Glecaprevir/Pibrentasvir for HCV Genotype 3 Patients with Cirrhosis and/or Prior Treatment Experience: A Partially Randomized Phase III Clinical Trial

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ABBREVIATIONS: AEs, adverse events; CI, confidence interval; DAA, direct-acting antiviral; GT, genotype; IFN, interferon; LLOD, lower limit of detection; LLOQ, lower limit of quantification; SVR, sustained virologic response; SVR12, sustained virologic response at post-treatment week 12

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ABSTRACT

Background: This study assessed the efficacy and safety of ribavirin (RBV)-free coformulated glecaprevir/pibrentasvir (G/P) in patients with hepatitis C virus (HCV) genotype (GT) 3 infection with either prior treatment experience and/or compensated cirrhosis, a patient population with limited treatment options.

Methods: SURVEYOR-II, Part 3 was a partially-randomized, open-label, multicenter, phase 3 study. Treatment-experienced (prior interferon (IFN) or pegIFN ± ribavirin or SOF plus ribavirin ± pegIFN therapy) patients without cirrhosis were randomized 1:1 to receive 12 or 16 weeks of G/P (300 mg/120 mg) once daily. Treatment-naïve or treatment-experienced patients with compensated cirrhosis were treated with G/P for 12 or 16 weeks, respectively. The primary efficacy endpoint was the percentage of patients with sustained virologic response at post-treatment week 12 (SVR12). Safety was evaluated throughout the study.

Results: There were 131 patients enrolled and treated. Among treatment-experienced patients without cirrhosis, SVR12 was achieved by 91% (20/22; CI 72–97) and 95% (21/22; CI 78–99) of patients treated with G/P for 12 or 16 weeks, respectively. Among those with cirrhosis, SVR12 was achieved by 98% (39/40; CI 87–99) of treatment-naïve patients treated for 12 weeks, and 96% (45/47; CI 86–99) of patients with prior treatment experience treated for 16 weeks. No adverse events (AEs) led to discontinuation of study drug and no serious AEs were related to study drug.

Conclusions: Patients with HCV GT3 infection with prior treatment experience and/or compensated cirrhosis achieved high SVR12 rates following 12 or 16 weeks of treatment with G/P. The regimen was well tolerated.

Infection with hepatitis C virus (HCV) genotype (GT) 3 is associated with higher rates of liver steatosis(1-3), and achieving sustained virologic response (SVR) quantifiably reverses its progression in those patients.(4-6) GT3 has been shown as an independent predictor of fibrosis progression,(7, 8) and is associated with a higher incidence of hepatocellular carcinoma (HCC).(9) Thus, effective HCV treatment options are critical for patients with HCV GT3 infection, particularly those with advanced liver disease and/or prior treatment experience.

GT3 is considered the most difficult-to-cure genotype with currently available RBV-free direct-acting antiviral (DAA) regimens, particularly in patients with cirrhosis and/or prior treatment experience. Sofosbuvir (SOF) and daclatasvir (DCV) for 12 weeks resulted in suboptimal SVR12 rates in treatment-naïve and -experienced patients with HCV GT3 infection and compensated cirrhosis (58% and 69%, respectively);(10) addition of RBV and/or extended therapy duration modestly increased SVR12 rates in these populations.(11) Current treatment guidelines recommend SOF + DCV with or without RBV for 24 weeks in patients with GT3 infection and compensated cirrhosis.(12, 13) The DAA combination of SOF and velpatasvir (VEL) for 12 weeks resulted in SVR12 rates between 89 – 91% for HCV GT3-infected patients with compensated cirrhosis and/or prior treatment experience.(14) The American Association for the Study of Liver Diseases (AASLD) recommends viral resistance testing prior to treatment with SOF/VEL in treatment-naïve patients with compensated cirrhosis or in prior pegylated interferon (pegIFN)/RBV treatment experienced-patients without cirrhosis; coadministration of weight-based RBV is recommended if testing for Y93H is positive.(12) Additionally, AASLD recommends 12 weeks of SOF/VEL plus RBV, regardless of viral resistance testing, for prior pegIFN/RBV treatment experienced-patients with compensated cirrhosis, in part based on a modest increase in SVR12 rate observed with RBV coadministration in cirrhotic patients with prior IFN-based treatment experience.(15) The European Association for the Study of the Liver (EASL) recommends that patients with compensated cirrhosis and/or prior treatment experience who test positive for Y93H in NS5A should also have weight-based RBV coadministered with SOF/VEL.(13)

Glecaprevir (GLE) is an HCV NS3/4A protease inhibitor (PI) that has pangenotypic antiviral activity, with half-maximal effective concentration (EC_{50}) values ≤5 nanomolar across all major HCV GTs.(16) Pibrentasvir (PIB) is a novel pangenotypic NS5A inhibitor with EC_{50} values of <5 picomolar across all major HCV GTs, and a high barrier to resistance and maintains activity against single amino acid substitutions known to confer high degrees of resistance to earlier-generation NS5A inhibitors.(17, 18) Importantly, resistance-associated NS5A substitutions in HCV GT3, such as M28T, A30K, or Y93H, each confer less than 2.5-fold increase to the effective half-maximal concentration (EC_{50}) of PIB.(18, 19) In addition, both GLE and PIB have negligible renal excretion and do not require dose adjustment for patients with end-stage renal disease,(20) thus are suitable for HCV GT3-infected patients with severe renal impairment, for whom there are currently limited treatment options.

