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Short-duration Treatment With Elbasvir/Grazoprevir and Sofosbuvir for Hepatitis C: A Randomized Trial

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Abbreviations: AE, adverse event; DAAs, direct-acting antiviral agents; EBR, elbasvir; GT, genotype; GZR, grazoprevir; HCV, hepatitis C virus; NGS, next-generation sequencing; RAV, resistance-associated variant; SOF, sofosbuvir; SVR12, sustained virologic response of HCV RNA <15 IU/mL 12 weeks after the end of therapy.

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Online summary

In the C-SWIFT study, high efficacy was achieved in patients with GT1 or 3 hepatitis C virus infection receiving 8-week treatment regimens of elbasvir/grazoprevir and sofosbuvir. Re-

treatment of the patients with who failed short-duration therapy was achieved regardless of the presence of RAVs through extended treatment duration and the addition of ribavirin.

Abstract

Direct-acting antiviral agents (DAAs) represent the standard of care for patients with hepatitis C virus (HCV) infection. Combining DAAs with different mechanisms may allow for shorter treatment durations that are effective across multiple genotypes. The aim of the C-SWIFT study was to identify the minimum effective treatment duration across multiple genotypes. C-SWIFT was an open-label, single-center trial in treatment-naïve patients with chronic HCV genotype (GT)1 or 3 infection. All patients received elbasvir (EBR) 100 mg/grazoprevir (GZR) 50 mg with sofosbuvir (SOF) 400 mg for 4–12 weeks. Patients with GT1 infection who failed therapy were eligible for retreatment with EBR/GZR + SOF and ribavirin for 12 weeks. The primary efficacy endpoint was SVR12 (sustained virologic response, HCV RNA <15 IU/mL 12 weeks after the end of therapy). Rates of SVR12 were 32% (10/31) and 87% (26/30) in noncirrhotic patients with GT1 infection treated for 4 and 6 weeks, and 80% (16/20) and 81% (17/21) in cirrhotic GT1 patients treated for 6 and 8 weeks. Among GT3-infected noncirrhotic patients, SVR12 was 93% (14/15) and 100% (14/14) after 8 and 12 weeks. SVR12 in cirrhotic GT3-infected patients was 83% (10/12) after 12 weeks of treatment. Twenty-three GT1 patients who relapsed following initial treatment completed re-treatment; all achieved SVR12. In the initial treatment phase, there was 1 serious adverse event of pneumonia which led to treatment discontinuation, and during retreatment 1 patient discontinued ribavirin due to pruritus. Data from this study support the use of 8-week treatment regimens that maintain high efficacy, even for patients infected with HCV GT3 infection. Retreatment of the patients who failed short-duration therapy was achieved through extended treatment duration and addition of ribavirin.

Direct-acting antiviral agents (DAAs), combined in multidrug all-oral regimens, now represent standard-of-care therapy for patients with hepatitis C virus infection (HCV). Treatment durations of currently approved regimens vary according to patient characteristics (notably HCV genotype and degree of liver fibrosis), but are typically between 8 and 24 weeks.[1,2] Combining highly potent DAAs with different mechanisms of action may allow for shorter treatment durations that are effective across multiple genotypes. The short-duration, 6-week treatment regimen of sofosbuvir (SOF)/ledipasvir/vedroprevir demonstrated promising results in treatment-naïve patients with HCV genotype (GT)1 infection (SVR [sustained virologic response] of 95%[3]), but less promising results when the same regimen was administered for 6 weeks in GT1 patients with F3/F4 fibrosis (SVR of 76%[4]) or for 4 weeks in GT1 noncirrhotic patients (SVR of 20%-40%[5]). In these studies, relapse was the most common form of virologic failure. Successful retreatment of patients who relapsed following short duration, all-oral therapy has been reported.[6] Among 34 patients who failed 4–6 weeks of treatment with ledipasvir/SOF with GS-9669 and/or GS-9451, retreatment with ledipasvir/SOF for 12 weeks achieved SVR rates of 91% (31 of 34); 1 patient relapsed and 2 patients withdrew from treatment.[6]

