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Glecaprevir/pibrentasvir expands reach while reducing cost and duration of hepatitis C virus therapy

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Abstract

Hepatitis C virus (HCV) treatments have dramatically progressed from poorly tolerated, moderately successful interferon-based therapies to highly effective all-oral interferon-free regimens. While sustained virologic responses have significantly improved with fixed-dose combinations (FDC) of these direct-acting antivirals (DAA), cost remains high and certain populations of patients remain difficult to treat. Glecaprevir (GLE, an NS3/4A protease inhibitor) and pibrentasvir (PIB, NS5A inhibitor) were recently approved as a FDC therapy for HCV, and have expanded reach, reduced cost, and in certain populations, reduced HCV treatment duration. GLE/PIB is effective across all genotypes, and has been shown to be effective in HIV-infected patients, patients with chronic kidney disease, and Child–Pugh A-compensated cirrhosis. GLE/PIB is also effective for a shortened duration of 8 weeks in treatment-naïve non-cirrhotic patients.

Keywords

Glecaprevir; Pibrentasvir; ABT-493; ABT-530; Mavyret; FDC

Introduction

The advent of direct-acting antivirals (DAA) has revolutionized hepatitis C virus (HCV) treatment in recent years. While many DAAs are now available, few span all HCV genotypes and special patient populations, including patients with cirrhosis or end-stage renal disease, organ transplant recipients, and treatment-experienced patients that make up the estimated 71 million HCV patients worldwide [1, 2]. On August 3, 2017, the United States Food and Drug Administration (US FDA) approved the fixed-dose combination of glecaprevir (GLE) and pibrentasvir (PIB) (brand name: Mavyret, Abbvie) for a wide variety

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Compliance with ethical standards

Conflict of interest Ameer Abutaleb declares that he has no conflict of interest. Shyam Kottilil declares that he has no conflict of interest. Eleanor Wilson declares that she has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

of indications, including all major HCV genotypes and several special patient populations (“Box 1”) [3]. GLE/PIB also boasts a shorter 8-week duration of therapy in non-cirrhotic treatment-naïve patients and has since been incorporated in the American Association for the Study of Liver Diseases (AASLD) guidelines as one of the first-line therapies for HCV treatment [4].

Background

HCV, which chronically infects 71 million people, is the leading cause of liver transplantation in the world, and is associated with significant morbidity and mortality when left untreated [1]. HCV treatment was historically very difficult, with poorly tolerated interferon (IFN)-based regimens that could last upwards of a year, and very modest rates of success, measured by rates of sustained virologic response (SVR), currently defined as the absence of plasma HCV RNA 12 weeks after completion of therapy [5]. Development of DAAs shortened therapy duration and improved SVR rates, opening the possibility of IFN-free regimens, a concept that excited both patients and providers. Current first-line HCV therapies include DAA combinations which achieve SVR rates of over 95%, both in clinical trials and real-world use [6, 7]. Efficacy, safety, tolerability, cost-effectiveness, and adherence have also all improved with DAA regimens [8–12].

DAAs act at different stages of the HCV life cycle and have shown to be most successful in HCV cure when used in combination [13]. Combination regimens typically include inhibitors which target the NS3/4A, NS5A, and NS5B viral proteins [6]. Several two-, three-, and four-drug IFN-free regimens have been used in patients across various clinical trials over the past several years [14]. Three items consistently explored across these trials were efficacy of treatment across HCV genotypes, optimal duration of treatment, and efficacy of treatment in special populations. Despite aggressive drug development programs, a safe and effective HCV therapy for all genotypes remained elusive until the US FDA approval of sofosbuvir/velpatasvir (SOF/ VEL) in June of 2016 [15]. While this was a major step, SOF/VEL cannot be used in certain populations of patients, such as patients with severe renal impairment. Many groups continue to attempt shortening HCV treatment duration below 12 weeks, and these efforts have brought mixed results [16, 17]. Among special populations of patients, cirrhosis remains as an impediment to achieving SVR [18], and progress in this area has been difficult.

