatment-emergent substitutions in NS3 (Y56H, Q80R, A156G, or Q168L/R).[109] In an integrated analysis of CERTAIN-1 and CERTAIN-2, baseline NS3 polymorphisms (e.g., D168E/T/V) had no impact on treatment outcomes in genotype 1 and 2 and could not be assessed for genotype 3.[110] A systematic review and meta-analysis evaluating the impact of baseline NS3 polymorphisms did not find baseline A156 mutations in any of the patients, but treatment-emergent substitutions were found in 22% of patients.[111] Overall, baseline NS3 or NS5A polymorphisms decreased the odds of achieving SVR12 in genotype 3 patients, but it is not clear if NS3 polymorphisms alone contribute to this reduction.

Pibrentasvir is a second-generation HCV NS5A inhibitor with a high barrier to resistance. Unlike other NS5A inhibitors, pibrentasvir does not select single-position NS5A substitutions.[112] Treatment-emergent NS5A substitutions resistant to pibrentasvir are almost exclusively double-position substitutions.[112] *In vitro* resistance profile of pibrentasvir demonstrated that it remains active against common NS5A substitutions that confer resistance to other NS5A inhibitors (e.g., K30, M31).[36,55,56,109] Y93H mutation in genotype 3b can reduce susceptibility to pibrentasvir >6000 times.[109] Mutations in NS5A leading to resistance typically preserve viral fitness and last long after the end of failed treatment, particularly in genotype 1a and 3.[113] Therefore, they may have significant effect on treatment outcomes. In EXPEDITION-1, only 1 patient with genotype 1a had a relapse and this patient had baseline Y93N substitution and treatment-emergent Q30R-H58D substitutions in NS5A.[48] In SURVEYOR-II Part 3, all 3 patients with virologic failure had treatment-emergent substitutions in NS3 and NS5A (A30K, L31F, or Y93H); however, patients with a baseline NS5A polymorphism had a SVR12 rate of 100% (15/15).[50] Given the small sample size, it was difficult to evaluate the impact of baseline polymorphisms on treatment outcome. In EXPEDITION-4, viral sequencing data were available for 96 patients and while 28 of these patients had baseline polymorphism in NS3 or NS5A, none of them had virologic failure [51]. In SURVEYOR-II Part 4, there were 2 relapses but there were no treatment-emergent substitutions but both had baseline M31 polymorphism in NS5A.[49] M31 polymorphism has been shown to confer resistance to other NS5A inhibitors such as ledipasvir and daclatasvir.[55,56] However, there were 21 patients in this study with HCV GT 2 having this polymorphism at baseline and SVR12 was achieved in 90% of them. In ENDURANCE-3, SVR12 was achieved in 5/5 (100%) and 10/11 (91%) in the 8-week and 12-week GLE-PIB groups in patients with baseline GT3 Y93H variant.[53] In patients with baseline GT3 A30K variant, SVR12 was achieved in 12/16 (75%) and 9/10 (90%) in the 8-week and 12-week GLE-PIB groups. In ENDURANCE-5,6, baseline polymorphism in NS3 or NS5A did not affect treatment outcomes.[57] In EXPEDITOIN-3, baseline NS5A polymorphisms were detected in 26% of patients and the only patient who had a relapse had baseline and treatment-emergent polymorphisms in NS5A.[58] Overall, baseline polymorphisms in NS3 or NS5A did not seem to impact outcomes. In EXPEDITION-8, one patient with genotype 3a relapsed and had treatment-emergent A30K and Y93H in NS5A [59]. Baseline NS3 or NS5A polymorphisms did not affect SVR12 rates. In EXPEDITION-2, there were no relapses and baseline NS5A polymorphism did not affect SVR12.[60] In EXPEDITION-5, baseline NS5A polymorphisms were detected in 45% of patients but had no impact on outcomes.[61] In MAGELLAN-1 Part 2, the SVR12 rate was 100% in patients with no baseline substitutions in either NS3 or NS5A, or with substitutions in NS3 alone.[62] The SVR12 rate in patients with baseline substitutions in NS5A alone was 83% (95% CI, 64-93) in the 12-week group (2 out of 24 patients had failure) and 96% (95% CI, 79-99) in the 16-week group (1 out of 23 patients had failure). In MAGELLAN-2, 1 patient with baseline Y93H polymorphism in NS5A had a relapse and 1 had on-treatment virologic failure.[63] However, the patient with relapse also had treatment-emergent Y56H in NS3. Overall, baseline polymorphism in NS3 or NS5A did not affect SVR12, although only 3 patients had GT3 Y93H in NS5A. In HCV-TARGET, about three quarter of the patients had baseline polymorphisms in NS5A and were present in 12 out of 14 patients with virologic failure.[64] In MAGELLAN-3, baseline NS5A polymorphisms were present in 91% of patients and 61% of patients had polymorphisms in both NS3 and NS5A.[65] NS5A polymorphisms (Q30K and Y93H) were identified at baseline and at the time of failure in the only patient who relapsed. In TARGET 3D Cohort 2, NS5A polymorphisms were not detected at baseline or posttreatment week 12 in the patient with relapse.[66] In DORA Part 1, baseline NS5A polymorphisms were detected in 25% of patients but had no impact on outcom.[68] In a pooled resistance analysis of 8 phase 2 and 3 trials, baseline Y93 substitution in NS5A was detected in 5% of patients infected with genotype 1, 3, or 6, but did not impact treatment outcomes.[109] However, numerically lower SVR12 rate was observed in patients with NS5A A30K who received 8 weeks of treatment compared to 12 weeks of treatment. However, the difference does not seem to be clinically significant.[109] In an integrated analysis of CERTAIN-1 and CERTAIN-2, baseline NS5A polymorphisms (e.g., Y93H, L31F/I/M/V, P32deletion) had no impact on treatment outcomes in genotype 1 and 2 and could not be assessed for genotype 3.[110] A systematic review and meta-analysis evaluating the impact of baseline NS5A polymorphisms found decreased odds of achieving SVR12 in genotype 3 patients with A30K and Y93H substitutions.[111] Therefore, treatment-experienced patients with genotype 3 who are more likely to have these substitutions benefit from 16 weeks of treatment with no clinical need for genotype testing.

