Efficacy of Sofofbuvir, Velpatasvir, and GS-9857 in Patients With Genotype 1 Hepatitis C Virus Infection in an Open-Label, Phase 2 Trial


1Texas Liver Institute, University of Texas Health Sciences Center, San Antonio, Texas; 2Rush University Medical Center, Chicago, Illinois; 3Orlando Immunology Center, Orlando, Florida; 4University of Pittsburgh, Pittsburgh, Pennsylvania; 5Schiff Center for Liver Diseases, University of Miami Miller School of Medicine, Miami, Florida; 6Gastrointestinal Specialists of Georgia, Marietta, Georgia; 7GastroOne, Germantown, Tennessee; 8Quality Medical Research Center, Nashville, Tennessee; 9University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; 10Sinai Medical Center, Los Angeles, California; 11Medical Associates Research Group, Inc, San Diego, California; 12Infectious Disease Care, Hillsborough, New Jersey; 13Gilead Sciences, Foster City, California; 14Atlanta Medical Center, Atlanta, Georgia; 15The Liver Institute of Virginia, Richmond, Virginia; 16Southwest CARE Center, Santa Fe, New Mexico; 17Beth Israel Deaconess Medical Center, Boston, Massachusetts; 18Mount Sinai Beth Israel, New York, New York

BACKGROUND & AIMS: The best regimen to re-treat patients who do not respond to direct-acting antivirals (DAAs) and the feasibility of further shortening regimens is unclear. We assessed the efficacy and safety of the combination of the nucleotide polymerase inhibitor sofofbuvir, the NS5A inhibitor velpatasvir, and the NS3/4A protease inhibitor GS-9857 in patients with hepatitis C virus genotype 1 infection. METHODS: We performed an open-label trial at 32 sites in the United States and at 2 sites in New Zealand of 197 patients with genotype 1 hepatitis C virus infection, with or without compensated cirrhosis, who were treatment-naïve or were treated previously with a DAA. Between March 2, 2015, and September 1, 2015, patients received sofofbuvir-velpatasvir (400 mg/100 mg in a fixed-dose combination) plus GS-9857 (100 mg) once daily for 6–12 weeks, plus ribavirin for 1 treatment group consisting of treatment-naïve patients with cirrhosis. The primary end point was sustained virologic response 12 weeks after treatment (SVR12). RESULTS: Among treatment-naïve patients without cirrhosis, 71% (24 of 34; 95% confidence interval [CI], 53–85) achieved SVR12 after 6 weeks of treatment and 100% (36 of 36; 95% CI, 90%–100%) achieved SVR12 after 8 weeks of treatment. Among treatment-naïve patients with cirrhosis, 94% (31 of 33; 95% CI, 80–99) achieved SVR12 after 8 weeks of treatment and 81% (25 of 31; 95% CI, 63–93) achieved SVR12 after 8 weeks of treatment with ribavirin. Among DAA-experienced patients treated for 12 weeks, 100% without cirrhosis (31 of 31; 95% CI, 89–100) and 100% with cirrhosis (32 of 32; 95% CI, 89–100) achieved SVR12. The most common adverse events were headache, diarrhea, fatigue, and nausea. One patient (<1%) discontinued treatment because of adverse events. CONCLUSIONS: In a phase 2 open-label trial, we found 8 weeks of treatment with sofofbuvir-velpatasvir plus GS-9857 to be safe and effective in treatment-naïve patients; 12 weeks was safe and effective in patients previously treated with DAAs. The combination was safe and effective in patients with or without compensated cirrhosis. clinicaltrials.gov no: NCT02378935.

Keywords: Direct-Acting Antiviral Agent; NS5A; NS5B; NS3/4A.