GLE/PIB has been able to move the field in a positive direction in all three of these key areas (pangenotypic therapy, reducing treatment duration, expanding access to special populations). Specifically, it is approved for all HCV genotypes with all stages of fibrosis up to and including compensated cirrhosis, making it the second FDC drug bearing this indication. GLE/PIB can be administered as an 8-week course in non-cirrhotic, treatment-naïve patients, and it can be utilized in several special populations, including patients with severe renal impairment, patients on renal replacement therapy, transplant patients, and patients with prior treatment experience, both IFN-based and combination DAA-based therapies. There is no need for ribavirin (RBV) with GLE/PIB therapy. The majority of trials show that pretreatment existence of resistance-associated substitutions (RAS) does not play

an impact in SVR with GLE/PIB; however, a recent study from Japan shows that NS5A-P32 deletion in genotype 1b infection may be a risk factor for treatment failure [19].

GLE inhibits the serine NS3/4A protease and PIB inhibits the NS5A non-structural protein [20]. Their combination in HCV treatment has been very effective. NS3/4A is an important precursor to HCV replication and survival, while NS5A is critical in HCV replication, assembly, and release [21]. GLE has a half-life of 6 h, and PIB has a half-life of 13 h. GLE is metabolized by the CYP3A enzyme. Both GLE and PIB are primarily excreted in stool with minimal amounts of each in the urine [22].

Perhaps what is most notable about GLE/PIB is its cost. A full course of treatment with GLE/PIB is less than one half the cost of other fixed-dose combinations (FDC) on the market in the United States (Table 1), bearing the potential to completely change future cost of HCV treatment and payer preferences. GLE/PIB also has a favorable drug interaction profile and can be administered with amiodarone, unlike other FDC DAAs.

Summary of clinical trials

Several randomized and non-randomized trials evaluating GLE/PIB for treatment of HCV have been reported, with major populations studied and comparisons summarized in Tables 2 and 3. We detail the findings of these studies thematically below:

Optimal GLE/PIB dosing and the utility of RBV

The SURVEYOR-I study, part 1 [23] was a phase 2, non-randomized open-label study that enrolled 79 patients, 39 of them receiving GLE 200 mg with PIB 40 mg, and the other 40 receiving GLE 200 mg with PIB 120 mg. All patients had genotype 1, were non-cirrhotic, and not co-infected with HIV or HBV. About two-thirds were treatment naïve, and the remaining one third were prior null responders to PEG-IFN + RBV treatment. All but one patient (78/79, 98.7%) achieved SVR12; the one patient with virologic relapse was in the GLE/PIB 40 mg arm and was found to have emergent NS5A RAS Q30 K and H58D (Table 4).

SURVEYOR-II, part 1, done by the same group [23], was a randomized, open-label trial with seven total arms, each offering 12 weeks of HCV treatment. Patients in this trial had either genotype 2 or 3 HCV, and otherwise shared similar inclusion criteria as the patients in SURVEYOR-I. Across the arms, PIB dose varied between 40 mg and 120 mg, and GLE dose varied between 200 mg and 300 mg. Two arms had RBV as part of their treatment regimen, which was dosed at 1000 or 1200 mg per day according to body weight (less than or greater than 75 kilograms). All patients with genotype 2 HCV who completed treatment achieved SVR12 regardless of regimen (one patient was lost to follow-up; the remaining 74 patients all achieved SVR12, 98.7% SVR by ITT). Among genotype 3 patients, 95% (87/91) had SVR12 with GLE 300 mg/PIB 120 mg, while 90% (27/30) had SVR12 with GLE 200 mg/PIB 40 mg. RBV did not provide any significant improvement in SVR12 rates for either genotype. This trial laid the framework for the selected dose in future studies to be GLE 300 mg/PIB 120 mg. It also showed no advantage to including RBV in the treatment regimen for

patients without cirrhosis. Similarly, RBV did not improve SVR12 rates in the MAGELLAN-I, part 1 study done by Poordad and colleagues [24], which we describe later.