Discussion and conclusion

HCV infection affects millions of people worldwide with a substantial disease burden. While there have been great advancements in HCV therapy, certain populations remain difficult to treat. Pan-genotypic, ribavirin-free GLE/PIB combination has the advantage of shorter duration of treatment of 8 weeks for most patients regardless of genotype, including those with ESKD. It can also be used in children over the age of 3years. However, it cannot be used in patients with decompensated cirrhosis. The evidence from clinical trials as well as real-world data suggest high rates of SVR12 (95-99%)

for most patients. Due to its high barrier to resistance, GLE/PIB is generally an option for most patients who have failed other HCV treatments. Glecaprevir-resistance associated mutations in NS3 are associated with a fitness cost are unlikely to have clinical significance. Pibrentasvir-resistance associated mutations in NS5A (e.g., Y93H), on the other hand, preserve viral fitness and are more likely to be clinically significant in patients who have failed prior NS5A inhibitors. The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) guidelines for HCV currently recommend daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for 8 weeks for most treatment-naïve non-cirrhotic patients except for people living with HIV who are coinfected with HCV genotype 5 or 6 (Table 3). The guidelines recommend 12 weeks of treatment for these patients likely due to very limited number of such patients included in the studies that evaluated 8 weeks of treatment. However, 8 weeks of treatment is very likely to be as effective as 12 weeks for such patients. In addition, 12 weeks of treatment is recommended for all HCV-HIV coinfected cirrhotic patients. Finally, 16 weeks of treatment is recommended for patients who have failed prior NS5B polymerase inhibitor (i.e., sofosbuvir) in combination with interferon or NS5A inhibitor, but not in patient with genotype 3 who are more likely to have Y93H substitutions. GLE/PIB is also not recommended for patient with prior sofosbuvir and NS3/4A protease inhibitor failure, due to lack of efficacy data. For treatment-experienced patients, especially NS5A-experienced patients, sofosbovir-velpatasvir-voxilaprevir is generally preferred over GLE/PIB due to shorter 12 weeks of treatment and proven efficacy data.[114] Regardless, GLE/PIB has an essential place in the treatment of HCV, which is vital for achieving World Health Organization's 2030 elimination targets.[1]