© 2016 by the AGA Institute. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license ( http://creativecommons.org/licenses/by-nc-nd/4.0/). 0016-5085 http://dx.doi.org/10.1053/j.gastro.2016.07.039
currently no approved regimen for patients who have failed an HCV regimen including an NS5A inhibitor. Current treatment recommendations for NS5A inhibitor-experienced patients suggest delaying therapy in those without urgent indications for treatment and, when treatment is necessary, long durations with the addition of ribavirin often are advised on the basis of minimal evidence. One possible strategy to address the need for a salvage regimen is to combine highly potent DAAs with enhanced activity against RASs. Such a combination regimen additionally may allow for shortening of treatment duration in patients who have not been treated previously for HCV.

Sofosbuvir is a nucleotide analogue inhibitor of the HCV NS5B polymerase approved for the treatment of genotypes 1–6 HCV infection in combination with other agents. Velpatasvir is a novel HCV NS5A inhibitor with pan-genotypic efficacy. The combination of sofosbuvir and velpatasvir has been shown in phase 3 clinical trials to be highly effective and safe in treatment-naïve and previously treated patients with HCV of all genotypes, including those with compensated and decompensated cirrhosis. GS-9857 is a novel macrocyclic NS3/4A protease inhibitor with potent in vitro antiviral activity against genotypes 1–6 HCV and broad coverage of NS3/4A protease polymorphisms, including RASs associated with first-generation NS3/4A protease inhibitors. In a phase 1 trial, administration of 100 mg of GS-9857 to patients with genotypes 1–4 HCV resulted in median maximum reductions in HCV-RNA levels of 3 log_{10} IU/mL or greater.

We assessed the efficacy and safety of 6–12 weeks of sofosbuvir-velpatasvir plus GS-9857 in treatment-naïve patients and patients previously treated with DAA-containing regimens with genotype 1 HCV, including those with compensated cirrhosis.

Materials and Methods

Study Design

This open-label, 2-cohort, phase 2 study was conducted between March 2, 2015, and September 1, 2015, at 32 sites in the United States and at 2 sites in New Zealand. Cohort 1 enrolled treatment-naïve patients, and cohort 2 enrolled patients previously treated with regimens that contained an NS5A inhibitor alone, or 2 or more classes of DAAs.

Cohort 1. At the time the study was initiated, 2 groups of treatment-naïve patients were enrolled in cohort 1: a group of patients without cirrhosis, who received sofosbuvir-velpatasvir plus GS-9857 for 6 weeks, and a group of patients with cirrhosis, who received sofosbuvir-velpatasvir plus GS-9857 for 8 weeks. The protocol specified that if the rate of relapse among patients with cirrhosis who received 8 weeks of treatment was 10% or less, there was an option that another group of patients could be enrolled to receive 8 weeks of treatment. This option was not exercised. Instead, preliminary results from these first 2 groups prompted us to amend the protocol to add 2 groups to this cohort: a group of patients without cirrhosis, who received 8 weeks of sofosbuvir-velpatasvir plus GS-9857, and a group of patients with cirrhosis, who received 8 weeks of sofosbuvir-velpatasvir plus GS-9857 with ribavirin.

Cohort 2. Two groups of DAA-experienced patients—those with and without cirrhosis—were enrolled in cohort 2. Both groups received 12 weeks of sofosbuvir-velpatasvir plus GS-9857. The protocol specified that if the rate of relapse in either group was 10% or less, there was an option that another group of patients could be enrolled to receive 8 weeks of treatment. This option was not exercised.

Patients. Enrollment was open to patients at least 18 years of age chronically infected with genotype 1 HCV with serum HCV levels of at least 10,000 IU/mL. Cirrhosis was defined as any one of the following: biopsy showing cirrhosis (Metavir score of 4 or Ishak score of ≥5), transient elastography (FibroScan; Echosens, Paris, France) result greater than 12.5 kPa, or a FibroTest (Biopredictive, Paris, France) score greater than 0.75 together with an aspartate aminotransferase-to-platelet ratio index greater than 2 during screening. Exclusion criteria included a platelet count less than 50,000 cells/μL, hemoglobin level less than 110 g/L for women and less than 120 g/L for men, albumin level less than 30 g/L, creatinine clearance less than 60 mL/min as calculated by the Cockcroft-Gault equation, and prothrombin time or direct bilirubin greater than 1.5 times the upper limit of normal. Patients with evidence of decompensation (ie, clinical ascites, encephalopathy, or variceal hemorrhage) and those with hepatocellular carcinoma were excluded.