Shortening therapy from the standard 12 week course

Shortening HCV therapy without compromising its success has always been an objective for HCV providers as it confers many advantages including facilitating treatment for patients and reducing overall cost [25]. Several trials evaluated the efficacy of 8-week GLE/PIB treatment courses for a variety of HCV patient populations, all demonstrating positive results.

In SURVEYOR-I, part 2 [23], 33 (97%) of 34 non-cirrhotic genotype 1 HCV patients achieved SVR12 after 8 weeks of GLE/PIB (one patient achieved SVR4 but died prior to week 12 from adenocarcinoma). In SURVEYOR-II part 2, 98% (53/54) of genotype 2 non-cirrhotic patients achieved SVR12 after 8 weeks of GLE/PIB (one patient was lost to follow-up after treatment week 6 with undetectable RNA at that visit). 97% (28/29) of genotype 3 non-cirrhotic treatment-naïve patients achieved SVR12 after 8 weeks of GLE/PIB (one patient withdrew consent after 6 weeks on treatment). In another treatment arm of SURVEYOR-II (part 4), 97% (197/203) of non-cirrhotic genotype 2-, 4-, 5- or 6-infected patients achieved SVR after 8 weeks of GLE/PIB.

In ENDURANCE-I [26], a randomized, double-blind study, a head-to-head comparison was done between 8-week and 12-week courses of GLE/PIB for genotype 1-infected non-cirrhotic patients. Non-inferiority was demonstrated in the 8-week arm, with SVR12 rates of 99% by ITT (332/351 reached SVR12 primary endpoint) as compared to 99.7% by ITT (331/352 reached SVR12 primary endpoint) in the 12-week arm. There was no drop in SVR12 rate (100%) in the 8- or 12-week arms for HIV-co-infected (33/33) or treatment-experienced (3/3) subgroups. Similar results were shown for genotype 3-infected patients in ENDURANCE-3 [27], with 149 (95%) out of 157 patients achieving SVR12 (one patient had virologic breakthrough, five relapsed, and two were lost to follow-up). A high SVR12 rate of 99% (136/137) was demonstrated after 8 weeks of GLE/PIB in HIV-HCV co-infected patients with genotypes 1–6 in the EXPEDITION-2 study [28].

Shortening duration of GLE/PIB therapy to 8 weeks from 12 weeks was very successful in non-cirrhotic patients and did not compromise SVR12 rates. This was demonstrated across all HCV genotypes, in HIV-co-infected patients, and patients with treatment experience.

GLE/PIB efficacy across all genotypes

All HCV genotypes have been studied in GLE/PIB trials, although to varying degrees. The most extensively studied has been genotype 1, which is also the most prevalent HCV genotype globally, accounting for slightly less than half of all infections [29].

Half of the published studies looked at SVR12 after GLE/PIB therapy in genotype 1, 2, and 3 HCV (Table 1). Results were very favorable, showing that GLE/PIB was safe, well tolerated, and SVR12 rates were high (almost exclusively over 95%). Six studies enrolled patients with genotype 4, one study enrolled genotype 5, and two enrolled genotype 6, all

also showing favorable SVR12 rates. Aggregates of patient genotypes across studies varied, ranging from 32 genotype 5 patients to 1379 genotype 1 patients.

GLE/PIB utility in special populations

An ongoing challenge in HCV treatment is to sustain efficacy of treatment across all special populations, including patients co-infected with HIV, patients with cirrhosis, and patients with organ transplants. While many of these populations historically had much lower SVR rates, that paradigm is beginning to change with new therapies [30].