The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) recently approved the RBV-free, once-daily GLE/PIB (G/P) coformulation as a treatment for all six major HCV genotypes in patients without cirrhosis and with compensated cirrhosis.(21, 22) In phase 2 studies of patients with HCV GT3 infection, GLE and PIB for 12 weeks was well-tolerated and resulted in SVR12 rates of 92% and 100% in treatment-experienced patients without cirrhosis and treatment-naïve patients with compensated cirrhosis, respectively.(23) These results supported initiation of SURVEYOR-II Part 3, which further assessed the efficacy and safety of G/P in patients with HCV GT3 infection, including the most difficult-to-treat population: those with compensated cirrhosis and/or prior HCV treatment experience.

METHODS

Study overview and treatment. Part 3 of SURVEYOR-II (NCT02243293) was a phase 3, partially randomized, open-label, multicenter study that assessed the efficacy and safety of G/P in adults with chronic HCV GT3 infection, including those with compensated cirrhosis and/or prior HCV treatment experience. All patients signed informed consent, and the study was conducted in accordance with the International Conference on Harmonization guidelines and the ethics set forth by the Declaration of Helsinki. The full trial protocol is available as part of the online supplemental appendix.

Study design. A schematic of the trial design is outlined in **Figure 1** and flow of patients through the trial is shown in **Supporting Figure 1**. Treatment-experienced patients without cirrhosis were randomized 1:1 to receive either 12 or 16 weeks of coformulated GLE (discovered by AbbVie and Enanta) and PIB (G/P). Treatment-naïve or treatment-experienced patients with compensated cirrhosis received G/P for 12 or 16 weeks, respectively. For all patients, G/P was orally dosed once-daily as three 100 mg/40 mg tablets, for a total dose of 300 mg /120 mg.

Patient population. Patients were screened in the United States, Australia, Canada, France, New Zealand and the United Kingdom. Patients 18 years of age or older (no upper limit) were eligible if they had chronic HCV GT3 infection with HCV RNA >1000 IU/mL at screening. Patients were either treatment-naïve or treatment-experienced (previously treated with IFN or pegIFN ± RBV or SOF + RBV ± pegIFN regimens; those previously treated with NS5A or NS3/4A protease inhibitors were excluded). HCV genotype was assessed with the Versant® HCV Genotype Inno LiPA Assay, version 2.0 or higher, or Sanger sequencing of the NS5B region, if necessary. The absence of cirrhosis (e.g., METAVIR score ≤3, Ishak score ≤4) was determined by liver biopsy within 24 months prior to (or during) screening, transient elastography (eg, Fibroscan) score of <12.5 kPa within 6 months prior to (or during) screening, or a screening FibroTest score of ≤0.48 and an aspartate aminotransferase to platelet ratio index (APRI) <1. The presence of cirrhosis was delineated by prior histologic diagnosis of cirrhosis on liver biopsy

(eg, METAVIR score of >3 [including 3/4], Ishak score of >4), prior transient elastography (eg, Fibroscan) score of ≥14.6 kPa, or a screening FibroTest score of ≥0.75 and an APRI >2. Indeterminate Fibroscan or FibroTest scores required qualifying liver biopsy or Fibroscan (to confirm indeterminate FibroTest scores only) to determine cirrhosis status.

Patient exclusion criteria included coinfection with hepatitis B virus, human immunodeficiency virus, or non-GT3 HCV. Details on laboratory abnormality criteria (eg, alanine aminotransferase, platelets, and albumin), as well as all other inclusion and exclusion criteria, are shown in **Supporting Table 1**.

Assessment of Efficacy, Safety, and Virologic Resistance. The primary endpoint was the percentage of patients that achieved SVR12 (HCV RNA below the lower limit of quantification 12 weeks after the end of treatment). Secondary endpoints included the percentage of patients with on-treatment virologic failure and post-treatment relapse. Plasma samples were collected at screening, days 1 and 3, weeks 1 and 2, and every other week thereafter during the on-treatment period (or in the event of premature discontinuation), and at post-treatment weeks 2, 4, 8, 12, and 24. Plasma HCV RNA levels were determined for each collected sample using the Roche COBAS TaqMan® real-time reverse transcriptase PCR assay v2.0 with high pure system. The lower limit of detection (LLOD) for this assay was an HCV RNA of 15 IU/mL and the lower limit of quantification (LLOQ) was 25 IU/mL.

Patients receiving at least one dose of study drug were included in safety analyses, which included assessments of adverse events (AEs), vital signs, physical examinations, electrocardiograms, and laboratory tests. Treatment-emergent AEs were collected from the first administration of study drug until 30 days after study drug discontinuation. Assessment of the relatedness of each AE with respect to study drugs was determined by the treating physician, and the AE, as assigned by the study investigator, was classified using the MedDRA version 19.0 system organ class and preferred term.

Next-generation sequencing was conducted using a 15% detection threshold to detect the presence of baseline polymorphisms in NS3 and NS5A relative to subtype specific reference sequences. Treatment-emergent substitutions in NS3 and NS5A, defined as substitutions that were present at the time-of-failure were analyzed for the patients who had virologic failure. Additional information on resistance analyses is available in the Supporting Information.

