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Efficacy of Sofosbuvir and Velpatasvir, With and Without Ribavirin, in Patients With HCV genotype 3 Infection and Cirrhosis

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Role of the Study Sponsor

The study sponsor (Gilead) designed the study in collaboration with investigators, and collected, analyzed and interpreted the data.

Writing Assistance

Writing assistance was provided by Jenny Tan of Gilead Sciences.

Author Contributions

Brian McNabb, Luisa M. Stamm, Diana M. Brainard, and G. Mani Subramanian designed, and oversaw the conduct of the study. Rafael Esteban, Juan A. Pineda, Jose Luis Calleja, Marta Casado, Manuel Rodríguez, Juan Turnes, Luis Enrique Morano Amado, Rosa Maria Morillas, Xavier Forns, Juan Manuel Pascasio Acevedo, Raul J. Andrade, Antonio Rivero, José Antonio Carrión, Sabela Lens, Mar Riveiro-Barciela, and Maria Buti, served as study investigators. Brian McNabb, Gulan Zhang (statistician), Gregory Camus, and Luisa M. Stamm, analyzed the data. All authors reviewed the data and manuscript.

Conflict of Interest Statement

- Antonio Rivero: Advisor and speaker: AbbVie, Gilead Sciences, and MSD
- Brian McNabb is an employee of and holds stock in DocMatter.com and Gilead Sciences
- Gulan Zhang, Gregory Camus, Luisa M. Stamm, Diana M. Brainard, G. Mani Subramanian are employees of and hold stock in Gilead Sciences.
- José Antonio Carrión: Advisor and speaker: Gilead, AbbVie, and MSD
- Jose Luis Calleja: Advisor and speaker: Gilead, AbbVie, and MSD

- Juan A. Pineda has participated in research projects funded by Abbvie, Janssen, Gilead, MSD and Roche; has received honoraria for talks from Abbvie, Janssen, Gilead, MSD, and Roche; has been granted to attend educational activities by Janssen and Gilead and has taken part in advisory boards for Abbvie, Janssen, Gilead, and MSD.
- Juan Manuel Pascasio Acevedo: Advisor and Speaker: Gilead, AbbVie, and MSD
- Juan Turnes: Advisor and speaker: Abbvie, Gilead Sciences, and MSD
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Abstract

Background & Aims: In phase 3 trials and real-world settings, lower proportions of patients with genotype 3 hepatitis C virus (HCV) infection and cirrhosis have a sustained virologic response 12 weeks after treatment (SVR12) with the combination of sofosbuvir and velpatasvir than patients without cirrhosis. It unclear whether adding ribavirin to this treatment regimen increases SVRs among patients with genotype 3 HCV infection and cirrhosis.

Methods: We performed a phase 3 trial of 204 patients with genotype 3 HCV infection and compensated cirrhosis (mean age, 51 ± 7.4 years) at 29 sites in Spain from August 19, 2016 through April 18, 2017. The patients were assigned to groups given sofosbuvir/velpatasvir for 12 weeks (n=101) or sofosbuvir/velpatasvir plus ribavirin for 12 weeks (n=103). The primary efficacy endpoint was SVR12.

Results: The overall rates of SVR12 were 91% (92/101; 95% CI, 84%–96%) for the sofosbuvir/velpatasvir group and 96% (99/103; 95% CI, 90%–99%) for the sofosbuvir/velpatasvir plus ribavirin group. In the sofosbuvir/velpatasvir group, a lower proportion of patients with baseline resistance-associated substitutions (RASs) in NS5A achieved an SVR12 (84%) than patients without (96%). In the sofosbuvir/velpatasvir plus ribavirin group, baseline RASs had less impact on the proportion of patients with an SVR12 (96% for patients with baseline RASs; 99% for patients without). The most common adverse events (occurred in at least 10% of patients) in the sofosbuvir/velpatasvir group was asthenia (12%) and in the sofosbuvir/velpatasvir plus ribavirin group were asthenia (27%), headache (24%), and insomnia (12%).

