Sofosbuvir-velpatasvir-voxilaprevir with or without ribavirin in DAA-experienced patients with genotype 1 HCV

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Keywords: Retreatment, treatment failure, difficult to treat

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Two-Sentence Summary

In this phase 2 exploratory study, the efficacy, safety and tolerability of sofosbuvir-velpatasvir-voxilaprevir were evaluated in 33 DAA-experienced patients with chronic hepatitis C virus infection.

ClinicalTrials.gov Identifier: NCT02536313

List of abbreviations

HCV, hepatitis C virus; DAA, direct-acting antiviral; SVR12, sustained virologic response 12 weeks after treatment; CI, confidence interval; AE, adverse event; NS, nonstructural protein; SVR, sustained virologic response; ALT, alanine aminotransferase; ULN, upper limit of normal; INR, international normalized ratio; LLOQ, lower limit of quantification; RAS, resistant-associated substitution

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Conflicts of interest

Eric Lawitz has served as a speaker for AbbVie, Bristol-Myers Squibb, Gilead, Janssen, and Merck & Co, and has served as a consultant for AbbVie, Achillion Pharmaceuticals, Bristol-Myers Squibb, Enanta, Gilead Sciences, Janssen, Merck & Co., Novartis, Santaris, Regulus, and Theravance.

Fred Poordad has served as a speaker for AbbVie, Gilead, BMS, Merck, and Salix, has served as a consultant for AbbVie, Bristol-Myers Squibb, Gilead, Merck, and Salix, and has received research support from Abbvie, Achillion, Anadys, Biolex, Boehringer Ingelheim, Bristol-Myers Squibb, Genentech, Gilead, GlaxoSmithKline, GlobeImmune, Idenix, Idera, Intercept, Janssen,

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Medarex, Medtronic, Merck, Novartis, Santaris, Scynexis, Salix/Valeant, Vertex, and ZymoGenetics.

Robert H. Hyland, Yin Yang, Hadas Dvory-Sobol, Luisa M. Stamm, Diana M. Brainard, and John G. McHutchison are employed by and own stock in Gilead Sciences, Inc.

Jennifer Wells, Carmen Landaverde, and Julio Gutierrez report no conflicts of interest.

The concept and idea for this study originated from the funding source, Gilead Sciences, Inc.

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Abstract

The optimal retreatment strategy for hepatitis C virus (HCV) genotype 1-infected patients who fail direct-acting antiviral (DAA)–based regimens remains unknown. In this phase 2, open-label study conducted at a single center in the United States, patients with HCV genotype 1 infection who previously failed to achieve sustained virologic response on a DAA-based regimen were randomized to receive treatment with a fixed-dose combination tablet of sofosbuvir-velpatasvir-voxilaprevir with or without ribavirin for 12 weeks. Patients were stratified by their cirrhosis and prior NS5A inhibitor exposure. The primary efficacy endpoint was the proportion of patients with sustained virologic response at 12 weeks after treatment (SVR12). SVR12 was achieved by 24 of 24 patients (100%; 95% confidence interval [95% CI], 86% to 100%) receiving sofosbuvir-velpatasvir-voxilaprevir alone, and 24 of 25 patients (96%; 95% CI, 80% to 100%) receiving the same treatment with ribavirin. None of the patients discontinued sofosbuvir-velpatasvir-voxilaprevir therapy due to an adverse event (AE). The most commonly reported AEs with sofosbuvir-velpatasvir-voxilaprevir alone were diarrhea and bronchitis; and with sofosbuvir-velpatasvir-voxilaprevir plus ribavirin were fatigue, anemia, gastroenteritis, and nausea. *Conclusion:* A fixed-dose combination of sofosbuvir-velpatasvir-voxilaprevir was well-tolerated and effective at achieving virologic response in patients with HCV genotype 1 infection and prior DAA treatment experience.