Statistical analyses. No formal statistical hypothesis was to be tested in this study; for this reason, initial patient enrollment goals were not designed to power statistical comparisons, but were driven by availability of smaller patient subgroups within the study (eg, treatment-experienced patients with cirrhosis). The intent-to-treat population was defined as all patients receiving at least one dose of study drug, and was used to calculate the percentage of patients achieving SVR12 in each arm. Additional prespecified analyses assessed outcomes in subpopulations within or across arms (eg, treatment-experienced patients without cirrhosis). All confidence intervals (CI) were calculated as two-sided 95% CIs using the Wilson score method for binomial proportions. Statistical summaries were performed using SAS® software.

RESULTS

Baseline patient demographics. In total, 189 patients were screened between January 15th, 2016 and April 5th, 2016; 57 patients failed screening, and 131 patients with HCV GT3 infection were enrolled and treated (**Supporting Figure 1**). Forty-four treatment-experienced patients without cirrhosis were randomized (1:1) to receive either 12 or 16 weeks of G/P. Among patients with compensated cirrhosis, 40 treatment-naïve patients were assigned to G/P for 12 weeks, while 47 treatment-experienced patients were assigned to 16 weeks of G/P treatment. Overall, a majority of patients were male (67%) and white race (89%), and the mean baseline HCV RNA was 6.20 $\log_{10}$ IU/mL. Amongst patients with prior HCV treatment-experience (with or without cirrhosis), 46% (42/91) of patients had prior SOF-based treatment; 37 of them were previously treated with SOF plus RBV alone, while 5 patients were treated with SOF plus pegIFN/RBV. Baseline NS5A polymorphisms were detected in 24/129 (19%) patients. Demographics and baseline characteristics were comparable among the treatment-experienced patients without cirrhosis randomized to 12 or 16 weeks of treatment. Complete patient demographics and baseline characteristics are available in **Table 1**.

Efficacy. In the non-randomized patients with cirrhosis, treatment-naïve patients treated for 12 weeks had an SVR12 rate of 98% (39/40, 95% CI 87 – 99), with no virologic failures (one patient had missing SVR12 data due to being lost to follow up, but did achieve SVR4), and those with prior treatment experience had an SVR12 rate of 96% (45/47; 95% CI 86 – 99) after 16 weeks of G/P treatment (**Figure 2**). Treatment-experienced patients without cirrhosis received either 12 or 16 weeks of G/P treatment; the SVR12 rates were 91% (20/22; 95% CI 72 – 97) and 95% (21/22; 95% CI 78 – 99), respectively; within this population, the difference in SVR12 for patients receiving 12 and 16 weeks of treatment was -4.5% (95% CI -23.6 – 13.9) with 2 relapses and 1 relapse in each arm, respectively. One treatment-experienced patient with cirrhosis (16-week arm) had virologic breakthrough; this patient had study drug exposures greater than 50% lower than average at most study visits, with suspected non-compliance. Among all patients with virologic failure, treatment-emergent substitutions detected at the

time of failure included Y56H, A156G, or Q168R in NS3, and A30K, L31F or Y93H in NS5A (**Table 2**). On-treatment response at weeks 4, 8, 12, and 16 (as applicable) are shown in **Supporting Table 2**.

Patients with prior SOF-based treatment experience had a 98% (41/42; 95% CI 88 – 99) SVR12 rate. Patients with compensated cirrhosis had an SVR12 rate of 97% (84/87; 95% CI 90 – 99), compared to 93% (41/44; 95% CI 82 – 98) for those without cirrhosis (**Table 3**). Additionally, the SVR12 rate in those without or with baseline NS3 polymorphisms was 96% (105/109; 95% CI 91 – 99) and 95% (18/19; 95% CI 75 – 99), respectively. Among all patients with cirrhosis (including those with prior treatment experience), the SVR12 rate in those without or with baseline NS5A polymorphisms was 97% (68/70; 95% CI 90 – 99) and 100% (15/15; 95% CI 80 – 100), respectively. Among treatment-experienced patients without cirrhosis, the SVR12 rate in those without NS5A polymorphisms was 100% (34/34; 95% CI 90 – 100); for those with NS5A polymorphisms treated for 12 weeks or 16 weeks, 4/6 and 2/3 achieved SVR12, respectively (**Supporting Table 3**). Across all patients, baseline NS5A polymorphisms A30K/M/R/S/T/V and Y93H were the most frequent, detected in 12 (9.3%; 2 with A30K) and 8 (6%) patients, respectively (**Supporting Table 4**). Seven of 8 patients with Y93H in NS5A achieved SVR12 (**Supporting Table 3**). In addition, 10 of 12 patients with polymorphisms at NS5A amino acid position 30 achieved SVR12.

Safety, Adverse Events, and Laboratory Abnormalities. The majority of AEs were classified as mild and no patients prematurely discontinued study drug due to AEs (**Table 4**). Fatigue and headache were the only AEs reported in more than 10% of total patients across both treatment arms, at 22% and 19%, respectively. Six serious AEs were reported, none were attributed to study drugs by investigators, and none of the patients discontinued study drug (**Supporting Table 5**). The type and frequency of AEs appeared similar between 12 and 16 week durations of G/P treatment. No hepatic decompensation events were observed.