Conclusions: Consistent with findings from earlier studies, a high rate of patients (91% and 95%) with genotype 3 HCV infection with compensated cirrhosis achieved an SVR12 after 12 weeks of treatment with sofosbuvir/velpatasvir, with or without ribavirin. Among patients treated with sofosbuvir/velpatasvir without ribavirin, fewer patients with baseline NS5A RASs achieved an SVR12 rate compared to patients without baseline NS5A RASs. ClinicalTrials.gov no: NCT02781558

Key words: DAA, direct-acting antiviral agent, outcome, drug resistance

Introduction

The global prevalence of genotype 3 HCV infection is estimated to be 22% to 30% of all HCV infections (1,2). Moreover, genotype 3 HCV infection may be associated with a more rapid progression of fibrosis, leading to a higher risk of developing cirrhosis and hepatocellular carcinoma (3). Thus, genotype 3 HCV infection is a particularly important genotype in the global effort to curb the morbidity and mortality of HCV infection.

Recent discovery of direct-acting antivirals (DAAs) has revolutionized the treatment of HCV infection, where practically all patients can expect a sustained virologic response (SVR) rate above 95% with simple, all-oral DAA-based regimens (4,5). Despite these advances, patients with genotype 3 HCV infection, particularly those with cirrhosis, have emerged as a more difficult-to-cure population (6).

For patients with genotype 3 HCV infection without cirrhosis or with compensated cirrhosis, the single-tablet regimen of sofosbuvir (an NS5B inhibitor) combined with velpatasvir (an NS5A inhibitor) for 12 weeks demonstrated overall high efficacy and improvement in patient outcomes in clinical studies including ASTRAL-3 and POLARIS-3 (SVR12 95% and 96%, respectively) (7-12). These SVR12 rates represented a significant increase in efficacy over previous standards of care for genotype 3 HCV infected patients (as examples, 24 weeks of sofosbuvir with ribavirin resulted in an SVR12 rate of 81% in ASTRAL-3 and 12 weeks of sofosbuvir with daclatasvir resulted in an SVR12 rate of 89% in ALLY-3 [13]).

Based on post-hoc analyses of subgroups and trials in related populations, guidelines had recommended consideration of adding ribavirin to sofosbuvir/velpatasvir for genotype 3 HCV-infected patients with compensated cirrhosis and baseline Y93H resistance associated substitutions (RASs) (4,5,14). In ASTRAL-3, the SVR12 rate was 91% for genotype 3 HCV-infected patients with compensated cirrhosis and 97% for those without cirrhosis; 84% for genotype 3 HCV infected patients with baseline Y93H RASs and 97% for those without baseline Y93H RASs (15,16). These subgroup analyses suggest that patients with cirrhosis or with baseline Y93H RASs may benefit from the addition of ribavirin. ASTRAL-4 was a study conducted in patients with HCV infection and decompensated cirrhosis, where genotype 3 HCV infected patients appeared to benefit from the addition of ribavirin to sofosbuvir/velpatasvir for 12 weeks (SVR12 83% without ribavirin and 94% with ribavirin), although it was not designed to answer specifically this question (17). Further, earlier in development in small cohorts within a Phase 2 study, sofosbuvir +velpatasvir for 12 weeks in genotype 3 patients with cirrhosis led to an SVR12 rate of 88% and sofosbuvir +velpatasvir with ribavirin led to an SVR12 rate of 96% (18). Together, these results led to the hypothesis that the addition of ribavirin to the sofosbuvir/velpatasvir regimen may increase the SVR rate for patients with genotype 3 HCV and compensated cirrhosis. The current study was designed to explore that hypothesis by evaluating the efficacy and safety of sofosbuvir/velpatasvir with or without ribavirin for 12 weeks in patients with genotype 3 HCV infection and compensated cirrhosis.

Methods

Patients

Patients were enrolled and treated from 29 sites in Spain from August 19, 2016, through April 18, 2017. Eligible patients were males and females, 18 years of age or older with confirmed chronic genotype 3 HCV infection and compensated cirrhosis. Patients with human immunodeficiency virus (HIV) and prior-treatment experience (including NS5B inhibitors and NS3/4 protease inhibitors) were eligible. Patients with prior NS5A inhibitor experience were excluded.

Study design

Patients were randomized in a 1:1 ratio to receive open label sofosbuvir/velpatasvir 400/100 mg once-daily or sofosbuvir/velpatasvir 400/100 mg once-daily with weight-adjusted ribavirin (1,000 or 1,200 mg/day) administered twice-daily in a divided dose. Randomization was stratified by prior treatment experience.