Table 3 AASLD-IDSA Recommendations for Glecaprevir-Pibrentasvir Use

Prior treatment	No cirrhosis	Compensated cirrhosis	Post liver or kidney transplantation
Treatment-naïve	GT 1-4: 8 weeks (even if HIV positive) GT 5-6: 8 weeks if HIV-negative, otherwise 12 weeks	8 weeks if HIV-negative, otherwise 12 weeks	12 weeks
Interferon-experienced	Same as above	Same as above	Same as above
Elbasvir/grazoprevir-experienced	16 weeks	Same as no cirrhosis	Not recommended
Sofosbuvir-experienced	16 weeks	Same as no cirrhosis	Not recommended
Sofosbuvir/NS5A inhibitor-experienced	Not recommended for GT3, otherwise 16weeks	Same as no cirrhosis	Not recommended
Sofosbuvir/NS3/4A protease inhibitor-experienced	Not recommended	Not recommended	Not recommended
Glecaprevir/Pibrentasvir-experienced	16 weeks (add sofosbuvir and ribavirin)	Same as no cirrhosis	Not recommended

GT, genotype

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Conflicts of interest

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References

1. Spearman CW, Dusheiko GM, Hellard M, et al. Hepatitis C. *Lancet.* 2019;394(10207):1451-1466.
2. Thomas DL. Global Elimination of Chronic Hepatitis. *N Engl J Med.* 2019;380(21):2041-2050.
3. Rosen HR. Chronic hepatitis C infection. *N Engl J Med.* 2011;364(25):2429-2438.
4. FakhriRavari A, Malakouti M, Brady R. Interferon-Free Treatments for Chronic Hepatitis C Genotype 1 Infection. *J Clin Transl Hepatol.* 2016;4(2):97-112.
5. Petruzziello A, Marigliano S, Loquercio G, et al. Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes. *World J Gastroenterol.* 2016;22(34):7824-7840.
6. Edlin BR, Eckhardt BJ, Shu MA, et al. Toward a more accurate estimate of the prevalence of hepatitis C in the United States. *Hepatology.* 2015;62(5):1353-1363.
7. Westbrook RH, Dusheiko G. Natural history of hepatitis C. *J Hepatol.* 2014;61(1S):S58-S68.
8. Aisyah DN, Shallcross L, Hully AJ, et al. Assessing hepatitis C spontaneous clearance and understanding associated factors-A systematic review and meta-analysis. *J Viral Hepat.* 2018;25(6):680-698.
9. Butt AA, Yan P, Lo Re V, et al. Liver fibrosis progression in hepatitis C virus infection after seroconversion. *JAMA internal medicine.* 2015;175(2):178-185.
10. Rajbhandari R, Jun T, Khalili H, et al. HBV/HIV coinfection is associated with poorer outcomes in hospitalized patients with HBV or HIV. *J Viral Hepat.* 2016;23(10):820-829.v
11. Chen JY, Feeney ER, Chung RT. HCV and HIV co-infection: mechanisms and management. *Nat Rev Gastroenterol Hepatol.* 2014;11(6):362-371.v
12. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology.* 2013;57(4):1333-1342.

13. Choo QL, Kuo G, Weiner AJ, et al. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science.* 1989;244(4902):359-362.v

14. Liang TJ, Ghany MG. Current and future therapies for hepatitis C virus infection. *N Engl J Med.* 2013;368(20):1907-1917.

15. Scheel TK, Rice CM. Understanding the hepatitis C virus life cycle paves the way for highly effective therapies. *Nat Med.* 2013;19(7):837-849.v

16. Moradpour D, Penin F, Rice CM. Replication of hepatitis C virus. *Nat Rev Microbiol.* 2007;5(6):453-463.

17. 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(1):318-327.

18. Borgia SM, Hedskog C, Parhy B, et al. Identification of a Novel Hepatitis C Virus Genotype From Punjab, India: Expanding Classification of Hepatitis C Virus Into 8 Genotypes. *J Infect Dis.* 2018;218(11):1722-1729.

19. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology.* 2015;61(1):77-87.

20. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA.* 2012;308(24):2584-2593.

21. Backus LI, Boothroyd DB, Phillips BR, et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clin Gastroenterol Hepatol.* 2011;9(6):509-516 e501.

22. Berenguer J, Rodriguez E, Miralles P, et al. Sustained virological response to interferon plus ribavirin reduces non-liver-related mortality in patients coinfected with HIV and Hepatitis C virus. *Clin Infect Dis.* 2012;55(5):728-736.