Written informed consent was obtained from all patients before enrollment and before any study procedures were performed. The study was approved by the institutional review board or independent ethics committee at all participating sites and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The sponsor (Gilead Sciences) collected the data, monitored the study conduct, and performed the statistical analyses. All authors had access to the study data and reviewed and approved the final manuscript.

Procedures

All patients received a fixed-dose combination tablet of sofosbuvir 400 mg and velpatasvir 100 mg once daily, along with a 100-mg tablet of GS-9857 once daily, taken with food. Ribavirin was administered 1000–1200 mg/day (1000 mg for patients weighing <75 kg and 1200 mg for patients weighing ≥75 kg) in a divided daily dose. This was an open-label study, in which patients were enrolled by investigators at the study centers. No participants or study personnel were blinded to treatment assignments at any time during the study.

Assessments

Serum HCV-RNA concentrations were measured using the COBAS AmpliPrep/COBAS TaqMan HCV Test, v2.0 (Roche, Indianapolis, IN) with a lower limit of quantification for HCV RNA of less than 15 IU/mL. HCV genotype and subtype were determined using the Siemens Versant HCV Genotype INNO-LIPA 2.0 assay (Tarrytown, NY). For all patients, the interleukin 28B genotype was determined by polymerase chain reaction amplification and sequencing of the rs12979860 single-nucleotide polymorphism.

Deep sequencing of the NS3A, NS5A, and NS5B regions of the HCV RNA using MiSeq technology (DDL Diagnostic Laboratory, Rijswijk, The Netherlands) was performed at baseline for all patients and at the time of virologic failure for all
patients who did not achieve SVR 12 weeks after treatment (SVR12). The resulting sequences were compared with reference sequences or sequences from baseline samples to determine the prevalence of RASs and the association of RASs with virologic outcomes. RASs present at greater than 1% and 15% of sequence reads were reported, unless specified.

Safety was assessed in all patients at all on-treatment visits and for 30 days after the completion of treatment by physical examination and review of adverse events and laboratory test results.

Outcomes

The primary efficacy end point of this study was SVR12 (serum HCV-RNA level <15 IU/mL) in all patients who were enrolled and received at least 1 dose of study drug. The secondary efficacy end points included the proportion of patients with virologic failure. The primary safety end point was any adverse event leading to the permanent discontinuation of study treatment.

Statistical Analysis

For this exploratory phase 2 study we did not plan or conduct any inferential statistics. No formal sample size calculations were used to determine the group size of 30. The SVR12 rate in each of the treatment groups was calculated with 2-sided 95% exact confidence intervals (CIs) based on the Clopper–Pearson method.

Role of the Funding Source

The study sponsor oversaw trial management, data collection, statistical analyses, and the writing and review of the report. All authors had access to the study data and had reviewed and approved the final manuscript.

Results

Of the 247 patients screened, 197 were enrolled and received treatment: 34 treatment-naive patients without cirrhosis, 33 treatment-naive patients with cirrhosis, 31 previously treated patients without cirrhosis, and 32 previously treated patients with cirrhosis (Supplementary Figure 1). Reasons for screen failure are listed in the Appendix. Baseline characteristics of patients are shown in Table 1. The groups were balanced overall with regard to baseline characteristics. A majority of patients in all groups were men, of white race, with genotype 1a infection and non-CC interleukin 28B genotypes. Among the DAA-experienced patients in cohort 2, 46% previously received a NS5A inhibitor (ledipasvir, n = 7; daclatasvir, n = 11; other, n = 11) and 54% previously received a NS3/4A protease inhibitor and a NS5B polymerase inhibitor (simeprevir with sofosbuvir, n = 25; other, n = 9).