No patients experienced clinically significant alanine aminotransferase (ALT) elevations. Two treatment-experienced patients without cirrhosis (12-week treatment arm) with baseline elevated ALT (one had grade 2

and one grade 3 ALT levels at baseline) had post-nadir grade 3 increases in ALT (from a previous grade 2) within the first 8 days of treatment; this is consistent with the expected, physiologic range of fluctuation in patients with high baseline ALT levels. The ALT elevations were not associated with bilirubin elevations or adverse events, and thereafter steadily decreased without intervention or interruption of study drug. Both patients completed treatment and had SVR12. One patient with baseline elevated Grade 2 bilirubin had sporadic increases in total bilirubin with indirect predominance to Grade 3 at treatment weeks 1, 12, and 16, without concomitant ALT elevations. This patient completed treatment without interruption and had SVR12.

DISCUSSION

The patient population treated with G/P in Part 3 of SURVEYOR-II included some of the most difficult to treat patients with HCV infection, incorporating many current and historic negative predictors of response to HCV therapy; the treated population, including patients with HCV genotype 3, compensated cirrhosis, and prior treatment experience (including treatment with SOF-based regimens), was the largest such patient group to date.(10, 11, 14) Among patients with GT3 infection and compensated cirrhosis, treatment with 12 and 16 weeks of RBV-free G/P yielded high rates of SVR12 in treatment-naïve and –experienced patients, respectively. Additionally, the regimen was well tolerated with no serious adverse events related to study drug and no adverse events leading to study drug discontinuation.

Treatment options for patients with HCV GT3 infection and compensated cirrhosis and/or prior treatment experience are currently limited and often require testing for baseline polymorphisms, and/or coadministration of RBV, or treatment duration of 24 weeks to maximize SVR12 rates. Due to higher rates of relapse observed with SOF/VEL treatment in GT3-infected patients with NS5A polymorphisms, particularly those with Y93H (20% [3/15] relapse rate(24)), pre-treatment testing for the presence of Y93H is recommended when using this regimen for patients with treatment experience and/or cirrhosis.(12, 13) Coadministration of RBV with SOF/VEL is recommended: if a patient has prior SOF-containing therapy experience, if Y93H is present upon testing,(12, 13) or regardless of baseline polymorphism testing for patients with both treatment experience and cirrhosis.(12) Similarly, among GT3-infected patients with treatment experience and/or cirrhosis, RBV coadministration is recommended when using the combination of SOF plus DCV in patients with baseline Y93H or regardless of baseline polymorphism testing for patients with both prior treatment experience and compensated cirrhosis. Extended 24 week treatment duration of SOF/DCV is also recommended for all patients with cirrhosis.(10, 11) *In vitro*, the Y93H polymorphism results in a greater than 100-fold reduction in VEL susceptibility and more than 3700-fold reduction in DCV susceptibility.(24, 25) Similarly, susceptibility to VEL and

DCV is reduced by 16-fold and 117-fold, respectively, in the presence of A30K.(25) In contrast, these single A30K or Y93H polymorphisms confer minimal changes to *in vitro* PIB susceptibility (less than 2.5-fold each).(18, 19)

In this study, treatment with G/P for 12 and 16 weeks achieved 95% or greater rates of SVR12 in treatment-naïve and treatment-experienced patients, respectively. While treatment-naïve and treatment-experienced patients with cirrhosis were treated for 12 weeks and 16 weeks, respectively, treatment-experienced patients without cirrhosis were randomized to either 12 or 16 weeks of G/P treatment, achieving SVR12 rates of 91% (20/22) and 95% (21/22), respectively. The difference in SVR12 rate between 12 and 16 weeks of treatment was driven by a single additional relapse in the 12-week arm, making it difficult to determine the optimal treatment duration for this population based on these results alone. However, results from prior phase 2 studies in treatment-experienced GT3-infected patients without cirrhosis treated for 12 weeks demonstrated a similar tendency toward lower efficacy, with an SVR12 rate of 89% (24/27) with 2 relapses.(23) Notably, the 16-week regimen of G/P is now approved by the US FDA and EMA for the treatment of GT3-infected patients with prior treatment experience (with or without cirrhosis), supported by data from prior phase 2 studies and this phase 3 study, demonstrating an overall 96% (66/69) SVR12 rate in this subpopulation.(21, 22)

Amongst patients with baseline NS5A polymorphisms and compensated cirrhosis (n = 15; including 5 with Y93H at baseline), all patients achieved SVR12. Among treatment-experienced patients without cirrhosis, 3 patients had Y93H at baseline and 2/3 (67%) achieved SVR12; both patients with A30K at baseline had virologic failure. With a limited sample size available and the low prevalence of these polymorphisms in this NS5A-inhibitor naïve population, it is difficult to determine the true impact of such polymorphisms on treatment outcome. Prior studies have also reported low prevalence of both the Y93H (8.3-8.8%(11, 26)) and A30K (4.5-6%(26, 27)) polymorphisms in patients with HCV genotype 3. Moreover, as discussed, neither of these polymorphisms have a significant impact on *in vitro* susceptibility to pibrentasvir.(18) In support of these data, per the US FDA and

EMA product use labels, GT3-infected patients with compensated cirrhosis and/or prior treatment experience do not require viral resistance testing prior to treatment with G/P.(21, 22)

Altogether, the efficacy results from this study demonstrate that G/P is an all-oral DAA regimen with high cure rates that does not require ribavirin coadministration in HCV GT3-infected patients, regardless of other traditional negative predictors of response such as prior treatment experience or compensated cirrhosis. Retreatment of the patients that had virologic failure to G/P therapy may require a regimen with more than two mechanisms of action, such as G/P plus SOF, which is a DAA combination currently being evaluated in an ongoing clinical study (registered clinical trial: NCT02939989).