HIV co-infection—The ENDURANCE-I and EXPEDITION-II trials both enrolled HIV-HCV co-infected patients. In ENDURANCE-I, HIV-co-infected patients were enrolled if they were ARV naïve (HIV RNA below 1000 copies per ml and CD4 greater than or equal to 500/mm³) or on antiretroviral therapy with HIV RNA below detection limits. Depending on which arm patients were randomized to, they either received 8 or 12 weeks of GLE/PIB and were followed for SVR12. HIV-co-infected patients represented 5% of the total cohort (33 patients). All had functional cure, regardless of treatment duration.

EXPEDITION-II exclusively enrolled HIV-co-infected patients in a two parallel arm, open-label study. Non-cirrhotic patients ($n = 137$) received 8 weeks of GLE/PIB, and cirrhotic patients ($n = 16$) received 12 weeks. SVR12 in the non-cirrhotic arm was 99.3% (136/137, one patient had missing data), and 87.5% in the cirrhotic arm (14/16, one discontinuation for an adverse event and one HCV virologic breakthrough). There was no HIV virologic breakthrough.

Cirrhosis—Six trials enrolled patients with cirrhosis. In EXPEDITION-I [31], 146 genotype 1-, 2-, 4- and 6-infected patients with compensated cirrhosis were given 12 weeks of GLE/PIB. Treatment was well tolerated with no discontinuations from adverse events and 99% (145/146) achieved SVR12. One patient with genotype 1a was a prior non-responder to PEG-IFN + RBV and relapsed in the 8th week of treatment. We mentioned previously that 16 cirrhotic patients were enrolled in EXPEDITION-II and treated with 12 weeks of GLE/PIB. The SVR12 rate was 87.5% (14/16), with one discontinuation for an adverse event and one virologic breakthrough.

In SURVEYOR-I and II, part 2 [23], 82 patients with genotype 1 and 3-HCV with cirrhosis were enrolled to receive either 12 or 16 weeks of GLE/PIB with or without RBV (treatment was extended to 16 weeks in 4 patients who previously received PEG-IFN + RBV). Enrolled patients were not co-infected with HIV or HBV, but may have had prior treatment experience. SVR12 rates were all above 95% (26/27, 27/28, 27/27) in treatment groups, regardless of genotype or cirrhotic status. Two relapses occurred, one patient with genotype 1a and one with genotype 3, and were found to have emerging Y93N and M28G RAS, respectively. There were no failures in the GLE/PIB + RBV group.

In SURVEYOR-II part 3 [23], 40 treatment-naïve cirrhotic patients were enrolled to receive 12 weeks of GLE/PIB and compared with 47 treatment-experienced cirrhotic patients who received 16 weeks of GLE/PIB. SVR12 in the treatment-naïve arm was 98% (39/40, one

patient lost to follow-up) and 96% in the 16-week arm (45/47, one virologic breakthrough, one relapse).

The MAGELLAN-I, part 2 [32] and EXPEDITION-IV [33] study both enrolled cirrhotic patients; however, these were DAA failure and chronic kidney disease (CKD) focused trials and will be discussed in further detail in those respective sections.

Renal disease—EXPEDITION-IV [33] enrolled patients with renal impairment for HCV treatment. Exclusively enrolling patients with either stage IV or V CKD, 104 participants received 12 weeks of GLE/PIB in a single-arm, open-label study. All genotypes were represented, about 40% of the patients had treatment experience, and about 20% had cirrhosis. By intention-to-treat analysis, 102/104 (98%) had SVR12. One patient had treatment discontinuation due to diarrhea, and one was lost to follow-up. There were no virologic failures. CERTAIN-I, a Japanese study, had a group of 12 patients with severe renal impairment, defined as an estimated glomerular filtration rate less than 30 mL/min. All achieved SVR [19].

Organ transplantation—The MAGELLAN-II study [34] was a non-randomized open-label study specifically focusing on HCV-infected patients with solid organ transplants. One hundred patients from around the world that were recipients of either a liver or kidney transplant and on a stable immunosuppression regimen received 12 weeks of GLE/PIB and were followed for SVR12. No patient was cirrhotic, and there were no HIV or HBV co-infections. SVR12 rate was 98% (98/100). One patient was lost to follow-up, and one genotype 3a patient relapsed after 4 weeks of treatment.