SOF is an NS5B inhibitor that is approved in combination with ledipasvir for the treatment of patients with HCV GT1 infection.[7] Elbasvir (EBR; MK-8742), an NS5A inhibitor, and grazoprevir (GZR; MK-5172), a potent NS3/4A inhibitor, have broad genotypic activity and have shown high efficacy across a wide spectrum of patients in phase II/III clinical trials.[8–14] Given the differing mechanisms of action, broad *in vitro* genotypic activity, and high barrier to resistance of these 3 agents, we speculated that treatment regimens composed of these 3 potent DAAs administered

for <12 weeks would be efficacious in patients with HCV GT1 or 3 infection. As GT3 has emerged as a particularly challenging genotype to treat with an all-oral regimen, this population was included to test the limits of efficacy of the 3-drug regimen. Our objective was therefore to identify the minimum effective treatment duration across multiple genotypes that would subsequently support a pan-genotypic development program. In addition, enrolling a DAA-exposed, resistance-associated variant (RAV)-enriched GT1a population offered a unique opportunity for assessing retreatment of prior DAA treatment failures. Herein, we report the results of the C-SWIFT study, which evaluated the safety and efficacy of the combination of EBR/GZR with SOF for 4, 6, or 8 weeks in previously untreated patients with or without cirrhosis with HCV GT1 or 3 infection. Due to the increased potential for relapse with short-duration therapy, we also report the outcomes of retreatment of GT1 patients who relapsed after initial short-duration therapy.

Methods

STUDY PATIENTS

The C-SWIFT study (ClinicalTrials.gov #NCT02133131; protocol PN074) enrolled treatment-naïve adults aged ≥18 years with chronic HCV GT1 or 3 infection (HCV RNA >10,000 IU/mL) with or without compensated cirrhosis (determined by a liver biopsy, FibroScan®, or FibroTest™ plus aspartate aminotransferase-to-platelet ratio index; see Supporting Information). Patients with HIV, decompensated liver disease, previous receipt of any anti-HCV treatment, alanine aminotransferase >10× upper limit of normal, aspartate aminotransferase >10× upper limit of

normal, creatinine clearance <50 mL/min, platelets <50 × 10^3/μL, or serum albumin <3.0 g/dL were excluded.

STUDY DESIGN

This was an open-label, single-center, multiple-arm trial. All patients initially received the open-label, fixed-dose combination of EBR 100 mg/GZR 50 mg in combination with SOF 400 mg. Noncirrhotic patients with GT1 infection were randomized to 4 or 6 weeks of therapy and cirrhotic patients with GT1 infection were randomized to 6 or 8 weeks of therapy, while noncirrhotic patients with HCV GT3 infection were randomized to 8 or 12 weeks of therapy and cirrhotic patients with HCV GT3 infection received treatment for 12 weeks. Within the first three cohorts (GT1 non-cirrhotic and cirrhotic, and GT3 non-cirrhotic), a separate randomization will assign patients into one of two groups defined by duration of therapy (4 or 6 weeks, 6 or 8 weeks, and 8 or 12 weeks) according to a computer generated allocation schedule. All randomized patients were assigned a unique patient number, and treatment duration was provided within sealed disclosure envelopes that were opened at TW4 for patients with GT1 infection and week 8 for those with GT3 infection. Within the fourth cohort (GT3 cirrhotic), patients will all be assigned to the 12 week duration group (no randomization). Randomization of patients within the GT1 cohorts was stratified based on genotype subtype (1a vs. non-1a). At the time of enrollment, the investigators and the patients were blinded to the treatment duration.