Treatment with G/P was safe and well-tolerated, regardless of treatment duration or baseline patient characteristics. Previous-generation NS3/4A protease inhibitor-containing regimens have been associated with AEs, including severe rash, marked hyperbilirubinemia, neutropenia, anemia, and elevated ALT, particularly in patients with cirrhosis.(28) However, all of these events were absent or rarely observed in SURVEYOR-II Part 3, even in patients with compensated cirrhosis. No patients discontinued or interrupted study drugs due to AEs. Moreover, there were no incidences of drug-induced liver injury or hepatic decompensation. Overall, the safety profile of patients with compensated cirrhosis was similar to those without cirrhosis. Serious AEs reported in this study were uncommon (n = 6), and none were deemed related to study drugs. The most commonly reported AEs were fatigue and headache, and they were reported at rates similar to placebo control groups in other clinical trials.(29, 30)

A potential limitation of this study was the relatively low patient numbers within individual subpopulations (eg, treatment-experienced non-cirrhotics). However, these patient numbers are not inconsistent with other studies within similar subpopulations.(11, 14) Moreover, the largest cohort was patients with both treatment experience and cirrhosis (n = 47), with a sample size larger than evaluated in other studies; an SVR12 rate of 96% was observed in this more difficult-to-cure population after 16 weeks of G/P treatment. Finally, GT3-infected

patients with prior exposure to NS5A inhibitor-containing regimens were not studied here; thus, the impact of treatment-emergent NS5A resistance associated substitutions on the efficacy of G/P in this patient subpopulation is currently unknown.

In summary, SURVEYOR-II Part 3 enrolled and treated some of the most difficult-to-cure HCV patients: those with GT3 infection and prior treatment experience and/or cirrhosis. Overall, the fixed-dose combination of once-daily RBV-free G/P was well-tolerated and demonstrated high SVR12 rates (≥95%) in treatment-naïve patients with cirrhosis treated for 12 weeks, and treatment-experienced patients with or without cirrhosis treated for 16 weeks. Therefore, G/P provides an efficacious and well tolerated once-daily RBV-free treatment option for patients with HCV genotype 3 and prior treatment experience and/or cirrhosis.

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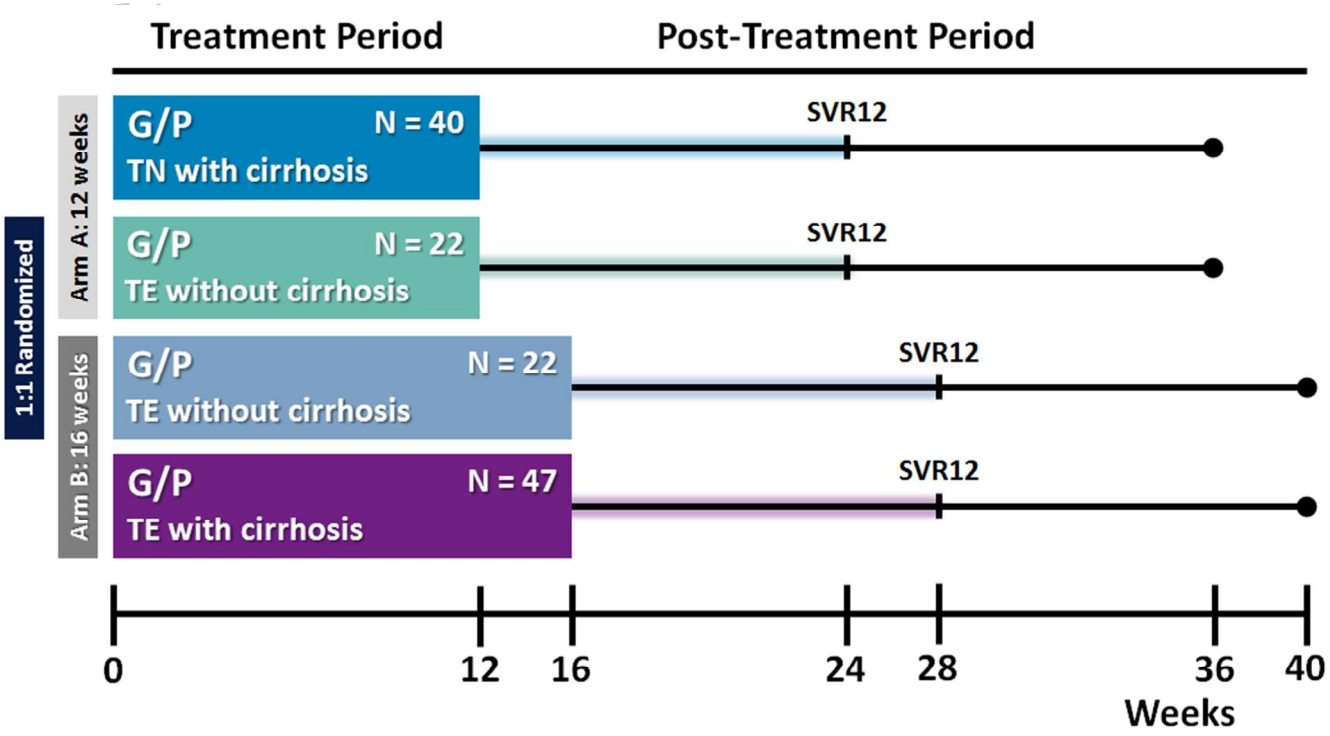