By week 4 of treatment, 68 of 70 (97%) treatment-naive patients without cirrhosis and 60 of 64 (94%) treatment-naive patients with cirrhosis had HCV-RNA levels less than 15 IU/mL. Among treatment-experienced patients, 29 of 31 (94%) without cirrhosis and 31 of 32 (97%) with cirrhosis had HCV-RNA levels less than 15 IU/mL by week 4 of treatment. By week 8 of treatment, all patients receiving at least 8 weeks of treatment had a HCV-RNA level less than 15 IU/mL. In treatment-naive patients with cirrhosis, the addition of ribavirin appeared to have no impact on HCV viral kinetics (Table 2).

Among treatment-naive patients without cirrhosis, rates of SVR12 were 71% (24 of 34; 95% CI, 53–85) in patients receiving 6 weeks of treatment, and 100% (36 of 36; 95% CI, 90–100) in patients receiving 8 weeks of treatment (Table 2). Among treatment-naive patients with cirrhosis, rates of SVR12 were 94% (31 of 33; 95% CI, 80–99) in patients receiving 8 weeks of sofosbuvir-velpatasvir plus GS-9857 and 81% (25 of 31; 95% CI, 63–93) in patients receiving 8 weeks of sofosbuvir-velpatasvir plus GS-9857 with ribavirin (Table 2). Among patients previously treated with DAA-containing regimen(s), rates of SVR12 were 100% (31 of 31; 95% CI, 89–100) in patients without cirrhosis receiving 12 weeks of treatment, and 100% (32 of 32; 95% CI, 89–100) in patients with cirrhosis receiving 12 weeks of treatment. Across the groups, no significant differences in SVR12 rates were observed based on baseline differences (Appendix). Eighteen patients with virologic failure relapsed after the end of treatment; no patient had a virologic breakthrough during treatment (Appendix).

Baseline sequencing was available for 197 of the 197 patients enrolled in the study. Overall, 63% (84 of 134) of treatment-naive and 83% (52 of 63) of DAA-experienced patients had baseline class RASs in at least 1 of the 3 target genes (NS3, NS5A, and NS5B), with a 1% deep sequencing assay cut-off level (Table 3). Among the DAA-experienced patients, 93% (27 of 29) of the NS5A inhibitor-experienced patients had NS5A RASs, as compared with 21% (7 of 34) of DAA-experienced patients who were not treated previously with an NS5A inhibitor (data not shown).

Table 3 shows the SVR rates for patients without RASs and with single and multiclass NS3, NS5A, and NS5B RASs with a 1% sequencing cut-off level. In treatment-naive patients, 8 weeks of treatment with sofosbuvir-velpatasvir plus GS-9857 without ribavirin led to SVR12 in 96% (23 of 24) and 98% (44 of 45) of patients without and with baseline RASs, respectively. Use of a 15% sequencing cut-off level led to a similar result (Supplementary Material). All DAA-experienced patients, regardless of the presence of single or multiclass RASs, achieved SVR12 after 12 weeks of treatment with sofosbuvir-velpatasvir plus GS-9857. There were 12 DAA-experienced patients with the NS5A RAS Y93H/N at baseline, all of whom achieved SVR12.

Sequencing data were available for all 18 treatment-naive patients who relapsed. Eleven of 18 patients (61%) had the same number of or fewer RASs at the time of virologic relapse than at baseline. Four of 18 patients (22%) had no RASs both at baseline and at virologic relapse. Only 3 patients had treatment-emergent RASs, all in the NS3 gene and all at frequencies less than 2% of the viral population. The treatment-emergent NS3 RASs included V170T, Q418R/A156T, and V36M. Of these, only A156T resulted in an ~500-fold shift in median effective concentration in genotype 1a and 1b replicon assays.