Patients with HCV GT1 infection who failed initial therapy were eligible for retreatment with EBR/GZR + SOF and weight-based ribavirin (800–1400 mg/day) for 12 weeks. To be eligible for retreatment, patients were required to have documented HCV GT1 infection prior to initial treatment and have failed initial treatment due to relapse. Patients with a serious AE during initial treatment, alanine aminotransferase/aspartate aminotransferase >10× upper limit of normal, decompensated liver disease, or hemoglobin <11 g/dL (female) or <12 g/dL (male) were excluded from retreatment. There was no specified minimum/maximum time between initial relapse and commencement of retreatment. Treatment of patients with HCV GT3 infection who failed initial therapy was continued outside the C-SWIFT protocol.

EFFICACY AND SAFETY ASSESSMENTS

The primary efficacy endpoint in both the initial treatment and re-treatment phases was SVR12, defined as HCV RNA <15 IU/mL 12 weeks after the end of all study therapy. Virologic failure was defined as breakthrough (confirmed HCV RNA ≥25 IU/mL after being <25 IU/mL previously while on treatment); nonresponse (detectable HCV RNA at end of treatment without achieving HCV RNA <25 IU/mL during treatment); rebound (confirmed >1 $\log_{10}$ increase in HCV RNA from nadir while on treatment); or relapse (confirmed HCV RNA ≥25 IU/mL following end of all study therapy after having HCV RNA <25 IU/mL at end of treatment). Confirmation of HCV RNA status was achieved by testing of HCV viral load from a separate blood draw taken within 2 weeks of the initial test. Patients with confirmed virologic breakthrough or rebound were discontinued from study medication. Safety was assessed through monitoring of AEs, physical examination, vital signs, and standard laboratory evaluations. All patients were followed for 24 weeks after

the end of all study therapy for efficacy outcomes and for 14 days after the end of all study therapy for safety analyses.

PROCEDURES

Plasma HCV-RNA was measured using the Roche cobas® AmpliPrep/cobas® TaqMan® HCV Test, version 2.0 (Roche Molecular Diagnostics, Branchburg, NJ) on blood samples drawn from each patient at screening, days 1, 3, and 7, treatment weeks 2 and 4 (and 6, 8, and 12 if in 6-week, 8-week, or 12-week arm), and follow-up weeks 2, 4, 8, 12, and 24. The lower limit of quantification was 25 IU/mL and limit of detection was 15.1 IU/mL.

In treatment and re-treatment phases, blood samples for viral resistance assays were collected from all patients at baseline (day 1), and at the time of failure in patients with confirmed virologic failure. In the initial treatment study, population sequencing was used to detect the presence of variants known to confer resistance to NS3, NS5A, or NS5B polymerase inhibitors present at approximately 25% in the viral population. Complete NS3, NS5A, and NS5B genes were amplified using reverse transcriptase PCR and resultant sequences were compared with reference wild-type sequences as previously described (further details are also available in the Supporting Information).[10] Post-baseline analyses were conducted by comparing the amino acid sequences at the time of virologic failure to those at baseline (day 1, pre-dose). In the retreatment study, baseline blood samples were assessed for the presence of RAVs using next-generation sequencing (NGS). In 1 patient, NGS data were not available, so population sequencing data were utilized. HCV RNA was reverse-transcribed and amplified using reverse-

transcription polymerase chain reaction followed by library preparation, amplification using Nextera XT, and sequencing of the NS3, NS5A, and NS5B genes (Illumina, MiSeq). Data QC analysis and variant calling were performed using data with Q score >30. NGS data were analyzed at sensitivity thresholds of 1% and 15%.

STATISTICAL ANALYSIS

Approximately 30, 20, 15, or 10 patients were randomized to one of the 7 treatment arms based on genotype and presence of cirrhosis. Assuming a protocol violation rate of 10%, the per-protocol population was to include 27, 18, 14, or 9 patients. The primary efficacy objective was to estimate rates of SVR12 for each treatment arm. A 2-sided 95% confidence interval was constructed for each arm: no formal efficacy hypothesis testing was conducted.