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Introduction

Of the 6 major hepatitis C virus (HCV) genotypes, infection with genotype 1 is the most prevalent, accounting for nearly half of all HCV infections worldwide.[1] A paradigm shift in the treatment of patients with chronic HCV genotype 1 infection occurred in 2011 with the introduction of direct-acting antivirals (DAAs), which interfere with HCV replication by targeting viral proteins such as the nonstructural protein 3/4A (NS3/4A) serine protease, NS5A, and the polymerase NS5B.[2-4] For the few patients with genotype 1 infection who fail interferon-free DAA-based therapies, retreatment strategies remain unclear.

A fixed-dose combination of the nucleotide analog inhibitor of the NS5B polymerase sofosbuvir and the NS5A inhibitor velpatasvir is approved for the treatment of HCV genotype 1-6 infection.[5] Voxilaprevir is a potent inhibitor of the NS3/4A protease that maintains its activity against common genotype 1 NS3 variants.[6] In a previous phase 2 study, all DAA-experienced patients with genotype 1 infection achieved a sustained virologic response (SVR) upon the administration of a fixed-dose combination of sofosbuvir-velpatasvir plus voxilaprevir once daily for 12 weeks.[7] The addition of ribavirin has been shown to improve the rates of SVR in response to treatment with a number of regimens including sofosbuvir/velpatasvir for patients with decompensated cirrhosis.[8] The potential benefit to DAA-experienced patients with the addition of ribavirin to a sofosbuvir-velpatasvir-voxilaprevir regimen has not been explored.

In this study, we evaluated the efficacy and safety of a fixed-dose combination of sofosbuvir-velpatasvir-voxilaprevir with and without ribavirin administered once daily for 12 weeks in patients with genotype 1 HCV infection who were previously treated with a DAA-based regimen.

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Methods

Study design

This phase 2 study, open-label study was conducted between July 2015 and June 2016 at a single center in the United States (NCT02536313). Patients were randomized to receive a fixed-dose combination of sofosbuvir-velpatasvir-voxilaprevir (400 mg; 100 mg; 100 mg) once daily with or without weight-adjusted ribavirin (1000 or 1200 mg/day) administered twice daily in a divided dose for 12 weeks. Randomization was stratified by NS5A inhibitor experience and the presence of cirrhosis.

Patients

This study included patients with chronic HCV genotype 1 infection who were ≥18 years of age and had a body mass index ≥18 kg/m^2. Eligible patients were required to have HCV RNA ≥10^4 IU/mL at screening, and must have received prior HCV treatment for a duration of ≥6 weeks with a regimen containing at least one DAA (NS3/4A protease inhibitor, NS5A inhibitor, NS5B inhibitor) with or without RBV and/or PEG-IFN. The most recent treatment must have been completed ≥8 weeks prior to screening. Patients were excluded from the study if they met any of the following criteria at screening: had clinically significant electrocardiogram abnormalities; alanine aminotransferase (ALT) >10 × the upper limit of normal (ULN); aspartate aminotransferase levels >10 × ULN; direct bilirubin >1.5 ULN; platelets <75,000/μL for patients without cirrhosis or <50,000/μL for patients with cirrhosis; hemoglobin A1c >8.5%; estimated creatinine clearance <60 mL/min; hemoglobin <11 g/dL for female patients, and <12 g/dL for male patients; albumin <3 g/dL; or international normalized ratio (INR) >1.5 × ULN unless the patient had hemophilia or was receiving anticoagulants affecting INR. Patients with hepatitis B

or HIV infection, or those with current or prior history of clinical hepatic decompensation; solid organ transplantation; significant pulmonary or cardiac disease or porphyria were also excluded from the study.

All patients provided written informed consent before the initiation of any study-related procedures. This study was approved by an institutional review board, and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation guidelines.

Assessments

Plasma samples were collected at screening, predose, weeks 1, 2, 4, 8, and 12 of treatment, and at posttreatment weeks 4, 12, and 24. HCV RNA levels were assessed using the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test, version 2.0 (lower limit of quantification [LLOQ] <15 IU/mL). HCV genotype and subtype were identified using the Siemens VERSANT HCV genotype INNO-LiPA 2.0 assay. IL28B genotype was determined by polymerase chain reaction amplification of the rs12979860 locus. Deep sequencing of the HCV NS3, NS5A, and NS5B coding regions was performed on samples obtained from all patients at baseline and at virologic failure; resistance-associated substitutions (RASs) are reported using a 15% cutoff.[9]

Safety assessments included recording of adverse events (AEs), clinical laboratory tests, physical examinations, and vital sign measurements.