The most common adverse events were headache, nausea, fatigue, and diarrhea (Table 4). Overall, 64% of
<table>
<thead>
<tr>
<th>Treatment naive</th>
<th>DAA experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Age, y</strong></td>
<td>53</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>23 (68)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>31 (91)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Hawaiian or Pacific Islander</td>
<td>0</td>
</tr>
<tr>
<td><strong>Mean BMI, kg/m² (SD)</strong></td>
<td>26.1 (4.64)</td>
</tr>
<tr>
<td><strong>HCV RNA level, log_{10} IU/mL</strong></td>
<td>6.2 (0.51)</td>
</tr>
<tr>
<td><strong>HCV genotype</strong></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>27 (79)</td>
</tr>
<tr>
<td>1b</td>
<td>7 (21)</td>
</tr>
<tr>
<td>IL28b</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>12 (35)</td>
</tr>
<tr>
<td>CT</td>
<td>15 (44)</td>
</tr>
<tr>
<td>TT</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
</tr>
<tr>
<td><strong>Baseline ALT level, U/L (SD)</strong></td>
<td>61 (34.8)</td>
</tr>
<tr>
<td><strong>DAA experience</strong></td>
<td></td>
</tr>
<tr>
<td>NS5A inhibitor with or without other DAA(s)</td>
<td>NA</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>NA</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>NA</td>
</tr>
<tr>
<td>Other</td>
<td>NA</td>
</tr>
<tr>
<td>NS3/4A protease inhibitor and NS5B polymerase inhibitor</td>
<td>NA</td>
</tr>
<tr>
<td>Sofosbuvir-simeprevir</td>
<td>NA</td>
</tr>
<tr>
<td>Other</td>
<td>NA</td>
</tr>
</tbody>
</table>

BMI, body mass index; IL, interleukin; NA, not applicable; RBV, ribavirin; SOF-VEL, sofosbuvir-velpatasvir.
patients experienced at least 1 adverse event. Patients in the ribavirin-containing group had higher rates of fatigue (32%) and anemia (23%) than patients in the other groups. Two patients, both in the group of treatment-naive patients with cirrhosis receiving 8 weeks of treatment without ribavirin, had treatment-emergent serious adverse events: a 61-year-old white woman with valvular disease experienced atrial flutter on day 35 of treatment, and a 67-year-old white woman had vertigo on post-treatment day 26.

One patient discontinued treatment because of adverse events. This patient, a 50-year-old black woman with cirrhosis who was receiving sofosbuvir-velpatasvir plus GS-9857 with ribavirin, stopped study treatment on day 24 after having confirmed abnormally high levels of alanine aminotransferase (ALT) (grade 3) and aspartate aminotransferase (grade 2). A single grade 1 increase in total bilirubin was observed at study treatment week 2, and remained within normal limits at all other timepoints. Aminotransferase levels returned to normal 4 weeks after stopping the study drug. An evaluation for acute causes of hepatitis was negative. Another patient in the same treatment group discontinued ribavirin after experiencing diarrhea, nausea, vomiting, and rib soreness on day 2 of treatment. This patient continued sofosbuvir-velpatasvir plus GS-9857 without ribavirin and achieved SVR12.

One treatment-naive patient with cirrhosis who received 8 weeks of treatment died on day 175 of follow-up evaluation. The cause of death was atypical pneumonia.

Overall, 19 patients (10%) had grade 3 laboratory abnormalities and 2 patients (1%) had grade 4 laboratory abnormalities. Grades 3 and 4 laboratory abnormalities occurred almost exclusively in patients with cirrhosis. There were 4 patients with cirrhosis who had postbaseline hemoglobin values less than 10 g/dL; all were receiving ribavirin. One patient (mentioned earlier) had a grade 3 ALT increase (>5 \times \text{ upper limit of normal (ULN)})]. No patient had a grade 2 ALT increase (an increase of >2.5 to 5 \times \text{ ULN}) and 2 patients (both cirrhotic) had a grade 1 ALT increase (increases to 1.25–2.5 \times \text{ ULN}).