Assessments

Serum HCV RNA levels were measured using the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test, version 2.0 (Roche Molecular Systems, Branchburg, NJ, USA) with a lower limit of quantification of 15 IU/mL. The presence of cirrhosis at screening was confirmed by either liver biopsy showing cirrhosis, transient elastography (FibroScan) results > 12.5 kPa, or FibroTest result > 0.75 and an AST platelet ratio index (APRI) > 2 . To evaluate drug-class RASs, the HCV NS5A and NS5B coding regions were deep sequenced by DDL Diagnostic Laboratory (Rijswijk, The Netherlands) using the Illumina MiSeq system (Illumina, San Diego,

CA, USA) for all patients with documented virologic outcomes (Resistance Analysis Population) at baseline and for all patients with virologic failure at the time of failure and evaluated using the Basic Local Alignment Search Tool (BLAST). NS5A RASs were defined as substitutions that either confer a reduced susceptibility to any approved NS5A inhibitor (>2.5 -fold change in EC₅₀), or that commonly emerge in patients with virologic failure at the time of relapse and included M28A/G/T/V, A30E/G/H/K/S/V, L31F/I/M/V, P58D/G, Y93any. NS5B NI RASs included S96T, N142T, L159F, E237G, S282any, C289I/L, L320F/I/V, V321A/I. All RASs that exceeded a 15% cut off were reported. Adverse events and laboratory tests were conducted during this study and at post-treatment for safety evaluation. Monitoring and grading of adverse events (AEs) and serious AEs (SAEs), vital sign measurements, and standard laboratory assessments were included. All reported AEs and SAEs were treatment-emergent (occurred after at least 1 dose of study drug and up to 30 days after the last dose of study drug).

Endpoints and statistical methods

The primary efficacy endpoint was SVR12 (ie, HCV RNA less than the lower limit of quantification 12 weeks after the end of therapy). Patients with missing SVR12 data were assumed to be a treatment failure. Point estimation and 2-sided 95% CIs were constructed by the Clopper-Pearson method for each group. The sample size of 100 per treatment group was based on practical considerations as there was high interest in generating data in a timely manner within this specific subpopulation of patients who are increasingly difficult to identify given that they have been prioritized for treatment. The primary safety endpoint was discontinuations due to AEs.

Study oversight

This study was approved by an independent ethics committee at each participating site and was conducted in compliance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. The study was designed and conducted according to the protocol by the sponsor (Gilead Sciences) in collaboration with the investigators. The sponsor collected the data, monitored the study conduct, and performed the statistical analyses. All authors participated in the acquisition of data, analysis and interpretation of the data, had access to the study data, and reviewed and approved the final manuscript.

Results

Patient characteristics

Of the 269 patients screened for this study, 204 patients with genotype 3 HCV infection and cirrhosis were randomized and began treatment: 101 patients were assigned to receive sofosbuvir/velpatasvir for 12 weeks and 103 were assigned to receive sofosbuvir/velpatasvir plus ribavirin for 12 weeks (Figure 1). Of the 65 patients who were not enrolled, 58 did not meet eligibility criteria, 3 were lost to follow-up, 3 withdrew consent, and 1 missed the enrollment window (Supplemental Table 1). The mean (SD) age of patients was 51 (7.4) years, 79% of patients were male, and 88% were white (Table 1). All of the patients had confirmed genotype 3 HCV infection and compensated cirrhosis. The majority of patients (95%) had cirrhosis determination by transient elastography. For patients with available data, the mean (SD) platelet count was 149 (66) $\times 10^3/\mu\text{L}$ and the mean (SD) FibroScan score was 21 (9) kPa. Approximately 27% had previous HCV treatment-experience (32 patients failed prior treatment with pegylated interferon plus ribavirin; 20 patients failed prior HCV treatments that included non-pegylated

interferon, or interferon or pegylated interferon alone; and 3 patients failed a previous treatment with sofosbuvir with or without simeprevir) and 15% were coinfecting with HIV.