Outcomes

The primary objectives of the study were to evaluate the proportion of patients achieving sustained virologic response 12 weeks after the end of treatment (SVR12), and to assess the

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safety and tolerability of sofosbuvir-velpatasvir-voxilaprevir. Secondary endpoints included determining the proportion of patients with virologic failure, and assessing the emergence of viral resistance to sofosbuvir, velpatasvir, and voxilaprevir during and after the end of treatment.

Statistical analysis

A formal statistical hypothesis testing was not performed in this study. All patients who received ≥1 dose of study drug were included in the primary efficacy and safety analysis sets. The 95% confidence intervals for the SVR12 were calculated using the Clopper-Pearson method. Statistical analyses were summarized using SAS software (SAS Institute, Cary, North Carolina).

Results

Patient characteristics

A total of 61 patients with HCV genotype 1 were screened for this study, of whom 49 were randomized to receive treatment (**Figure 1**). Among these patients, 24 and 25 patients received sofosbuvir-velpatasvir-voxilaprevir without and with ribavirin, respectively. A majority of the patients were male (65%), white (80%), and under 65 years of age (90%; **Table 1**). Slightly more than half of patients presented with cirrhosis at baseline (51%). Most patients had been treated for HCV infection only once prior to this study (88%), and 40.8% had previously received an NS5A inhibitor with or without another DAA. Five patients overall had a history of prior interferon-based therapy.

Baseline deep sequencing data was available for 48 patients, among whom 35 (73%) had resistance-associated substitutions. Of these patients, 15% had NS5A RASs only, 31% with NS3 RASs only, and 27% with multiple class RASs.

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Response during treatment

By week 4 of treatment, HCV RNA levels were <LLOQ for all 24 patients receiving sofosbuvir-velpatasvir-voxilaprevir therapy, and for 23 of 25 patients (92%) receiving sofosbuvir-velpatasvir-voxilaprevir plus ribavirin (**Table 3**). All patients in both treatment groups achieved HCV RNA <LLOQ by week 8 of treatment, which was sustained through the end of treatment.

Post-treatment response and viral resistance testing

Overall, 24 of 24 patients (100%) receiving sofosbuvir-velpatasvir-voxilaprevir alone, and 24 of 25 patients (96%) receiving sofosbuvir-velpatasvir-voxilaprevir with ribavirin achieved SVR12 (**Table 2**). A 61-year-old black male with HCV subtype 1a infection, cirrhosis, and IL28B CC genotype with undetectable HCV RNA from treatment weeks 2 through 12 relapsed at follow-up week 4. This patient, who had previously received treatment with ledipasvir-sofosbuvir for 24 weeks, presented with the NS5A RAS L31M at baseline; no RASs were detected in NS3 and NS5B. At relapse, M28T, Q30R, L31M RASs were observed in NS5A, and V36M, Q41R, D168G in NS3.

Virologic response was achieved by 13 of 13 (100%) patients without baseline RASs, and by 34 of 35 (97%) patients with baseline RASs (**Figure 2**). Subgroup analyses indicated that treatment was effective regardless of the presence or absence of cirrhosis, NS5A inhibitor exposure, and the number of DAA classes used in prior therapy.