23. Berenguer J, Alvarez-Pellicer J, Martin PM, et al. Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfected with human immunodeficiency virus and hepatitis C virus. *Hepatology.* 2009;50(2):407-413.

24. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med.* 2007;147(10):677-684.

25. Poynard T, McHutchison J, Manns M, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. *Gastroenterology.* 2002;122(5):1303-1313.

26. Cacoub P, Desbois AC, Comarmond C, Saadoun D. Impact of sustained virological response on the extrahepatic manifestations of chronic hepatitis C: a meta-analysis. *Gut.* 2018;67(11):2025-2034.v

27. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. *Ann Intern Med.* 2013;158(5 Pt 1):329-337.

28. Li J, Gordon SC, Rupp LB, et al. Sustained virological response to hepatitis C treatment decreases the incidence of complications associated with type 2 diabetes. *Aliment Pharmacol Ther.* 2019;49(5):599-608.

29. Force USPST, Owens DK, Davidson KW, et al. Screening for Hepatitis C Virus Infection in Adolescents and Adults: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2020;323(10):970-975.

30. Schillie S, Wester C, Osborne M, et al. CDC Recommendations for Hepatitis C Screening Among Adults - United States, 2020. *MMWR Recomm Rep.* 2020;69(2):1-17.

31. Chan A, Patel K, Naggie S. Genotype 3 Infection: The Last Stand of Hepatitis C Virus. *Drugs.* 2017;77(2):131-144.

32. Mavyret(TM) [package insert]. AbbVie INC., North Chicago, IL; 2019.

33. Lawitz EJ, O'Riordan WD, Asatryan A, et al. Potent Antiviral Activities of the Direct-Acting Antivirals ABT-493 and ABT-530 with Three-Day Monotherapy for Hepatitis C Virus Genotype 1 Infection. *Antimicrob Agents Chemother.* 2015;60(3):1546-1555.v

34. Ng TI, Tripathi R, Reisch T, et al. In Vitro Antiviral Activity and Resistance Profile of the Next-Generation Hepatitis C Virus NS3/4A Protease Inhibitor Glecaprevir. *Antimicrob Agents Chemother.* 2018;62(1).v

35. Hubbard H, Lawitz E. Glecaprevir + pibrentasvir (ABT493 + ABT-530) for the treatment of Hepatitis C. *Expert Rev Gastroenterol Hepatol.* 2018;12(1):9-17.

36. Ng TI, Krishnan P, Pilot-Matias T, et al. In Vitro Antiviral Activity and Resistance Profile of the Next-Generation Hepatitis C Virus NS5A Inhibitor Pibrentasvir. *Antimicrob Agents Chemother.* 2017;61(5):e02558.

37. Lin CW, Dutta S, Ding B, et al. Pharmacokinetics, Safety, and Tolerability of Glecaprevir and Pibrentasvir in Healthy White, Chinese, and Japanese Adult Subjects. *J Clin Pharmacol.* 2017;57(12):1616-1624.

38. Oberoi RK, Zhao W, Sidhu DS, et al. A Phase 1 Study to Evaluate the Effect of Crushing, Cutting Into Half, or Grinding of Glecaprevir/Pibrentasvir Tablets on Exposures in Healthy Subjects. *J Pharm Sci.* 2018;107(6):1724-1730.

39. Pradaxa(R) [package insert]. Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT; 2018.

40. Forns X, Mensa FJ. Proton-pump inhibitors and glecaprevir plus pibrentasvir in HCV infection - Authors' reply. *Lancet Infect Dis.* 2017;17(12):1240.

41. Flamm S, Reddy KR, Zadeikis N, et al. Efficacy and Pharmacokinetics of Glecaprevir and Pibrentasvir With Concurrent Use of Acid-Reducing Agents in Patients With Chronic HCV Infection. *Clin Gastroenterol Hepatol.* 2019;17(3):527-535 e526.

42. Kosloski MP, Zhao W, Asatryan A, et al. No Clinically Relevant Drug-Drug Interactions between Methadone or Buprenorphine-Naloxone and Antiviral Combination Glecaprevir and Pibrentasvir. *Antimicrob Agents Chemother.* 2017;61(10).v

43. Kosloski MP, Wang H, Pugatch D, et al. Pharmacokinetics and safety of glecaprevir and pibrentasvir in HCV-negative subjects with hepatic impairment. *Eur J Clin Pharmacol.* 2019;75(2):217-226.v

44. Kwo PY, Poordad F, Asatryan A, et al. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis. *J Hepatol.* 2017;67(2):263-271.