Efficacy

After 12 weeks of treatment, SVR12 (n/N; 95% CI) was 91% (92/101; 83.8% to 95.8%) for patients randomized to sofosbuvir/velpatasvir, and 96% (99/103; 90.4% to 98.9%) for patients randomized to sofosbuvir/velpatasvir plus ribavirin (Table 2). In a post-hoc analysis, using a Cochran-Mantel-Haenszel test stratified by prior HCV treatment experience, the SVR12 rate for sofosbuvir/velpatasvir plus ribavirin was not statistically superior to sofosbuvir/velpatasvir ($p = 0.14$). In the sofosbuvir/velpatasvir group, there were 6 (6%) patients who experienced virologic failure (5 relapses and 1 on-treatment virologic failure), 2 who were lost to follow-up (both with undetectable HCV RNA at last assessment [Week 12 and post-treatment Week 4, respectively]), and 1 who discontinued treatment on Day 1 due to AEs of dizziness and anxiety. In the sofosbuvir/velpatasvir plus ribavirin group, 2 (2%) patients experienced virologic failure (both relapses) and 2 patients were lost to follow-up (both with HCV RNA < LLOQ at last assessment [Week 4 and post-treatment Week 4, respectively]). There were no clinically relevant differences in the SVR12 rates among subgroups due to the low number of patients with virologic failure (Supplemental Table 2). Of note, patients with prior treatment experience had a numerically higher SVR12 rate compared with patients who were treatment naive in the sofosbuvir/velpatasvir group (96% versus 89%), and no difference in SVR12 rates among patients treated with sofosbuvir/velpatasvir plus ribavirin (96% regardless of prior treatment experience).

Viral Resistance

Of the 204 randomized patients, 199 (98% overall: 98/101 [97%] in the sofosbuvir/velpatasvir group and 101/103 [98%] in the sofosbuvir/velpatasvir plus ribavirin group) had virologic outcomes and sequencing available and were included in the resistance analysis. Overall, 41 of 199 patients (21%) had baseline NS5A RASs (19 of 98 [19%] in the sofosbuvir/velpatasvir group and 22 of 101 [22%] in the sofosbuvir/velpatasvir plus ribavirin group). Substitutions at NS5A position 30 (A30K/S/V) were the most commonly observed variants (28 patients). Overall, 13 patients had Y93H at baseline: 11 as a single RAS, and 2 in combination with A30V. The patient with genotype 3b HCV infection had both the NS5A RASs A30K and L31M at baseline.

In the sofosbuvir/velpatasvir group, 16 of 19 patients (84%) with baseline NS5A RASs and 76 of 79 patients (96%) without baseline NS5A RASs achieved SVR12 (Table 3). Of the 4 patients with Y93H at baseline, 2 patients (50%) achieved SVR12. In the sofosbuvir/velpatasvir plus ribavirin group, 21 of 22 patients (95%) with baseline NS5A RASs and 78 of 79 patients (99%) without baseline NS5A RASs achieved SVR12 (Table 3). Of the 9 patients with Y93H at baseline, 8 (89%) achieved SVR12.

The NS5A RASs for the patient with virologic failure are shown in Supplemental Table 3. Three of the 5 patients who experienced viral relapse after treatment with sofosbuvir/velpatasvir, and 1 of the 2 patients in the sofosbuvir/velpatasvir plus ribavirin group had emergent NS5A RASs. The patient who had on-treatment virologic failure in the sofosbuvir/velpatasvir group had no emergent RAS.

There were 2 patients in the sofosbuvir/velpatasvir group and 1 patient in the sofosbuvir/velpatasvir plus ribavirin group with NS5B nucleoside inhibitor RASs (N142T or L159F) in the study, all of whom achieved SVR12. No patient with virologic failure had emergent NS5B nucleoside inhibitor (NI) RASs.

Safety

Overall, sofosbuvir/velpatasvir with or without ribavirin was well tolerated (Table 4). A total of 2 patients prematurely discontinued sofosbuvir/velpatasvir due to AEs that were assessed as unrelated to study drug: 1 patient in the sofosbuvir/velpatasvir group with a medical history of anxiety depressive syndrome prematurely discontinued treatment after 1 dose due to AEs of dizziness and anxiety and 1 patient in the sofosbuvir/velpatasvir plus ribavirin group discontinued treatment on Day 20 due to abnormal total bilirubin. One patient discontinued ribavirin on Day 35 due to anemia that was assessed as related to study drug; this patient relapsed after completing treatment with sofosbuvir/velpatasvir.

More patients in the sofosbuvir/velpatasvir plus ribavirin group experienced an AE compared to the sofosbuvir/velpatasvir group (74.8% versus 47.5%), but most AEs in both groups were mild in severity. The most common adverse events ($\geq 10\%$) were asthenia (12%) in the sofosbuvir/velpatasvir group and asthenia (27%), headache (24%), and insomnia (12%) in the sofosbuvir/velpatasvir plus ribavirin group.