According to the study protocol, the primary efficacy endpoint in the initial treatment study was assessed in the per-protocol population, which excluded patients with important deviations from the protocol that may substantially affect the primary efficacy analysis. A supportive analysis was performed based on the full analysis set, which included all allocated patients who received at least 1 dose of study medication. For reasons of transparency, in this report we have elected to describe the efficacy outcomes based on the full analysis set population, which are considered more representative of real-world clinical practice. The safety analysis was based on the All Subjects as Treated population, which included all patients who received at least 1 dose of study medication. For the purposes of this study, the full analysis set and All Subjects as Treated populations were identical. The resistance-analysis population (RAP)

included all patients with baseline resistance data and a virologic outcome of either SVR or relapse.

STUDY OVERSIGHT

The study was conducted in accordance with principles of Good Clinical Practice and the ethical guidelines of the Declaration of Helsinki and approved by the appropriate institutional review boards and regulatory agencies at each site. All patients provided written informed consent. Merck & Co., Inc. (the sponsor) contributed to the design and execution of the study and collection and analysis of the data. All co-authors had access to the study data, approved the final version of this report, and accept full responsibility for the veracity of the data. The protocol is available in the Supporting Information.

Results

PATIENTS

The study was initiated in June 2014 and the final patient completed treatment in November 2015. A total of 162 patients were screened; 19 failed to meet inclusion/exclusion criteria and 143 were randomized (GT1, n = 102; GT3, n = 41; Fig. 1). In total, 41 of 102 patients with GT1 infection and 12 of 41 patients with GT3 infection were cirrhotic. Forty-four percent (63 of 143) of patients had baseline HCV RNA levels >2,000,000 IU/mL (Table 1).

EFFICACY

Rates of SVR12 in noncirrhotic patients with GT1 infection were 32% (10 of 31) and 87% (26 of 30) in patients treated for 4 and 6 weeks, respectively (Fig. 2). In cirrhotic GT1 patients, SVR was 80% (16 of 20) in the 6-week treatment arm with 4 virologic failures, and 81% (17 of 21) in the 8-week treatment arm with 2 relapses (GT1 at baseline and GT1 at failure), 1 patient lost to follow-up, and 1 patient with a reinfection (GT1 at baseline and GT2 at failure). The rate of relapse in cirrhotic patients with GT1 infection was 20% (4 of 20) with a 6-week duration and 10% (2 of 21) with an 8-week duration. Overall, 33 GT1 patients failed to attain SVR; 3 were discontinued for reasons unrelated to study medication and 30 relapsed, and no patient had on-treatment virologic breakthrough. One cirrhotic patient with HCV GT1 infection treated for 8 weeks was initially considered as a relapse, and was subsequently found to have HCV GT2 infection at the time of relapse and was thus re-classified as a reinfection. The majority of relapse patients (20 of 30) were treated for 4 weeks: only 1 patient in the 8-week regimen had a true relapse.

All patients with GT1 infection had undetectable HCV RNA after 2 weeks of therapy (Supporting Table S1). Among GT3-infected noncirrhotic patients, SVR12 was 93% (14 of 15) after 8 weeks of treatment and 100% (14 of 14) after 12 weeks of treatment. SVR12 in cirrhotic HCV GT3-infected patients was 83% (10 of 12). Of the 41 enrolled patients, 1 patient with GT3 infection discontinued for reasons unrelated to study drug (withdrawal due to work schedule) and 2 patients, one with cirrhosis and one without, who were randomized to the 8-week treatment arm relapsed. SVR12 was 95% (35 of 37) in patients with GT3 infection and baseline NS3 RAVs, and 100% (3 of 3) in those with baseline NS5A RAVs (including A30K, L31M, and Y93H).