Figure 1. SURVEYOR-II, Part 3 Study Design. Patients were enrolled into two arms to be treated with either 12 weeks (Arm A) or 16 weeks (Arm B) of G/P. Treatment-naïve (TN) patients with cirrhosis received 12 weeks of treatment, while those with prior treatment experience (TE) and cirrhosis received 16 weeks. Patients with prior treatment experience but without cirrhosis were randomized 1:1 for treatment with either 12 or 16 weeks of G/P. Patients were followed for 24 weeks post-treatment to monitor safety and sustained virologic response.

Table 1. Patient demographics and baseline characteristics

	Arm A (12 weeks G/P)		Arm B (16 weeks G/P)	
		1:1 Randomized		
Characteristic	**Treatment-naïve w/ cirrhosis N = 40**	**Treatment-experienced w/o cirrhosis N = 22**	**Treatment-experienced w/o cirrhosis N = 22**	**Treatment-experienced w/ cirrhosis N = 47**
Male, n (%)	24 (60)	14 (64)	14 (64)	36 (77)
White race, n (%)	37 (93)	17 (77)	20 (91)	42 (89)
Age, median years (range)	56 (36 – 70)	56 (35 – 68)	59 (29 – 66)	59 (47 – 70)
IL28B non-CC genotype	20 (50)	15 (68)	19 (86)	34 (72)
BMI, median kg/m^2 (range)	29 (21 – 51)	26 (19 – 42)	28 (22 – 48)	27 (21 – 42)
HCV RNA, median $\log_{10}$ IU/mL (range)	6.2 (4.2 – 7.1)	6.6 (5.1 – 7.5)	6.1 (4.7 – 7.3)	6.5 (4.6 – 7.2)
Baseline ALT, mean U/L (± SD)	127.1 (± 94.0)	92.2 (± 54.7)	78.6 (± 65.8)	120.5 (± 82.1)
Total bilirubin, mean mg/dL (± SD)	0.67 (± 0.34)	0.52 (± 0.17)	0.60 (± 0.22)	0.76 (± 0.45)
Platelets, median $\times 10^9$/L (range)	140 (64 – 405)	210 (105 – 291)	235 (132 – 365)	123 (62 – 315)
Albumin, median g/L (range)	39 (29 – 47)	41 (35 – 45)	42 (38 – 48)	40 (33 – 47)
Prior treatment history, n (%)				
Naïve	40 (100)	0	0	0
IFN/pegIFN ± RBV	0	14 (64)	13 (59)	22 (47)
SOF + RBV ± pegIFN	0	8 (36)	9 (41)	25 (53)
Baseline Fibrosis Stage[a], n (%)				
F0-F1	0	11 (50)	15 (68)	0
F2	0	4 (18)	2 (9)	0
F3	0	7 (32)	5 (23)	0
F4	40 (100)	0	0	47 (100)
Child-Pugh score, n (%)				
5	35 (88)	0	0	37 (79)
6	5 (13)	0	0	10 (21)
Baseline polymorphisms, n (%)[a]				
Any polymorphism	10 (26)	6 (27)	3 (14)	7 (15)
NS3 only	1 (3)	0	0	1 (2)
NS5A only	9 (23)	6 (27)	3 (14)	6 (13)
Both NS3 and NS5A	0	0	0	0

BMI, body mass index; IFN, interferon; *IL28B*, interleukin 28; NS, non-structural protein; pegIFN, pegylated interferon; SOF, sofosbuvir
Baseline polymorphisms detected by next generation sequencing at a 15% threshold in samples that had sequences available for both targets (N) at amino acid positions 155, 156, 168 in NS3, and 24, 28, 30, 31, 58, 92, 93 in NS5A
[a]Data missing for 1 patient in Arm A (column 1) and 1 patient in Arm B (column 3); percentages calculated with modified N reflecting this