Serious adverse events were rare in this study. Four patients (4%) in the sofosbuvir/velpatasvir group had SAEs (accident at work, hepatocellular carcinoma, pharyngotonsillitis, and urinary tract infection). Two patients (2%) in the sofosbuvir/velpatasvir plus ribavirin group had SAEs (hepatic cancer and non-small cell lung cancer). All SAEs were assessed as unrelated to study treatment by the investigator.

Laboratory abnormalities reported for both treatment groups were overall low. Consistent with the known toxicities of ribavirin and relative to the sofosbuvir/velpatasvir group, the sofosbuvir/velpatasvir plus ribavirin group experienced more hemoglobin values below 10 g/dL (5% versus 1%) and increases in total bilirubin above 2.5 x the upper limit of normal (2% versus 0) (Table 4). The HIV RNA levels and CD4 cell counts for the 30 patients with HIV coinfection remained stable for the duration of the study (data not shown).

Discussion

In this multicenter, randomized, open-label trial, genotype 3 HCV infected patients with compensated cirrhosis achieved high rates of SVR with sofosbuvir/velpatasvir with or without ribavirin. The addition of ribavirin to the sofosbuvir/velpatasvir regimen resulted in a numerical increase in the SVR12 rate, with 96% of patients in the sofosbuvir/velpatasvir plus ribavirin group and 91% in the sofosbuvir/velpatasvir group achieving SVR12. The numeric difference was smaller when focusing on the percentage of patients who experienced virologic relapse: 5% for subjects treated with sofosbuvir/velpatasvir and 2% for subjects treated with sofosbuvir/velpatasvir plus ribavirin.

Overall, these response rates are consistent with those observed in patients with genotype 3 HCV infection and cirrhosis treated with sofosbuvir/velpatasvir for 12 weeks in ASTRAL-3 (SVR12 rate 91%) and POLARIS-3 (SVR12 rate 96%) (8,9). Interestingly, compared to these prior studies with sofosbuvir/velpatasvir for 12 weeks in which treatment-experienced patients with genotype 3 and cirrhosis had lower SVR12 rates compared to those who were treatment-naïve (89% and 93% in ASTRAL-3; 91% and 99% in POLARIS-3, respectively), treatment-experienced patients in the current study had the same or numerically higher SVR12 rates compared to treatment-naïve patients.

Although not statistically significant, the small difference in treatment outcome between the two treatment groups may be attributable to the presence of pretreatment NS5A RASs. A numerically lower SVR12 rate for sofosbuvir/velpatasvir-treated patients with pretreatment NS5A RASs was observed (84% versus 96%). Among sofosbuvir/velpatasvir plus ribavirin-treated patients, pretreatment RASs had less effect on SVR12 rates (96% versus 99%). Of note, the overall prevalence of NS5A RASs was 21% in the current study, slightly higher than previously reported in Europe and North America (17 and 16%, respectively [19]) primarily due to the definition of NS5A RASs used in this study being updated and more inclusive than that used in previous studies. The prevalence of NS5A RASs associated with highly reduced susceptibility to NS5A inhibitors in the current study (6.5%) was comparable to previously reported rates (4%) (20).

The patients enrolled in the study were representative of those with compensated cirrhosis. A significant number had baseline thrombocytopenia and nearly all patients had a fibroscan performed at baseline and the median fibroscan score was 21 kPa. Despite the advanced liver

disease of the patients, sofosbuvir/velpatasvir was well tolerated in this study (7,21). Though more patients in the sofosbuvir/velpatasvir plus ribavirin group had an AE during the study compared to patients in the sofosbuvir/velpatasvir group, AEs were mild in severity and did not result in higher rates of study drug discontinuation. There was an increased rate of decreased hemoglobin laboratory abnormalities for the sofosbuvir/velpatasvir plus ribavirin group, which is consistent with the known toxicity of ribavirin (22,23).