**Discussion**

The development of oral DAAs represents a major advance in the treatment of HCV in patients of all genotypes. Currently available DAA combination regimens offer SVR rates well over 90% overall and in most patient subpopulations. Nevertheless, some patients do not achieve SVR with existing regimens. Patients who have failed prior treatment with first-generation NS3/4A protease inhibitors (eg, telaprevir, boceprevir, or simeprevir) may be re-treated with ledipasvir-sofosbuvir, but patients who have been treated unsuccessfully with a regimen that includes an NS5A inhibitor have no approved re-treatment options. In a previous trial, patients with genotype 1 HCV who did not achieve SVR after 8 or 12 weeks of ledipasvir-sofosbuvir-based regimens and subsequently were re-treated with 24 weeks of ledipasvir-sofosbuvir had an SVR12 rate of only 71%. In this population, the presence of baseline NS5A RASs was associated with a higher rate of...
virologic failure. In another small trial, 14 of 16 patients (88%) who previously failed a daclatasvir-containing regimen achieved SVR12 after re-treatment with simeprevir-sofosbuvir for 12 weeks. Thirteen of the 16 patients had NS5A RASs at baseline, and, of these 13, 11 (85%) achieved SVR12. The 2 patients who did not achieve SVR12 had Q30K and L31M substitutions as the dominant viral populations at re-treatment baseline.

In this open-label, phase 2 study, 12 weeks of treatment with sofosbuvir-velpatasvir plus GS-9857 was safe and highly effective in patients with HCV genotype 1, with and without cirrhosis, who did not achieve SVR after prior treatment with DAAs, including those who previously received an NS5A inhibitor. In treatment-naive patients, the 8-week regimen was safe and effective, regardless of cirrhosis status. Among the treatment-naive patients who relapsed, the presence of baseline RASs appeared to have no impact on treatment outcome. Treatment-emergent RASs by deep sequencing with a 1% cut-off rate were rare (3 of 18; 17%), and no treatment-emergent RASs among relapers were detected with the 15% cut-off level. This is consistent with the anticipated high barrier of resistance of the combination therapy based on in vitro data.

Treatment-naive patients without cirrhosis treated for 8 weeks achieved a SVR12 rate of 100%, which was higher than results reported in a recent study of combining 3 DAAs for treatment for the same population and treatment duration. Treatment-naive patients with cirrhosis treated for 8 weeks had lower SVR12 rates (81%–94%) than patients without cirrhosis. Larger studies will determine whether this short duration is adequate for this patient population.

One unexpected result in our trial was the apparent lack of benefit of the addition of ribavirin to sofosbuvir-velpatasvir plus GS-9857 for treatment-naive patients with cirrhosis. Although patients in this group receiving ribavirin had a numerically lower rate of SVR12 than treatment-naive patients with cirrhosis who received sofosbuvir-velpatasvir plus GS-9857 without ribavirin (81% vs 94%), the confidence intervals overlap and it is likely that this reflects the small sample sizes.

Factors limiting the interpretation of the results of this trial include its small size and the uncontrolled, open-label design. Although the trial enrolled only patients with genotype 1 HCV, another trial of similar design has been conducted to assess this combination regimen in patients with non-genotype 1 HCV.