Treatment experience and DAA failures—All of the currently published clinical trials on GLE/PIB included patients with prior treatment experience in their enrollment, mostly IFN-experienced, and comparable SVR rates were reproducibly shown when compared to treatment-naïve patients. What remained to be seen was the utility of GLE/PIB as a retreatment option in patients who previously failed DAA therapy.

MAGELLAN-I, part 1 [24] enrolled 50 total non-cirrhotic patients with prior failure to a DAA regimen (stratified by prior treatment, either NS5A-inhibitor experienced, NS3/4A PI-experienced + NS5A-inhibitor naïve, or other). Six patients were enrolled in a low-dose GLE/ PIB arm that was halted due to emerging data supporting use of a higher dose. Of the remaining patients, 22 received 12 weeks of GLE/PIB with RBV, and 22 received GLE/ PIB alone. SVR12 rate was 95% (21/22) in the GLE/PIB arm with RBV and 86% (19/22) in the arm without RBV. There were a total of two virologic failures in genotype 1a-infected patients. One patient relapsed in the RBV arm, and one had virologic breakthrough in the non-RBV arm. Two patients were lost to follow-up in the non-RBV arm. Over eighty percent of patients had baseline mutations in NS3 or NS5A; however, this did not seem to impact SVR12.

GLE/PIB retreatment in DAA failures were further explored in MAGELLAN-I part 2 [32], this time incorporating patients with cirrhosis. Forty-four non-cirrhotic HCV-infected patients with prior DAA failure (NS3/4A only, NS5A only, NS3/4A + NS5A combination)

received 12 weeks of GLE/PIB and were compared to 47 cirrhotic patients who received GLE/PIB for 16 weeks. The majority of patients were genotype 1-infected, and the majority had a baseline NS3 or NS5A mutation. SVR12 rates were 89 (39/44) and 91 (43/47) percent in the 12- and 16-week arms, respectively. There were nine virologic failures, 5 in the 12-week arm, and 4 in the 16-week arm. Patients with prior PI failure who were NS5A-inhibitor naïve had 100% SVR12 rates (14/14 in the 12-week arm and 13/13 in the 16-week arm), while lower SVR12 rates were found in who previously failed both PI and NS5A inhibitor (11/14, 79% in the 12-week arm and 13/16, 81% in the 16-week arm). Increasing treatment duration to 16 weeks in prior NS5A-inhibitor failures increased SVR12 rates from 88 to 94% (14/16 to 17/18). In CERTAIN-I, 31/33 (93.9%) patients with history of DAA failure achieved SVR [19].

Drug interaction studies

GLE/PIB has a favorable drug interaction profile and can be safely co-administered with many different medications. Co-administration of GLE/PIB with substrates of CYP3A, CYP1A2, CYP2C9, CYP2C19, CYP2D6, or UGT1A1, UGT1A4 in vitro did not result in any drug–drug interactions [22]. Weak CYP3A4 inhibition was noted to increase amiodarone exposure, and patients taking GLE/PIB while on amiodarone should be monitored by electrocardiogram or therapeutic drug monitoring. GLE/PIB co-administration with HMG-CoA reductase inhibitors increases their serum concentration at varying levels. Fluvastatin and pitavastatin should be administered at their lowest dose, and rosuvastatin dose should not exceed 10 mg. Pravastatin dose should be reduced by 50%, and patients should not take GLE/PIB with atorvastatin, lovastatin, or simvastatin. Co-administration of GLE/PIB with carbamazepine or efavirenz may reduce GLE/PIB concentrations, and taking these drugs in combination with GLE/PIB is not recommended [22]. Proton pump inhibitors (PPI) have been historically difficult to dose with other combination DAA therapies, but co-administration of GLE/PIB PPIs is safe and well tolerated [22].