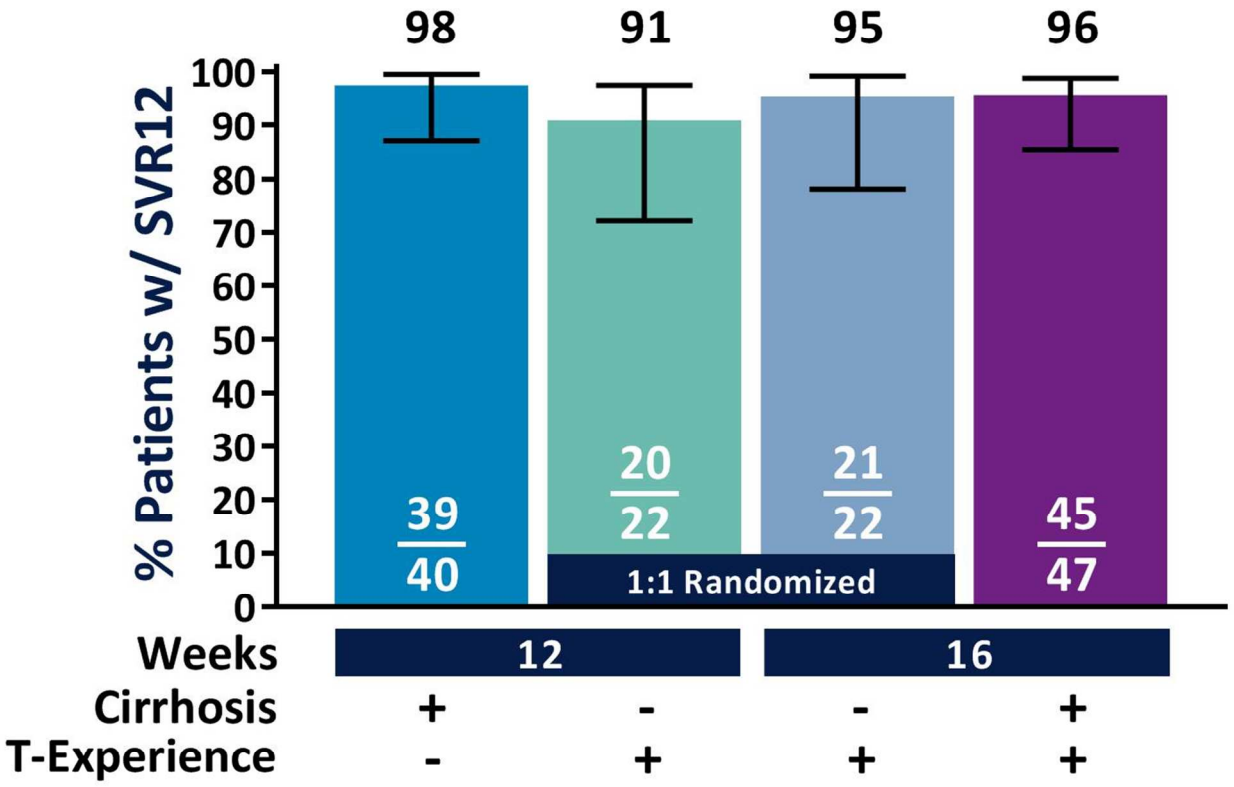


Figure 2. Sustained virologic response at post-treatment week 12. The number and percentage of patients that achieved SVR12 in each treatment arm is summarized here. Treatment-naïve patients with compensated cirrhosis were treated with G/P for 12 weeks, and patients with both compensated cirrhosis and prior treatment-experience (denoted T-Experience, above) were treated for 16 weeks. Patients without cirrhosis that had prior treatment-experience were randomized 1:1 to receive either 12 or 16 weeks of G/P. Two-sided 95% confidence intervals were calculated using the Wilson score method for binomial proportions.

Table 2. Patients with Virologic Failure: NS3 and NS5A Variants at Baseline and Time of Failure

					NS3 Variants		NS5A Variants	
Treatment Duration	Prior HCV Treatment	Cirrhosis; Fibrosis	Baseline HCV RNA (IU/mL)	Failure	Baseline	At Failure	Baseline	At Failure
12 weeks	pegIFN/RBV	No; F2	8,140,000	Relapse	None	None	Y93H	Y93H
12 weeks	pegIFN/RBV	No; F0-F1	15,700,000	Relapse	None	None	A30K	A30K+Y93H
16 weeks	pegIFN/RBV	No; F0-F1	18,900,000	Relapse	None	Y56H+Q168R	A30K	A30K+Y93H
16 weeks	SOF/RBV	Yes; F4	2,840,000	Relapse	None	None	None	L31F+Y93H
16 weeks	pegIFN/RBV	Yes; F4	17,400,000	Breakthrough[a]	A166S	A156G+A166S	None	A30K+Y93H

Variants were present in ≥15% of viral population as detected by next generation sequencing; variants assessed at NS3 positions: 36, 43, 54, 55, 56, 80, 155, 156, 166, and 168; and NS5A positions: 24, 28, 29, 30, 31, 32, 58, 92, and 93