Safety

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There were no discontinuations from sofosbuvir-velpatasvir-voxilaprevir therapy due to AEs (**Table 3**), while 3 patients (6%) discontinued ribavirin as a result of the AEs of anemia, fatigue, and rash, respectively. Ribavirin dose was modified or interrupted for 3 patients (12%) due to the AE of anemia. AEs were reported in 11 patients (46%) receiving sofosbuvir-velpatasvir-voxilaprevir alone, and in 15 patients (60%) receiving sofosbuvir-velpatasvir-voxilaprevir plus ribavirin, most of which were mild or moderate in severity. The most common AEs were diarrhea (13%) and bronchitis (8%) in patients receiving sofosbuvir-velpatasvir-voxilaprevir alone, and fatigue (36%), anemia (16%), gastroenteritis (8%), and nausea (8%) in those receiving sofosbuvir-velpatasvir-voxilaprevir plus ribavirin. Overall, 1 serious AE – pneumonia – was reported in a patient receiving sofosbuvir-velpatasvir-voxilaprevir alone, and was considered unrelated to treatment. Grade 3 laboratory abnormalities were detected in 1 patient receiving sofosbuvir-velpatasvir-voxilaprevir, and in 6 patients receiving sofosbuvir-velpatasvir-voxilaprevir plus ribavirin; no grade 4 abnormalities were reported. Platelet abnormalities were reported for 1 patient in the sofosbuvir-velpatasvir-voxilaprevir group. In the sofosbuvir-velpatasvir-voxilaprevir plus ribavirin group, abnormalities in hemoglobin were observed in 4 patients (16%), lymphocytes in 1 patient (4%), platelets in 1 patient (4%), ALT in 1 patient (4%), and serum glucose in 1 patient (4%).

Discussion

Although interferon-free DAA-based regimens are highly successful for the vast majority of patients with genotype 1 HCV infection, a few patients nevertheless fail treatment. Retreatment options for these patients remain unclear. Current guidelines from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America recommend delaying

treatment for these patients until the emergence of new data, provided they do not have cirrhosis or do not require immediate retreatment.[10]

A few studies involving a small number of patients have explored retreatment options in genotype 1-infected patients who failed to achieve a virologic response with interferon-free DAA-based therapies. Retreatment approaches in these studies include prolonging treatment duration, or supplementing therapy with ribavirin or other DAAs. For example, among patients who failed 8 or 12 weeks of prior ledipasvir-sofosbuvir-containing therapy, administration of a fixed-dose combination of ledipasvir-sofosbuvir for 24 weeks resulted in an SVR12 rate of only 71%.[11] The presence of baseline NS5A RASs increased the likelihood of treatment failure in these patients. In the C-SWIFT retreatment study, 25 patients who failed short-term (4–8 weeks) treatment with a fixed-dose combination of the NS5A inhibitor elbasvir and the NS3/4A protease inhibitor grazoprevir plus sofosbuvir were retreated with the same regimen supplemented with ribavirin for 12 weeks and all patients completing treatment achieved SVR12.[12] In the QUARTZ-1 study, 21 of 22 (95%) patients who were unsuccessfully treated with prior DAA-based therapies achieved virologic response upon retreatment with ombitasvir-paritaprevir-ritonavir and dasabuvir plus sofosbuvir for 12 or 24 weeks depending on genotype 1 subtype and cirrhosis status.[13] In another study, administration of sofosbuvir-velpatasvir plus voxilaprevir for 12 weeks resulted in a virologic response in all 61 patients who had previously failed a DAA-based regimen, regardless of their cirrhosis status.[7]

In this open-label study, a fixed-dose regimen of sofosbuvir-velpatasvir-voxilaprevir with or without ribavirin administered for 12 weeks was highly effective in patients with HCV genotype 1 infection who were previously unsuccessfully treated with a DAA-based therapy. Only 1 patient in the sofosbuvir-velpatasvir-voxilaprevir plus ribavirin treatment arm of the

study relapsed after the end of treatment. This patient had genotype 1a infection, cirrhosis, and the baseline NS5A RASs L31M, which confers 16-fold shift in EC_{50} to velpatasvir. At virologic failure, the NS5A RASs M28T, Q30R, and L31M were detected. The double mutant Q30R+L31M is predicted to confer >100-fold resistance to velpatasvir.[13] Additionally, no NS3 RASs were detected at baseline, but V36M, Q41R, and D168G emerged at relapse. The triple mutant V36M+Q41R+D168G confer 11.5-fold resistance to voxilaprevir. Overall, treatment efficacy was maintained regardless of the presence of baseline RASs, status of cirrhosis or prior NS5A inhibitor therapy, or the number of DAA classes used in previous therapy regardless of the presence of ribavirin. It appears that the combination of three highly potent DAAs can obviate the need for ribavirin to be included in a regimen to maximize efficacy. Study treatment was also well-tolerated with the observed safety profile consistent with earlier findings. This study is limited by its relatively small sample size, lack of enrollment of Asian patients and open-label design. In four subsequent phase 3 registrational trials, patients of all genotypes and treatment histories were enrolled in blinded and open-label studies, in which treatment was similarly well-tolerated and efficacious.[15,16]