Subgroups typically included only small numbers of patients; however, suggestions of higher efficacy in patients with GT1 infection were noted in those with favorable characteristics, such as female sex, baseline viral load <800,000 IU/mL, *IL28B*-CC, and absence of baseline RAVs (Table 2). In the 6-week treatment arms, it is notable that all 8 relapsers were male and *IL28B* non-CC, and all except 1 had baseline viral load >800,000 IU/mL. In the 4-week treatment arm, SVR12 rates were low (30%–40%) regardless of the presence or absence of NS3 or NS5A RAVs at baseline. SVR12 rates increased in the 6-week treatment arms, and were similar regardless of the presence or absence of NS3 RAVs (81% [26 of 32] and 89% [16 of 18], respectively). They were also similar in patients without NS5A RAVs at baseline (87% [40 of 46]). However, only 2 of 4 GT1 patients with NS5A RAVs at baseline receiving 6 weeks of therapy attained SVR12 (50% [2 of 4]). Rates of SVR12 were generally high, regardless of presence or absence of NS3 or NS5A RAVs, in GT1 patients treated for 8 weeks. Overall, the higher SVR seen with 8 weeks of therapy may suggest that extending treatment duration beyond 6 weeks is able to overcome the negative influence of factors such as high baseline viral load, presence of baseline RAVs, and *IL28B* non-CC.

A more detailed analysis of the impact of RAVs on SVR12 is shown in Supporting Tables S2–S6. Supporting Table S2 shows that although the prevalence of baseline NS3 RAVs was 66% (65 of 98), there was no significant impact on the SVR12 rates in patients who received 4, 6, or 8 weeks of treatment, with an overall SVR12 rate of 76% (25 of 33) in patients without baseline NS3 RAVs compared with 69% (44 of 64) in those with baseline NS3 RAVs. In contrast, the

presence of baseline NS5A RAVs did impact the SVR12 rates in patients treated for 6 or 8 weeks. The prevalence of baseline NS5A RAVs was 10% (7 of 69) in the 6- and 8-week treatment groups, with an overall SVR12 rate of 90% (55 of 61) in patients without baseline NS5A RAVs compared with 57% (4 of 7) in those with baseline NS5A RAVs. Efficacy was low in the 4-week treatment group, regardless of the presence or absence of baseline NS5A RAVs (33% vs. 30%, respectively).

There were two patients with GT3 infection who relapsed. Overall subgroup analyses of the GT3 population are based on small groups of patients and do not suggest any strong associations between patient characteristics and treatment outcomes.

RE-TREATMENT

Twenty-five of the 30 patients (83%) with HCV GT1 infection who relapsed following the initial treatment were retreated with EBR/GZR + SOF and ribavirin for 12 weeks (Table 1). Overall, 88% (n = 22) were male, all were white, 88% (n = 22) had GT1a infection, and 20% (n = 5) were cirrhotic. Mean baseline viral load was 6.19 $\log_{10}$ IU/mL. Seventeen re-treated patients were previously treated for 4 weeks and 8 were previously treated for 6–8 weeks. Two patients were lost to follow-up (at day 3 and treatment week 4) and were therefore excluded from the efficacy analysis. The mean time from virologic failure to enrollment in the retreatment study was 214 days (range, 182–260). All remaining 23 re-treated patients achieved SVR12, including 18 noncirrhotic and 5 cirrhotic patients, 15 patients previously treated for 4 weeks, and 8 patients previously treated for 6 or 8 weeks.

Analysis of the re-treatment baseline resistance profile was performed using NGS methodology at 1% sensitivity threshold for 22 of 23 patients who had NGS data available; population sequencing data were used for the 1 patient who did not have NGS data. Overall, 14 patients (61%) had baseline NS5A RAVs (most commonly at positions 28, 30, and 31), 17 patients (74%) had baseline NS3 RAVs (most commonly Q80K), and none had baseline NS5B RAVs. Eleven patients (48%) had both NS5A and NS3 RAVs at re-treatment baseline. All 23 re-treated patients in the efficacy analysis set achieved SVR12. Notably, these include 11 of 11 patients with baseline NS5A and NS3 RAVs and 5 of 5 cirrhotic patients (Fig. 3). In addition, 3 of 3 patients with GT1a infection and linked baseline NS5A RAVs achieved SVR; 2 had linked RAVs known to confer >1000-fold shift in potency to EBR *in vitro* (Q30K_Y93H and Q30H_Y93H). In these 2 patients, NGS sequencing indicated that both RAVs were present in >80% of patients, strongly suggesting that these were linked RAVs present within a single virus population.