Table 3. SVR12 rates for key patient subgroups

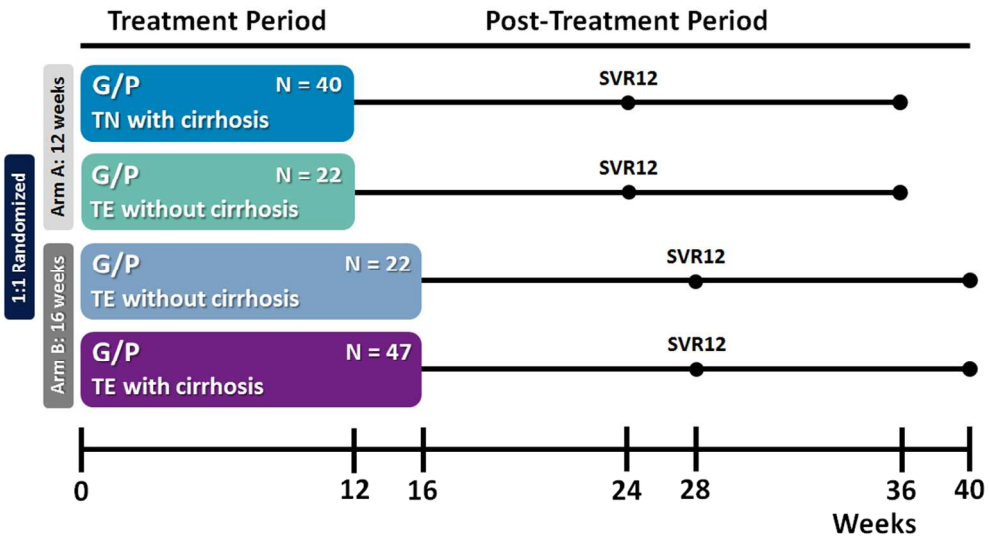
Patient subgroup	n/N	SVR12 (95% CI)
Treatment Duration		
12 weeks	59/62	95% (87 – 98)
16 weeks	66/69	96% (88 – 99)
Prior HCV Treatment		
Naïve	39/40	98% (87 – 99)
Any Experience	86/91	95% (88 – 98)
SOF-based	41/42	98% (88 – 99)
Compensated Cirrhosis		
With	84/87	97% (90 – 99)
Without	41/44	93% (82 – 98)

NS, non-structural; SVR12, sustained virologic response at post-treatment week 12

Table 4. Adverse events and key laboratory abnormalities

	Arm A (12 weeks G/P)		Arm B (16 weeks G/P)	
	1:1 Randomized			
Event, n (%)	**Treatment-naïve w/ cirrhosis N = 40**	**Treatment-experienced w/o cirrhosis N = 22**	**Treatment-experienced w/o cirrhosis N = 22**	**Treatment-experienced w/ cirrhosis N = 47**
Any AE	32 (80)	12 (55)	17 (77)	34 (72)
Serious AE	1 (3)	1 (5)	1 (5)	3 (6)
Serious AE related to study drugs	0	0	0	0
AE leading to study drug d/c	0	0	0	0
AEs occurring in ≥10% of patients				
Fatigue	5 (13)	4 (18)	4 (18)	16 (34)
Headache	10 (25)	5 (23)	4 (18)	6 (13)
Key Laboratory Abnormalities[a], n (%)				
Alanine aminotransferase[b]				
Grade ≥3 (>5 × ULN)	0	2 (9)	0	0
Total bilirubin				
Grade ≥3 (>3 × ULN)	0	0	0	1 (2)

AE, adverse event; DAA, direct-acting antiviral; d/c, discontinuation; G/P, coformulated glecaprevir and pibrentasvir; ULN, upper limit of normal
[a]Laboratory abnormalities based on the Common Terminology Criteria for Adverse Events version 4
[b]Alanine aminotransferase must have been increase post nadir in grade



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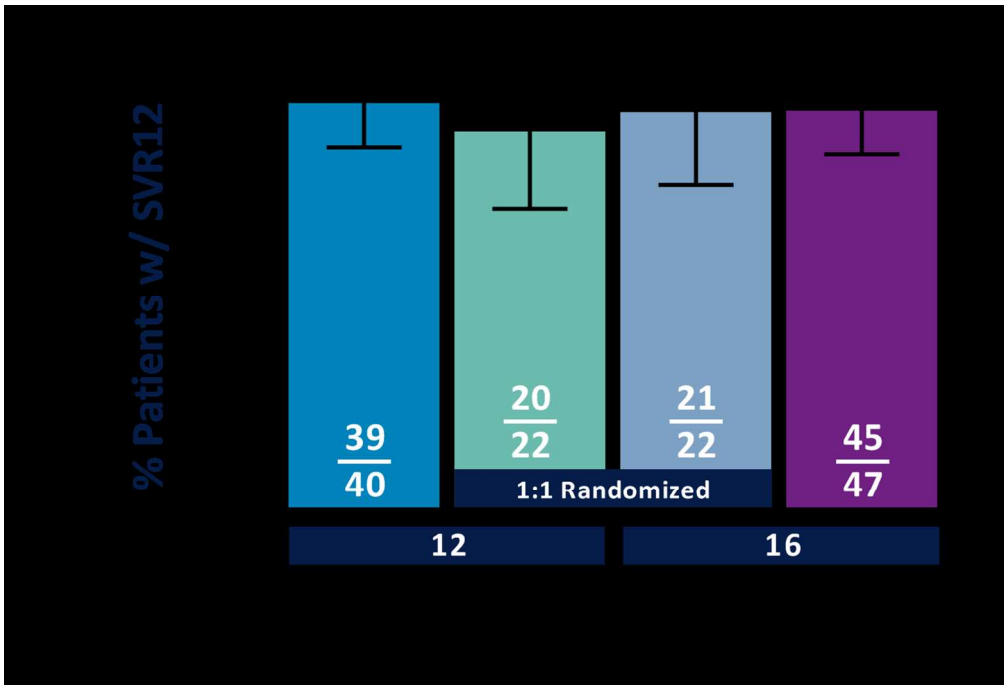

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