In the current era of direct-acting antivirals, patients with genotype 3 HCV infection and cirrhosis have emerged as a more difficult-to-cure population. However, newer regimens, including those evaluated in this study and others, with and without ribavirin for 12 and 16 weeks have greatly improved the SVR12 rates in this patient population. Within the ALLY-3 subgroup of patients with genotype 3 and cirrhosis, 12 weeks of sofosbuvir and daclatasvir led to SVR12 rates of 63% (13). In ALLY-3+, numeric improvements in the outcome of this regimen were seen with addition of ribavirin and extension of the duration: sofosbuvir, daclatasvir and ribavirin for 12 or 16 weeks led to SVR12 rates 83% or 89%, respectively. In patients with genotype 3 and cirrhosis who received glecaprevir/pibrentasvir in SURVEYOR-2, 12 weeks of treatment led to an SVR12 rate of 98% in those who were treatment naïve and 16 weeks led to and SVR12 rate of 96% in those with treatment experience (24).

The greatest limitation of the study is that it lacks the formal statistical comparison between the treatment groups; a study designed to do so would not have been practically feasible given the interest in generating data in a timely fashion and the limited number of patients within the subpopulation. For example, for a Cochran-Mantel-Haenszel test stratified by prior HCV

treatment experience and assuming 80% power, a study with an endpoint of determining superiority of 1 treatment group (assuming SVR rate to be 96%) compared to another treatment group (assuming SVR rate to be 91%) would require over 800 patients total. A study with an endpoint of determining noninferiority of two treatment groups at a margin of 5%, assuming 80% power and 91% as the true SVR rate for both arms would require over 1000 patients total. Importantly, the current study is the among the largest conducted in this subpopulation to date (second only to POLARIS-3, a global Phase 3 clinical trial of sofosbuvir/velpatasvir/voxilaprevir and sofosbuvir/velpatasvir, which enrolled 219 patients with genotype 3 and cirrhosis) (25). Another limitation of this study is the generalizability of the results from a clinical study conducted within a single European country. For example, as described above, the prevalence of NS5A RASs may vary geographically, with a comparatively high baseline prevalence in this study conducted in Spain, as compared to other regions.

The impact of the results of this study on clinical practice for this patient population are likely to be influenced by the cost and availability of resistance testing, treatment with ribavirin, as well as potential retreatment of virologic failures with salvage. The 3% lower relapse rate among patients receiving sofosbuvir/velpatasvir plus ribavirin is biologically plausible given the data generated in prior studies and based on additional evidence suggesting that ribavirin may prevent or delay the emergence of resistance which may impact outcome (26). In academic centers where RAS testing is available for use in clinical practice and ribavirin toxicity is easily managed by experienced practitioners, ribavirin may be considered. However, when considering the World Health Organization goal of HCV elimination (27), simplifying treatment for all HCV-infected patients, including the small subgroup of remaining genotype 3 patients with cirrhosis is

desirable. Indeed, this approach is being employed successfully by countries in national elimination programs, such as Iceland (28). Lastly, further support has been generated in real-world datasets from the Italian regional registry and the German Hepatitis C Cohort in which sofosbuvir/velpatasvir for 12 weeks in patients with genotype 3 and cirrhosis resulted in a SVR12 rate of 95% (16,29,30). The simplicity of a single tablet regimen given once daily for a uniform duration to patients irrespective of genotype or fibrosis stage is supported by these data, and particularly appropriate given the small percentage of patients with virologic relapse can be successfully retreated with sofosbuvir/velpatasvir/voxilaprevir (31).

In conclusion, consistent with earlier studies, patients with genotype 3 HCV infection with compensated cirrhosis achieved a high overall SVR12 rate when treated with 12 weeks of sofosbuvir/velpatasvir with or without ribavirin. Response rates were numerically higher when ribavirin was added to sofosbuvir/velpatasvir, largely due to the impact of baseline NS5A RASs. These data support treatment of genotype 3 HCV-infected patients with cirrhosis with either regimen based on local treatment guidelines, availability of RAS testing, and/or ability to monitor for ribavirin toxicity.