45. Poordad F, Landis CS, Asatryan A, et al. High antiviral activity of NS5A inhibitor ABT-530 with paritaprevir/ritonavir and ribavirin against hepatitis C virus genotype 3 infection. *Liver Int.* 2016;36(8):1125-1132.

46. Gane E, Poordad F, Wang S, et al. High Efficacy of ABT-493 and ABT-530 Treatment in Patients With HCV Genotype 1 or 3 Infection and Compensated Cirrhosis. *Gastroenterology.* 2016;151(4):651-659 e651.

47. Poordad F, Felizarta F, Asatryan A, et al. Glecaprevir and pibrentasvir for 12 weeks for hepatitis C virus genotype 1 infection and prior direct-acting antiviral treatment. *Hepatology.* 2017;66(2):389-397.

48. 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(10):1062-1068.v

49. 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(3):417-426.

50. Wyles D, Poordad F, Wang S, et al. Glecaprevir/pibrentasvir for hepatitis C virus genotype 3 patients with cirrhosis and/or prior treatment experience: A partially randomized phase 3 clinical trial. *Hepatology.* 2018;67(2):514-523.

Citation: FakhriRavari A, Nguyen MHC, Garcia RC. Glecaprevir-pibrentasvir for chronic hepatitis C – a clinical review. *Gastroenterol Hepatol Open Access.* 2021;12(5):135–150. DOI: 10.15406/ghoa.2021.12.00473

51. Gane E, Lawitz E, Pugatch D, et al. Glecaprevir and Pibrentasvir in Patients with HCV and Severe Renal Impairment. *N Engl J Med.* 2017;377(15):1448-1455.

52. Kosloski MP, Zhao W, Marbury TC, et al. Effects of Renal Impairment and Hemodialysis on the Pharmacokinetics and Safety of the Glecaprevir and Pibrentasvir Combination in Hepatitis C Virus-Negative Subjects. *Antimicrob Agents Chemother.* 2018;62(3):e01990-e01917.v

53. 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(4):354-369.

54. Fontana RJ, Lens S, McPherson S, et al. Efficacy and Safety of 8 Weeks of Glecaprevir/Pibrentasvir in Treatment-Naive, HCV-Infected Patients with APRI </= 1 in a Single-Arm, Open-Label, Multicenter Study. *Adv Ther.* 2019;36(12):3458-3470.

55. Cheng G, Tian Y, Doehle B, et al. In Vitro Antiviral Activity and Resistance Profile Characterization of the Hepatitis C Virus NS5A Inhibitor Ledipasvir. *Antimicrob Agents Chemother.* 2016;60(3):1847-1853.

56. Wang C, Jia L, O'Boyle DR, 2nd, et al. Comparison of daclatasvir resistance barriers on NS5A from hepatitis C virus genotypes 1 to 6: implications for cross-genotype activity. *Antimicrob Agents Chemother.* 2014;58(9):5155-5163.

57. Asselah T, Lee SS, Yao BB, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients with chronic hepatitis C virus genotype 5 or 6 infection (ENDURANCE-5,6): an open-label, multicentre, phase 3b trial. *Lancet Gastroenterol Hepatol.* 2019;4(1):45-51.

58. Peribanez-Gonzalez M, Cheinquer H, Rodrigues L, et al. Efficacy and safety of glecaprevir/pibrentasvir in treatment-naive adults with chronic hepatitis C virus genotypes 1-6 in Brazil. *Ann Hepatol.* 2021;20:100257.

59. 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(3):441-449.

60. 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(7):1010-1017.

61. Lawitz E, Flisiak R, Abunimeh M, et al. Efficacy and safety of glecaprevir/pibrentasvir in renally impaired patients with chronic HCV infection. *Liver Int.* 2020;40(5):1032-1041.

62. Poordad F, Pol S, Asatryan A, et al. Glecaprevir/Pibrentasvir in patients with hepatitis C virus genotype 1 or 4 and past direct-acting antiviral treatment failure. *Hepatology.* 2018;67(4):1253-1260.

63. 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(4):1298-1307.