Cost of therapy

An impediment to ubiquitous use of DAAs has always been their high price. While clinical practice guidelines certainly encourage DAA use for all HCV-infected patients, high price points set by pharmaceutical companies have ultimately led to restrictions by payers, largely limiting access to DAAs on a global scale [35]. GLE/PIB has been shown across several trials to be comparably effective to other DAAs and has the added benefit of having a much lower cost, giving it a very favorable cost/benefit ratio.

As more fixed-dose combinations become available, the price of HCV treatment has fallen. GLE/PIB's wholesale acquisition cost (WAC) is set at \$26,400 for an 8-week treatment course, which, while expensive, is much lower than other HCV treatment options [36]. While individual insurers often negotiate reduced rates [37], GLE/PIB's lower cost appears to allow other stakeholders to negotiate lower prices from manufacturers [38]. While the cost of therapy varies by insurer and location, the lower cost of GLE/PIB will likely increase treatment options and its availability in resource-limited countries [39].

Limitations

Currently, access to GLE/PIB in resource-limited countries is difficult and this may be an impediment if global use of GLE/PIB for HCV treatment. GLE/PIB is not recommended for use in patients with hepatic impairment (Child–Pugh B or C). There are also no data on GLE/PIB use in pregnancy or in pediatric patients.

Conclusions

GLE/PIB has been shown to be widely efficacious in treating HCV, with coverage that spans all genotypes and multiple special populations. It has dramatically reduced the cost of treatment compared to other available DAAs on the market and can be administered as a shortened therapy for treatment-naïve, non-cirrhotic patients. GLE/PIB is an excellent option for HCV treatment in notoriously difficult populations, including genotype 3-infected patients and patients with compensated cirrhosis. GLE/PIB has expanded access to treatment in patients with severe renal impairment, including those on renal replacement therapy. Further research is needed to determine utility of GLE/PIB therapy in HBV co-infected patients, and the role of RBV in combination with GLE/PIB for cirrhotic patients.

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Box 1.**List of US FDA-approved indications for prescribing GLE/PIB**

Treatment-naïve patients who are HCV genotype 1, 2, 3, 4, 5, or 6 AND

- Non-cirrhotic OR
- Have Child–Pugh A-compensated cirrhosis

Treatment-experienced patients who are HCV genotype 1 AND

- NS5A inhibitor experienced, NS3/4A protease inhibitor naïve OR
- NS3/4A protease inhibitor experienced, NS5A inhibitor naïve

Treatment-experienced patients who are HCV genotype 1,2,3,4,5, or 6 AND

- IFN, PEG-IFN, RBV and/or SOF experienced, but NS3/4A, NS5A inhibitor naïve

Table 1

US FDA-approved HCV regimens in the United States

	Harvoni	Viekira Pak	Zepatier	Epcus	Mavyret
Contains	LDV/SOF	PrOD	ELB/GRZ	SOF/VEL	GLE/PIB
Approved	October 2014	January 2015	January 2016	June 2016	August 2017
Duration	8–24 weeks	12–24 weeks	12–16 weeks	12–24 weeks	8–16 weeks
Cost (12 weeks)	\$94,500	\$83,319 ± RBV	\$5000 ± RBV	\$6700 ± RBV	\$74,760 ± RBV

Prices based on listed wholesale acquisition costs

LDV ledipasvir, *SOF* sofosbuvir, *PrOD* paritaprevir, ritonavir, ombitasvir, and dasabuvir, *ELB* elbasvir, *GRZ* grazoprevir, *VEL* velpatasvir, *GLE* glecaprevir, *PIB* pibrentasvir, *RBV* ribavirin

Table 2

Major GLE/PIB clinical trials, the populations they studied, and their major comparisons