In conclusion, 12 weeks of treatment with a fixed-dose combination of sofosbuvir-velpatasvir-voxilaprevir was effective and well tolerated among patients with genotype 1 infection who had previously failed a DAA-based regimen.

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Figure legends

Figure 1. Patient disposition.

Figure 2. Virologic response by baseline RASs using 15% assay cutoff. RAS, resistance associated substitutions; SVR12, sustained virologic response at 12 weeks posttreatment.

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Table 1. Demographic and baseline characteristics

Characteristic	SOF-VEL-VOX 12 Weeks N = 24	SOF-VEL-VOX + RBV 12 Weeks N = 25	Total N = 49
Mean age, years (range)	54 (18–71)	54 (22–75)	54 (18–75)
Male, n (%)	16 (67)	16 (64)	32 (65)
Mean BMI, kg/m^2 (range)	32 (21–55)	30 (20–50)	31 (20–55)
Race, n (%)			
White	17 (71)	22 (88)	39 (80)
Black	7 (29)	3 (12)	10 (20)
HCV genotype, n (%)			
1a	21 (88)	22 (88)	43 (88)
1b	3 (13)	3 (12)	6 (12)
Mean HCV RNA ± SD (log_{10} IU/mL)	6.2 ± 0.42	6.3 ± 0.46	6.3 ± 0.44
HCV RNA ≥800,000 IU/mL, n (%)	20 (83)	20 (80)	40 (82)
IL28B genotype, n (%)			
CC	2 (8)	5 (20)	7 (14)
CT	10 (42)	13 (52)	23 (47)
TT	12 (50)	7 (28)	19 (39)
Cirrhosis, n (%)	11 (46)	14 (56)	25 (51)
Alanine aminotransferase >1.5×ULN, n (%)	11 (46)	15 (60)	26 (53)
Prior HCV treatment experience, n (%)			
DAA-experienced	24 (100)	25 (100)	49 (100)
NS5A ± DAA (s)	10 (42)	10 (40)	20 (41)
NS5A alone	3 (13)	0	3 (6)
NS5A + NS5B	1 (4)	6 (24)	7 (14)
NS5A + NS5B + NS3	6 (25)	4 (16)	10 (20)
Non-NS5A ± DAA (s)	14 (58)	15 (60)	29 (59)
NS5B alone	5 (21)	3 (12)	8 (16)
NS3 alone	6 (25)	9 (36)	15 (31)
NS5B + NS3	3 (13)	3 (12)	6 (12)
Number of DAA classes exposed to in prior treatment(s), n (%)			
1	14 (58)	12 (48)	26 (53)
2	4 (17)	9 (36)	13 (27)
≥3	6 (25)	4 (16)	10 (20)
Number of prior HCV treatment regimens, n (%)			
1	20 (83)	23 (92)	43 (88)
2	2 (8)	2 (8)	4 (8)
≥3	2 (8)	0	2 (4)
Most recent HCV treatment response, n (%)			
Non-responder	5 (21)	5 (20)	10 (20)
Relapse/breakthrough	19 (79)	20 (80)	39 (80)

BMI, body mass index; DAA, direct-acting antivirals; HCV, hepatitis C virus; NS, nonstructural; RBV, ribavirin; SD, standard deviation; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir; ULN, upper limit of normal

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Table 2. Virologic response during and after treatment