A comparison of the prevalence of RAVs as assessed using NGS and population sequencing is shown in Table S7. Use of population sequencing (sensitivity threshold ≈20%) revealed a lower proportion of patients with baseline RAVs compared with NGS (sensitivity threshold 1%).

SAFETY

Across all treatment arms, the most common AEs (>2% incidence overall) were fatigue (6%), headache (4%), nausea (4%), diarrhea (2%), and rash (2%). There was one serious AE of pneumonia which led to discontinuation of therapy and was judged by the study investigator to

be unrelated to study medication (Table 3). There were no deaths, bilirubin elevations >5× baseline, or late elevations of alanine aminotransferase or aspartate aminotransferase >5× the upper limit of normal.

During re-treatment with EBR/GZR + SOF and ribavirin, the most common AEs were fatigue (16%), rash (12%), nausea (8%), and urinary tract infection (8%). Eight patients reported a total of 13 drug-related AEs (fatigue, n = 4; nausea, n = 2; insomnia, urinary tract infection, papular rash, diarrhea, anemia, pruritic rash, and vomiting, n = 1 each), all of which were mild-to-moderate in intensity and resolved with continued therapy. One patient reported a serious AE of emesis. This subject consumed an extra dose of EBR/GZR + SOF, which was followed by a single episode of emesis that lasted for 10 minutes and was not self-induced. One patient had a hemoglobin level <10 g/dL (this patient had a ribavirin dose reduction at treatment week 6 due to a hemoglobin level of 9.7 g/dL) and 1 patient discontinued ribavirin at treatment week 4 due to pruritus.

Discussion

This clinical study is the first to examine the treatment of patients infected with HCV GT1 or GT3 with or without cirrhosis with short durations of a novel regimen of EBR/GZR + SOF. Our data confirm that cirrhotic and noncirrhotic patients with HCV GT1 infection can be cured with 6–8 weeks of treatment, and that an 8–12 week regimen of EBR/GZR + SOF is safe and effective in cirrhotic and noncirrhotic patients with HCV GT3 infection, commonly regarded as one of the most challenging patient populations to treat. Together, these data support the hypothesis that

a DAA regimen of <12 weeks may be sufficient across multiple genotypes. Efficacy can be enhanced by including 3 mechanistically different agents, even in patients with cirrhosis. Furthermore, these data demonstrate that successful retreatment can be achieved with the same regimen by extending duration and adding ribavirin. An SVR rate of 100% was achieved with a 12-week regimen in a population highly enriched for RAVs and with the unfavorable demographics of HCV GT1a infection, cirrhosis, and high-impact RAVs.

The present study incorporates several novel design elements. SVR12 rates of 95% were achieved with LED/GS-9451+ SOF for 6 weeks in the SYNERGY study.[3] Preclinical and phase 1 data indicate that EBR/GZR+SOF is also a highly potent DAA combination, and therefore support the evaluation of this triple DAA regimen in a short-duration study.[15-17] The patient populations examined also add to the novelty of this study: this is the first study to examine short-duration all-oral therapy in patients with HCV GT3 infection, and also provides insight into the utility of short-duration therapy in cirrhotic patients (both GT1- and 3-infected). Our results suggest that high efficacy rates can be achieved with 6 weeks of treatment in noncirrhotic patients with GT1 infection and that an 8-week treatment duration may be sufficient in cirrhotic GT1-infected patients. The high efficacy rates achieved in patients with GT3 infection treated for 8–12 weeks provide proof of concept that an effective short-duration regimen might be achievable across even the hardest-to-treat patient populations. Limitations of the present study include the single-center design and the small number of patients included in each treatment arm. These data require verifying in larger patient groups with a broader demographic profile.