64. Lok AS, Sulkowski MS, Kort JJ, et al. Efficacy of Glecaprevir and Pibrentasvir in Patients With Genotype 1 Hepatitis C Virus Infection With Treatment Failure After NS5A Inhibitor Plus Sofosbuvir Therapy. *Gastroenterology.* 2019;157(6):1506-1517 e1501.

65. Wyles D, Weiland O, Yao B, et al. Retreatment of patients who failed glecaprevir/pibrentasvir treatment for hepatitis C virus infection. *J Hepatol.* 2019;70(5):1019-1023.

66. Martinello M, Orkin C, Cooke G, et al. Short duration pan-genotypic therapy with glecaprevir-pibrentasvir for six weeks among people with recent HCV infection. *Hepatology.*2020;72(1):7-18.

67. Sise ME, Goldberg DS, Kort JJ, et al. Multicenter Study to Transplant Hepatitis C-Infected Kidneys (MYTHIC): An Open-Label Study of Combined Glecaprevir and Pibrentasvir to Treat Recipients of Transplanted Kidneys from Deceased Donors with Hepatitis C Virus Infection. *J Am Soc Nephrol.* 2020;31(11):2678-2687.

68. Jonas MM, Squires RH, Rhee SM, et al. Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Adolescents With Chronic Hepatitis C Virus: Part 1 of the DORA Study. *Hepatology.* 2020;71(2):456-462.

69. Jonas MM, Rhee S, Kelly DA, et al. Pharmacokinetics, safety, and efficacy of glecaprevir/pibrentasvir in children with chronic hepatitis C virus: part 2 of the DORA study. *Hepatology.* 2021;74(1):19-24.

70. Chayama K, Suzuki F, Karino Y, et al. Efficacy and safety of glecaprevir/pibrentasvir in Japanese patients with chronic genotype 1 hepatitis C virus infection with and without cirrhosis. *J Gastroenterol.* 2018;53(4):557-565.

71. Toyoda H, Chayama K, Suzuki F, et al. Efficacy and safety of glecaprevir/pibrentasvir in Japanese patients with chronic genotype 2 hepatitis C virus infection. *Hepatology.* 2018;67(2):505-513.

72. Kumada H, Watanabe T, Suzuki F, et al. Efficacy and safety of glecaprevir/pibrentasvir in HCV-infected Japanese patients with prior DAA experience, severe renal impairment, or genotype 3 infection. *J Gastroenterol.* 2018;53(4):566-575.

73. Wei L, Wang G, Alami NN, et al. Glecaprevir-pibrentasvir to treat chronic hepatitis C virus infection in Asia: two multicentre, phase 3 studies- a randomised, double-blind study (VOYAGE-1) and an open-label, single-arm study (VOYAGE-2). *Lancet Gastroenterol Hepatol.* 2020;5(9):839-849.v

74. 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(2):293-300.

75. Flamm S, Mutimer D, Asatryan A, et al. Glecaprevir/Pibrentasvir in patients with chronic HCV genotype 3 infection: An integrated phase 2/3 analysis. *J Viral Hepat.* 2019;26(3):337-349.

76. Gane E, Poordad F, Zadeikis N, et al. Safety and Pharmacokinetics of Glecaprevir/Pibrentasvir in Adults With Chronic Genotype 1-6 Hepatitis C Virus Infections and Compensated Liver Disease. *Clin Infect Dis.* 2019;69(10):1657-1664.

77. Foster GR, Asselah T, Kopecky-Bromberg S, et al. Safety and efficacy of glecaprevir/pibrentasvir for the treatment of chronic hepatitis C in patients aged 65 years or older. *PLoS One.* 2019;14(1):e0208506.v

78. 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(8):951-960.

79. Grebely J, Dore GJ, Alami NN, et al. Safety and efficacy of glecaprevir/pibrentasvir in patients with chronic hepatitis C genotypes 1-6 receiving opioid substitution therapy. *Int J Drug Policy.* 2019;66:73-79.

80. Foster GR, Dore GJ, Wang S, et al. Glecaprevir/pibrentasvir in patients with chronic HCV and recent drug use: An integrated analysis of 7 phase III studies. *Drug Alcohol Depend.* 2019;194:487-494.