Reference	Study	1st author, year	Targeted HCV populations	Major comparisons
[26, 27, 40]	ENDURANCE-I	Zeuzem, 2018	GT 1 without cirrhosis	8 vs. 12 wks of GLE/PIB
	ENDURANCE-II	Asselah, 2017	GT 2 without cirrhosis	Treatment naïve vs. experienced
	ENDURANCE-III	Zeuzem, 2018	GT 3 without cirrhosis	12 GLE/PIB vs. 12 wks SOF/DAC 8 vs. 12 wks GLE/PIB
	ENDURANCE-IV	Asselah, 2017	GT 4, 5, 6 without cirrhosis	None
[28, 31, 33]	EXPEDITION-I	Forns, 2017	GT 1, 2, 4, 5, 6 + cirrhosis	None
	EXPEDITION-II	Rockstroh, 2017	GT 1–6	HIV + HCV cirrhotics vs. non-cirrhotics *
[24, 32, 34, 41]	EXPEDITION-IV	Gane, 2017	HIV ± cirrhosis	None
	MAGELLAN-I, part 1	Poordad, 2017	GT 1–6 + stage 4–5 CKD	GLE 200 mg vs. GLE 300 mg
			GT 1	PIB 80 mg vs. PIB 120 mg
			DAA failures + cirrhosis	RBV vs. no RBV
[23, 33, 40, 42]	MAGELLAN-I, part 2	Poordad, 2017	GT 1, 4 DAA failures ± cirrhosis	12 vs. 16 wks of GLE/PIB
	MAGELLAN-II	Reau, 2017	GT 1–6 solid-organ transplants	None
	SURVEYOR-I, part 1	Kwo, 2017	GT 1 without cirrhosis	PIB 40 mg vs. PIB 120 mg
	SURVEYOR-I, part 2	Kwo, 2017	GT 1, 4, 5, 6 without cirrhosis	8 vs. 12 wks of GLE/PIB
	SURVEYOR-II, part 1	Kwo, 2017	GT 2, 3 without cirrhosis	GLE 200 mg vs. GLE 300 mg *
				PIB 40 mg vs. PIB 120 mg *
[19]	SURVEYOR-II, part 2	Kwo, 2017	GT 2, 3 without cirrhosis	RBV vs. no RBV
	SURVEYOR-II, part 3	Wyles, 2017	GT 2, 3 ± treatment exp.	8 wks of GLE/PIB vs. 12 wks of GLE/PIB
			GT 3 ± cirrhosis	Treatment naïve vs. experienced
			GT 3 ± treatment exp.	12 wks of GLE/PIB vs. 16 wks of GLE/PIB
	SURVEYOR-II, part 4	Asselah, 2017	GT 2, 4, 5, 6 ± treatment exp.	Treatment naïve vs. experienced
	SURVEYOR-I,II, part 2	Gane, 2016	GT 1, 3 + cirrhosis	None
	CERTAIN-I	Kumada, 2018	DAA failures Stage 4–5 CKD GT 3	GLE 200 mg vs. GLE 300 mg
				RBV vs. no RBV
				None

GT genotype, wks weeks, GLE glecaprevir, PIB pibrentasvir, vs versus, HIV human immunodeficiency virus, HCV hepatitis C virus, DAA direct-acting antiviral, RBV ribavirin, CKD chronic kidney disease, exp experience

* Started comparison groups had SVR rates that were significantly higher than their counterparts