In conclusion, sofosbuvir-velpatasvir plus GS-9857 for 12 weeks provided a high rate of SVR12 (100%) and was well tolerated in a group of patients currently without treatment options—those with and without compensated cirrhosis who have not achieved SVR after previous treatment with a NS5A inhibitor-containing regimen. The addition of GS-9857 to sofosbuvir-velpatasvir also was safe in the treatment-naive population, in whom it was effective in reducing the treatment duration to 8 weeks while preserving a high rate of SVR12. These 3 potent pangenotypic DAAs have been co-formulated into a fixed-dose combination tablet. The phase 3 program will evaluate this fixed-dose combination...
**Table 4. Safety**

<table>
<thead>
<tr>
<th>Treatment naive</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No cirrhosis</td>
<td>Cirrhosis</td>
<td></td>
<td></td>
<td>No cirrhosis</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td>SOF-VEL plus</td>
<td>SOF-VEL plus</td>
<td>SOF-VEL plus</td>
<td>SOF-VEL plus</td>
<td>SOF-VEL plus</td>
<td>SOF-VEL plus</td>
</tr>
<tr>
<td></td>
<td>GS-9857 for 6 wk (n = 34)</td>
<td>GS-9857 for 8 wk (n = 36)</td>
<td>GS-9857 for 8 wk (n = 33)</td>
<td>GS-9857 plus RBV for 8 wk (n = 31)</td>
<td>GS-9857 for 12 wk (n = 31)</td>
<td>GS-9857 for 12 wk (n = 32)</td>
</tr>
</tbody>
</table>

| Any adverse event | 21 (62) | 24 (68) | 24 (73) | 24 (77) | 15 (48) | 16 (50) |
| AEs leading to discontinuation of all treatment | 0 | 0 | 0 | 1 (3) | 0 | 0 |
| Deaths | 0 | 0 | 1 (3) | 0 | 0 | 0 |
| AEs (occurring in ≥5% of patients in any cohort) | 11 (32) | 7 (19) | 7 (21) | 9 (29) | 4 (13) | 5 (16) |
| Headache | 2 (6) | 10 (28) | 7 (21) | 9 (29) | 3 (10) | 3 (9) |
| Nausea | 4 (12) | 7 (19) | 1 (3) | 10 (32) | 7 (23) | 3 (9) |
| Fatigue | 4 (12) | 6 (17) | 2 (6) | 3 (10) | 3 (10) | 3 (9) |
| Diarrhea | 5 (15) | 1 (3) | 0 | 3 (10) | 2 (6) | 0 |
| Insomnia | 0 | 4 (11) | 3 (9) | 1 (3) | 0 | 0 |
| Constipation | 1 (3) | 3 (8) | 1 (3) | 0 | 2 (6) | 0 |
| Nasopharyngitis | 0 | 0 | 7 (23) | 0 | 0 | 0 |
| Anemia | 1 (3) | 3 (8) | 0 | 0 | 1 (3) | 1 (3) |
| Cough | 2 (6) | 2 (6) | 1 (3) | 1 (3) | 0 | 0 |
| Dizziness | 0 | 0 | 4 (13) | 0 | 0 | 0 |

| Laboratory abnormalities |               |               |               |               |               |               |
| Hemoglobin level, <10.0 g/dL | 0 | 0 | 0 | 4 (13) | 0 | 0 |
| Platelets, 25,000 to <50,000/mm³ | 0 | 0 | 1 (3) | 0 | 0 | 2 (6) |
| INR, >2.0 to 3.0 × ULN | 0 | 0 | 1 (3) | 0 | 0 | 0 |
| ALT level, >5.00 to 10.00 × ULN | 0 | 0 | 0 | 1 (3) | 0 | 0 |
| Creatine kinase level, >10.0 to <20.0 × ULN | 0 | 1 (3) | 0 | 0 | 0 | 0 |
| Hyperglycemia, >250 to 500 mg/dL | 0 | 0 | 1 (3) | 1 (3) | 0 | 2 (6) |
| Lipase, >5.0 × ULN | 1 (3) | 0 | 0 | 4 (12) | 0 | 1 (3) |
| Hyperbilirubinemia, >2.5 to 5.0 × ULN | 0 | 0 | 3 (10) | 0 | 1 (3) | 0 |

AE, adverse event.
for 8 weeks in treatment-naive patients and for 12 weeks in DAA-experienced patients, including those who previously have received an NS5A inhibitor.