81. Wang X, Fan X, Deng H, et al. Efficacy and safety of glecaprevir/pibrentasvir for chronic hepatitis C virus genotypes 1-6 infection: A systematic review and meta-analysis. *Int J Antimicrob Agents.* 2019;54(6):780-789.

82. Xu HQ, Wang CG, Xiao P, Gao YH. Efficacy and Safety of Glecaprevir/Pibrentasvir for Chronic Hepatitis C Patients: A Systematic Review and Meta-analysis. *J Clin Transl Hepatol.* 2020;8(3):267-276.

83. 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(3):379-387.

84. Soria A, Fava M, Bernasconi DP, et al. Comparison of three therapeutic regimens for genotype-3 hepatitis C virus infection in a large real-life multicentre cohort. *Liver Int.* 2020;40(4):769-777.

85. Persico M, Aglitti A, Milella M, et al. Real-life glecaprevir/pibrentasvir in a large cohort of patients with hepatitis C virus infection: The MISTRAL study. *Liver Int.* 2019;39(10):1852-1859.

Citation: FakhriRavari A, Nguyen MHC, Garcia RC. Glecaprevir-pibrentasvir for chronic hepatitis C – a clinical review. *Gastroenterol Hepatol Open Access.* 2021;12(5):135–150. DOI: 10.15406/ghoa.2021.12.00473

86. 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.

87. 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(8):1052-1059.

88. Lampertico P, Mauss S, Persico M, et al. Real-World Clinical Practice Use of 8-Week Glecaprevir/Pibrentasvir in Treatment-Naive Patients with Compensated Cirrhosis. *Adv Ther.* 2020;37(9):4033-4042.

89. Hsu SJ, Chiu MC, Fang YJ, et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir in Asian patients with chronic hepatitis C. *J Formos Med Assoc.* 2019;118(8):1187-1192.v

90. Liu CH, Yang SS, Peng CY, et al. Glecaprevir/pibrentasvir for patients with chronic hepatitis C virus infection and severe renal impairment. *J Viral Hepat.* 2020;27(6):568-575.

91. Osawa M, Imamura M, Teraoka Y, et al. Real-world efficacy of glecaprevir plus pibrentasvir for chronic hepatitis C patient with previous direct-acting antiviral therapy failures. *J Gastroenterol.* 2019;54(3):291-296.

92. Suda G, Hasebe C, Abe M, et al. Safety and efficacy of glecaprevir and pibrentasvir in Japanese hemodialysis patients with genotype 2 hepatitis C virus infection. *J Gastroenterol.* 2019;54(7):641-649.

93. Ueda Y, Kobayashi T, Ikegami T, et al. Efficacy and safety of glecaprevir and pibrentasvir treatment for 8 or 12 weeks in patients with recurrent hepatitis C after liver transplantation: a Japanese multicenter experience. *J Gastroenterol.* 2019;54(7):660-666.v

94. Sugiura A, Joshita S, Yamashita Y, et al. Effectiveness of Glecaprevir/Pibrentasvir for Hepatitis C: Real-World Experience and Clinical Features of Retreatment Cases. *Biomedicines.* 2020;8(4):74.

95. Ogawa E, Furusyo N, Nakamuta M, et al. Glecaprevir and pibrentasvir for Japanese patients with chronic hepatitis C genotype 1 or 2 infection: Results from a multicenter, real-world cohort study. *Hepatol Res.* 2019;49(6):617-626.

96. Sezaki H, Suzuki F, Hosaka T, et al. Initial- and re-treatment effectiveness of glecaprevir and pibrentasvir for Japanese patients with chronic hepatitis C virus-genotype 1/2/3 infections. *J Gastroenterol.* 2019;54(10):916-927.

97. Morishita A, Ogawa C, Moriya A, et al. Clinical outcomes of hepatitis C virus elimination using glecaprevir and pibrentasvir in hemodialysis patients: A multicenter study. *Hepatol Res.* 2020;50(5):557-564.v

98. Atsukawa M, Tsubota A, Toyoda H, et al. The efficacy and safety of glecaprevir plus pibrentasvir in 141 patients with severe renal impairment: a prospective, multicenter study. *Aliment Pharmacol Ther.* 2019;49(9):1230-1241.

99. Tamori A, Inoue K, Kagawa T, et al. Intention-to-treat assessment of glecaprevir + pibrentasvir combination therapy for patients with chronic hepatitis C in the real world. *Hepatol Res.* 2019;49(12):1365-1373.