Variable	SOF-VEL-VOX 12 Weeks N = 24	SOF-VEL-VOX + RBV 12 Weeks N = 25
HCV RNA <15 IU/mL during treatment, n (%)		
Week 1	13 (54)	10 (40)
Week 2	19 (79)	15 (60)
Week 4	24 (100)	23 (92)
Week 8	24 (100)	25 (100)
SVR12, n (%)	24 (100)	24 (96)
95% CI	86 to 100%	80 to 100%
Virologic failure during treatment, n (%)	0	0
Relapse, n (%)	0	1 (4)

CI, confidence interval; HCV, hepatitis C virus; SOF, sofosbuvir; SVR12, sustained virologic response 12 weeks after the end of treatment; VEL, velpatasvir; VOX, voxilaprevir

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Table 3. Adverse events and laboratory abnormalities

Variable	SOF-VEL-VOX 12 Weeks N = 24	SOF-VEL-VOX + RBV 12 Weeks N = 25
Any treatment-emergent event	11 (46)	15 (60)
AEs leading to discontinuation of SOF-VEL-VOX	0	0
Deaths	0	0
Serious AEs	1 (4)	0
AEs (>5%)		
Fatigue	0	9 (36)
Anemia	0	4 (16)
Diarrhea	3 (13)	0
Gastroenteritis	1 (4)	2 (8)
Bronchitis	2 (8)	0
Nausea	0	2 (8)
Grade 3 or 4 Laboratory Abnormalities, n (%)	1 (4)	6 (24)
Decreased hemoglobin level		
<10 g/dL	0	6 (24)
<8.5 g/dL	0	2 (8)
Platelet count 25,000 to <50,000/mm^3	1 (4)	1 (4)
Lymphocyte count 350 to <500/mm^3	0	1 (4)
ALT >5.00 to 10.00 × ULN	0	1 (4)
Serum glucose >250 to 500 mg/dL	0	1 (4)

AE, adverse event; ALT, alanine aminotransferase; RBV, ribavirin; SOF, sofosbuvir; ULN, upper limit of normal; VEL, velpatasvir; VOX, voxilaprevir

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Figure 1. Patient disposition.