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ACCEPTED MANUSCRIPT

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FIGURE LEGEND**Figure 1. Patient Disposition**

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Table 1. Patient Demographics and Baseline Characteristics

	SOF/VEL 12 Weeks (N = 101)	SOF/VEL+RBV 12 Weeks (N = 103)
Mean (SD) age, y	51 (7.3)	51 (7.6)
Male, n (%)	75 (74)	87 (85)
Race, n (%)		
White	84 (83)	95 (92)
Asian	17 (17)	8 (8)
Mean (SD) BMI, kg/m ²	27 (5.1)	27 (4.9)
Genotype, n (%)		
3a	94 (93)	97 (94)
3b	0	1 (1)
3 (no confirmed subtype)	7 (7)	5 (5)
IL28B, n (%)		
CC	64 (63)	53 (52)
CT	31 (31)	43 (42)
TT	5 (5)	7 (7)
Missing	1 (1)	0
Mean (SD) HCV RNA, log ₁₀ IU/mL	6.2 (0.64)	6.3 (0.56)
Mean (SD) ALT, U/L	122 (81)	107 (76)
Mean (SD) platelets, x10 ³ /uL	150 (62)	148 (69)
Mean (SD) FibroScan Score (kPa)	20 (9)	21 (9)
Cirrhosis Determination Method, n (%)		
Fibrotest and APRI	1 (1)	8 (8)
Liver Biopsy	2 (2)	0
Transient Elastography	98 (97)	95 (92)
Prior HCV treatment, n (%)		
None	74 (73)	75 (73)
DAA+/-Peg-IFN+/-RBV	1 ^a (1)	2 ^b (2)
Peg-IFN+RBV	14 (14)	18 (17)
Other ^c	12 (12)	8 (8)
HIV coinfection, n (%)	16 (16)	14 (14)

APRI, aspartate aminotransferase to platelet ratio index; DAA, direct-acting antiviral; IFN, interferon; Peg-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir

a Previous DAA treatments included sofosbuvir and simeprevir

b Previous DAA treatment was with sofosbuvir for both patients

c Other prior HCV treatments included non-pegylated IFN+RBV and IFN or Peg-IFN alone.

Table 2. Treatment Response

	SOF/VEL 12 Weeks (N = 101)	SOF/VEL+RBV 12 Weeks (N = 103)
SVR12, N (%)	92 (91)	99 (96)
95% CI	84%-96%	90%-99%
Virologic failure, N (%)		
On treatment	1 (1)	0
Relapse	5 (5)	2 (2)
Other, N (%)	3 (3)	2 (2)

RBV, ribavirin; SVR12, sustained virologic response 12 weeks after treatment discontinuation (primary endpoint); SOF, sofosbuvir; VEL, velpatasvir

Table 3. SVR12 in Patients With and Without Baseline Resistance-Associated Substitutions (15% Cutoff)

n/N (%)	SOF/VEL 12 Weeks (N = 98)	SOF/VEL+RBV 12 Weeks (N = 101)
No NS5A RASs	76/79 (96)	78/79 (99)
Any NS5A RASs	16/19 (84) ^a	21/22 (95)

RAS, resistance associated substitution; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir

^aOne patient with a baseline NS5A RAS had an on-treatment virologic failure (all other patients who did not achieve SVR12 relapsed).

Table 4. Treatment-Emergent Adverse Events and Laboratory Abnormalities, N (%)

	SOF/VEL 12 Weeks (N = 101)	SOF/VEL+RBV 12 Weeks (N = 103)
Any AE	48 (47.5%)	77 (74.8%)
SAEs ^a	4 (4.0%)	2 (1.9%)
Adverse event leading to discontinuation of SOF/VEL	1 (1.0%)	1 (1.0%)
Deaths	0	0
Common AEs ^b		
Asthenia	12 (12)	28 (27)
Headache	8 (8)	25 (24)
Insomnia	1 (1)	12 (12)
Selected laboratory abnormalities		
Hemoglobin		
< 8.5 g/dL	0	0
< 10 g/dL	1 (1)	5 (4.9)
Lymphocytes		
350 to < 500/mm ³	1 (1)	0
< 350/mm ³	0	0
Platelets		
25,000 to < 50,000/mm ³	1 (1)	1 (1)
< 25,000/mm ³	0	0
Total bilirubin		
> 2.5 to 5 x ULN	0	2 (2)
> 5 x ULN	0	0

AE, adverse event; RBV, ribavirin; SAE, serious adverse event; SOF/VEL, sofosbuvir/velpatasvir; ULN, upper limit of normal.

a The SAEs reported in this study were accident at work, hepatic cancer, hepatocellular carcinoma, limb injury, non-small cell lung cancer, pharyngotonsillitis, and urinary tract infection; all were assessed as unrelated to study drug.

b Adverse events were considered to be common if they occurred in at least 10% of patients in either group.