100. Toyoda H, Atsukawa M, Watanabe T, et al. Real-world experience of 12-week direct-acting antiviral regimen of glecaprevir and pibrentasvir in patients with chronic hepatitis C virus infection. *J Gastroenterol Hepatol.* 2020;35(5):855-861.

101. 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(5):2267-2274.

102. Hammami MB, Aboushaar R, Alsabbagh E. Glecaprevir/pibrentasvir-associated acute liver injury in non-cirrhotic, chronic HCV infection without HBV co-infection. *BMJ Case Rep.* 2019;12(5).

103. Yoon JH, Kim SM, Kang G, Kim HJ, Jun CH, Choi SK. A case report of glecaprevir/pibrentasvir-induced severe hyperbilirubinemia in a patient with compensated liver cirrhosis. *Medicine (Baltimore).* 2019;98(39):e17343.

104. Hara T, Ohara T, Taniguchi M, et al. Severe liver injury associated with glecaprevir plus pibrentasvir therapy in a patient with treatment-naive hepatitis C virus infection. *Intern Med.* 2021;60(15):2437-2443.

105. Schneider A, Ramesh M. Angioedema following initiation of glecaprevir/pibrentasvir while on sitagliptin. *J Allergy Clin Immunol Pract.* 2019;7(6):2068-2069.

106. Brown A, Welzel TM, Conway B, et al. Adherence to pan-genotypic glecaprevir/pibrentasvir and efficacy in HCV-infected patients: A pooled analysis of clinical trials. *Liver Int.* 2020;40(4):778-786.

107. Tran TT, Mehta D, Mensa F, et al. Pan-Genotypic Hepatitis C Treatment with Glecaprevir and Pibrentasvir for 8 Weeks Resulted in Improved Cardiovascular and Metabolic Outcomes and Stable Renal Function: A Post-Hoc Analysis of Phase 3 Clinical Trials. *Infect Dis Ther.* 2018;7(4):473-484.

108. Pearlman B, Perrys M, Hinds A. Sofosbuvir/Velpatasvir/Voxilaprevir for Previous Treatment Failures With Glecaprevir/Pibrentasvir in Chronic Hepatitis C Infection. *Am J Gastroenterol.* 2019;114(9):1550-1552.

109. Krishnan P, Pilot-Matias T, Schnell G, et al. Pooled Resistance Analysis in Patients with Hepatitis C Virus Genotype 1 to 6 Infection Treated with Glecaprevir-Pibrentasvir in Phase 2 and 3 Clinical Trials. *Antimicrob Agents Chemother.* 2018;62(10).

110. Krishnan P, Schnell G, Tripathi R, et al. Integrated Resistance Analysis of CERTAIN-1 and CERTAIN-2 Studies in Hepatitis C Virus-Infected Patients Receiving Glecaprevir and Pibrentasvir in Japan. *Antimicrob Agents Chemother.* 2018;62(2):e02217-17.

111. Singh AD, Maitra S, Singh N, et al. Systematic review and meta-analysis: impact of baseline resistance-associated substitutions on the efficacy of glecaprevir/pibrentasvir among chronic hepatitis C patients. *Aliment Pharmacol Ther.* 2020;51(5):490-504.

112. Ng TI, Pilot-Matias T, Tripathi R, et al. Resistance Analysis of a 3-Day Monotherapy Study with Glecaprevir or Pibrentasvir in Patients with Chronic Hepatitis C Virus Genotype 1 Infection. *Viruses.* 2018;10(9):e01249-18.

113. Zeuzem S, Mizokami M, Pianko S, et al. NS5A resistance-associated substitutions in patients with genotype 1 hepatitis C virus: Prevalence and effect on treatment outcome. *J Hepatol.* 2017;66(5):910-918.

114. FakhriRavari A, Park L. Sofosbuvir-Velpatasvir-Voxilaprevir for Chronic Hepatitis C - A Review. *Gastroenterol Hepatol Open Access.* 2017;7(5):00254.

Citation: FakhriRavari A, Nguyen MHC, Garcia RC. Glecaprevir-pibrentasvir for chronic hepatitis C – a clinical review. *Gastroenterol Hepatol Open Access.* 2021;12(5):135–150. DOI: 10.15406/ghoa.2021.12.00473