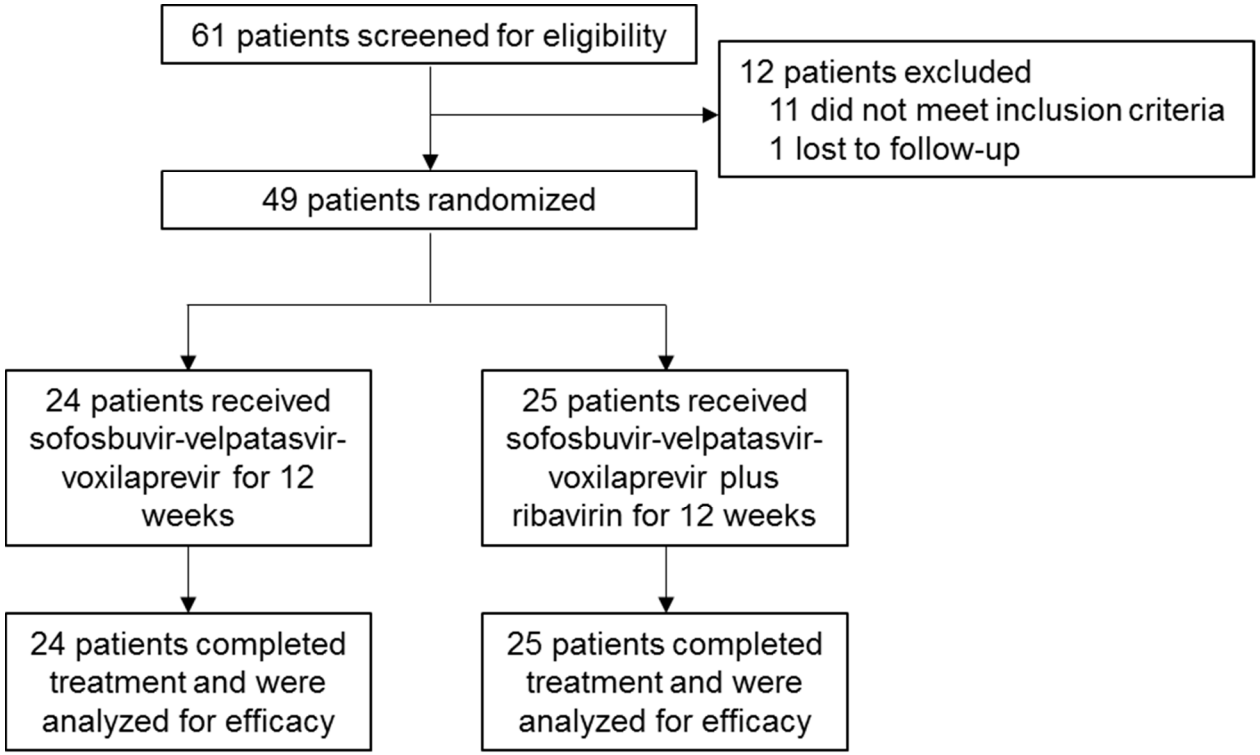

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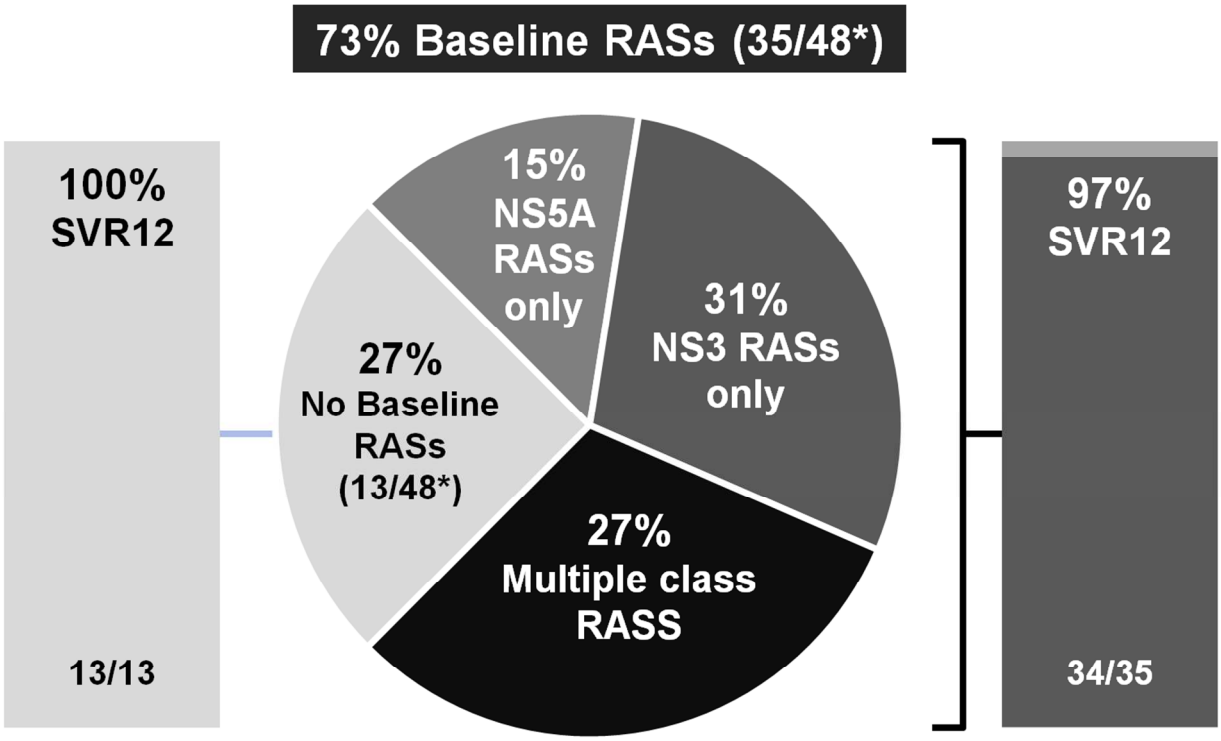
Figure 2. Virologic response by baseline RASs. RAS, resistance associated substitutions; SVR12, sustained virologic response at 12 weeks posttreatment.



*Deep sequencing with 15% assay cutoff; baseline sequence was not available for 1 patient