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Table 3

Major GLE/PIB clinical trials SVR results by category

Study	Arm	SVR by ITT (%)
(a) Dosing and RBV use		
SURVEYOR-I, part 1	GLE 200 mg/PIB 40 mg	97
SURVEYOR-I, part 1	GLE 200 mg/PIB 120 mg	100
SURVEYOR-II, part 1	GLE 300 mg/PIB 120 mg	97
SURVEYOR-II, part 1	GLE 200 mg/PIB 120 mg	93
SURVEYOR-II, part 1	GLE 200 mg/PIB 120 mg + RBV	97
SURVEYOR-II, part 1	GLE 200 mg/PIB 40 mg	90
SURVEYOR-II, part 1	GLE 300 mg/PIB 120 mg	96
SURVEYOR-II, part 1	GLE 200 mg/PIB 120 mg	100
SURVEYOR-II, part 1	GLE 200 mg/PIB 120 mg + RBV	100
(b) Duration of therapy		
SURVEYOR-I, part 2	8 weeks of GLE/PIB	97
SURVEYOR-I, part 2	12 weeks of GLE/PIB	100
SURVEYOR-II, part 2	8 weeks of GLE/PIB	98
SURVEYOR-II, part 2	8 weeks of GLE/PIB	97
SURVEYOR-II, part 2	12 weeks of GLE/PIB	92
SURVEYOR-II, part 4	8 weeks of GLE/PIB	97
ENDURANCE-I	8 weeks of GLE/PIB	99
ENDURANCE-I	12 weeks of GLE/PIB	100
ENDURANCE-III	12 weeks of GLE/PIB	95
ENDURANCE-III	8 weeks of GLE/PIB	95
EXPEDITION-II	8 weeks of GLE/PIB	99
(c) HIV co-infection		
ENDURANCE-I	No cirrhosis	100
EXPEDITION-II	No cirrhosis	99
EXPEDITION-II	Compensated cirrhosis	88
(d) Cirrhosis		

Study	Arm	SVR by ITT (%)
EXPEDITION-I	GT 1, 2, 4, 5, 6	99
EXPEDITION-II	GT 1, 2, 3, 4, 6	88
SURVEYOR-I and II, part 2	GT 1	96
SURVEYOR-I and II, part 2	GT 3 without RBV	96
SURVEYOR-I and II, part 2	GT 3 with RBV	100
SURVEYOR-II, part 3	GT 3, treatment naïve	98
SURVEYOR-II, part 3	GT 3, treatment experience	96
(e) Renal disease		
EXPEDITION-IV	GT 1, 2, 3, 4, 5, 6	98
CERTAIN-I	GT 1, 2	100
(f) Organ transplantation		
MAGELLAN-II	GT 1, 2, 3, 4, 6	98
(g) DAA failure		
MAGELLAN-I, part 1	GLE/PIB with RBV	95
MAGELLAN-I, part 1	GLE/PIB without RBV	86
MAGELLAN-I, part 2	No cirrhosis	89
MAGELLAN-I, part 2	Compensated cirrhosis	91
CERTAIN-I	N/A	94

SVR sustained virologic response, ITT intention-to-treat, GLE glecaprevir, PIB pibrentasvir, GT genotype, RBV ribavirin, DAA direct-acting antiviral

GLE/PIB treatment decisions across various populations (Adapted with permission from [22])

Table 4

HCV genotype	Treatment duration (weeks)		Child–Pugh A-compensated cirrhosis	Child–Pugh B- or C-compensated cirrhosis	Special populations ^a
	Non-cirrhotic	Child–Pugh A-compensated cirrhosis			
(a) Treatment-naïve patients					
1	8	12		Don't treat	No modification
2	8	12		Don't treat	No modification
3	8	12		Don't treat	No modification
4	8	12		Don't treat	No modification
5	8	12		Don't treat	No modification
6	8	12		Don't treat	No modification
HCV genotype	Treatment experience	Treatment duration (weeks)		Special populations*	
		Non-cirrhotic	Compensated cirrhosis (Child–Pugh)		
(b) Treatment-experienced patients					
1	NS5A experience	16	16	Don't treat	No modification
	NS3/4A naïve				
	NS3/4A experience	12	12		
	NS5A naïve				
1,2,4,5,6	IFN or SOF based	8	12	Don't treat	No modification
3	Any	16	16	Don't treat	No modification

^aSpecial populations include HIV co-infection, solid organ transplant recipients, chronic kidney disease, direct-acting antiviral (DAA) failures