Supplementary Material
Note: To access the supplementary material accompanying this article, visit the online version of Gastroenterology at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.07.039.

References

Received May 23, 2016. Accepted July 26, 2016.

Reprint requests
Address requests for reprints to: Eric Lawitz, MD, Texas Liver Institute, 607 Camden Street, San Antonio, Texas 78215. e-mail: lawitz@txliver.com; fax: 210-477-1808.

Conflicts of interest
These authors disclose the following: Eric J. Lawitz has served as a consultant for AbbVie, Achillion Pharmaceuticals, Bristol-Myers Squibb, Enanta, Gilead Sciences, Janseen, Merck & Co, Novartis, Sanitars Pharmaceuticals, Regulus, and Theravance, has received grants from AbbVie, Achillion Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, and Merck; Federico Pinho has served as an advisory board member for Gilead, Sanofi, Merck & Co; Nancy Reau has served as an advisory board member for AbbVie, Bristol-Myers Squibb, Gilead, and Merck, and has served as a speaker for AbbVie, Bristol-Myers Squibb, Gilead, and Merck; Ronald Nahass has served on the advisory board for Gilead, BMS, Merck, and AbbVie, and has performed research for Gilead, BMS, Merck, and AbbVie; Eugene Schiff has served as a consultant for Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, and Merck; and has performed research for AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, and Merck; K. Rajender Reddy has served as a speaker for AbbVie and Gilead; Brian D. Messina has performed research for Gilead, BMS, Merck, Janssen, and AbbVie, and owns stock in Gilead; John D. Flaxman has served on the advisory board for Gilead, Merck, and AbbVie, and has performed research for Gilead, Merck, and AbbVie; David A. Flaxman has served as a consultant for Boehringer Ingelheim, and has performed research for Gilead, Merck, and AbbVie; and David A. Flaxman has served as a consultant for Janssen, and has performed research for Boehringer Ingelheim, and has supervised research for Gilead, Merck, and AbbVie.

Copyright © 2016 by the AGA Institute
Pearlman has served as a consultant, speaker, and on the advisory board for Gilead, Merck, and J&J, and has performed research for BMS, BI, Gilead, Merck, and J&J; Mitchell Shiffman has served on the advisory board for Merck, Gilead, Boehringer-Ingelheim, Bristol-Myers-Squibb, AbbVie, Janssen, and Achillion, has served as a consultant for Roche/Genentech, has performed research for Merck, Gilead, Boehringer-Ingelheim, Bristol-Myers-Squibb, AbbVie, Beckman-Coulter, Achillion, Lumena, Intercept, Novartis, and Gen-Probe, and has served as a speaker for Roche/Genentech, Merck, Gilead, AbbVie, Janssen, and Bayer; Trevor Hawkins has served as a consultant for Bristol-Myers Squibb, and is an employee of and holds stock interest in Gilead; Michael Curry has served as a consultant for Gilead, AbbVie, and BMA, and has performed research for Gilead and Conatus; Ira Jacobson has served as a consultant for AbbVie, Achillion, Bristol-Myers Squibb, Gilead Sciences, Janssen, and Merck, has performed research for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and Tobira, and has served as a speaker for Bristol-Myers Squibb, Gilead Sciences, Janssen, and Merck; and Jenny C. Yang, Sophia Lu, Hadas Dvory-Sobol, Luisa M. Stamm, Diana M. Brainard, and John G. McHutchison are employees and/or hold stock interest in Gilead Sciences. The remaining authors disclose no conflicts.

**Funding**

This study was sponsored by Gilead Sciences. Clinical operations support was provided by Juan Betular, Jonathan Kong, Nikki Zona, Ken Imamura, Desiree Varela, and Erin Waller of Gilead Sciences; and writing assistance was provided by David McNeel and Sandra Chen of Gilead Sciences.
Supplementary Figure 1. Patient disposition. AE, adverse event.