The assessment of HCV RNA after 4 weeks of treatment provides insight into the limits of current therapeutic options. The high rates of relapse seen with 4 weeks of therapy in the present study and in more recent studies[5] suggests that this treatment duration is too short to be of clinical value. In SYNERGY, SVR12 was also not improved when using a 4-week, 4-drug regimen, with a higher barrier to resistance compared with the 3-drug regimen.[3] Collectively, these data suggest that there may be a minimum time required to eliminate wild-type virus with the potency of current agents, and thus that treatment duration and not virologic escape represents the principal limitation of the 4-week regimens. In the 6-week treatment arms, we noted a tendency towards higher SVR12 in patients with favorable characteristics such as *IL28B* (also known as *IFNL3*) CC, low baseline viral load, and absence of baseline RAVs compared with patients with unfavorable characteristics. Within the 8-week treatment arm, favorable responses were noted across most patient subgroups. In the 6- and 8-week arms, SVR12 rates were numerically higher in female patients compared with male patients, similar to data reported in treatment-naïve, noncirrhotic patients with HCV GT1 infection receiving ledipasvir/sofosbuvir for 8 weeks.[18] These data, in combination with previous reports, therefore suggest that a 6- to 8-week treatment duration represents the lower bound of clinical utility, and that for selected patients, durations of 6–8 weeks may be sufficient to achieve SVR. However, the benefits of short-duration therapy (which include reduced cost and therefore increased accessibility, and lower drug exposure/toxicity) must be balanced against the increased risk of relapse with these short-duration regimens. Therefore, for short-duration

regimens to have clinical utility, effective management protocols must be established for patients who relapse.

SVR12 in our re-treatment study was 100% in a patient population that was notable because it was enriched for GT1a infection and NS5A RAVs at baseline. Concerns regarding short-duration therapy include whether ultra-short durations of 4 weeks provide sufficient time for complete eradication of the viral population. It is unknown if the RAVs identified in patients at relapse were part of the existing quasi-species at baseline (at levels below those detected using population sequencing), or if they were treatment-emergent and selected for via drug pressure. Early data with another NS5A inhibitor, ledipasvir, suggest that RAVs emerging during treatment can persist through follow-up week 96 in up to 86% of treated patients, and that when present, these RAVs can impact future treatment attempts.[19,20] Our data show that re-treatment with a 12-week regimen incorporating 4 agents, each with a differing mechanism of action, provided an effective re-treatment option. Most patients (80% [20 of 25]) re-treated in our study were noncirrhotic and had relapsed after an initial 4-week treatment regimen. However, most patients also had detectable RAVs at baseline, and our re-treatment population included 5 cirrhotic patients who all attained SVR. The proportion of patients with NS5A and NS3 RAVs at baseline in the re-treatment study (61% and 74%) is driven primarily by the RAV profile within the population that relapsed following the initial 4-week treatment arm, which included a high proportion of patients with either baseline RAVs or treatment-emergent RAVs. It is unknown if extending or reducing the interval between initial treatment and retreatment (214 days, or approximately 7 months, in our study) would affect treatment outcome.

Collectively, our data suggest that many patients will attain SVR with 6−8 weeks of therapy and that high rates of SVR are achievable with 12 weeks of retreatment with a 4-drug regimen in patients who fail. With increased scrutiny regarding the costs of new DAA regimens, it is tempting to speculate that short-duration regimens may represent a simple approach to increasing accessibility to treatment for more patients, with effective retreatment protocols available for the few patients who relapse.

The concept of shortening HCV therapy to 8 weeks while maintaining high rates of efficacy in HCV GT1 and 3 patients, even in those patients with cirrhosis, has been demonstrated by this study. Data from the present study support the use of shorter 8-week regimens that maintain high efficacy, even for patients infected with the most challenging HCV GT3 genotype. This study helps define the limits of treatment duration with current therapies and also shows the advantage of a 3-drug regimen in overcoming the presence of baseline RAVs in HCV-infected patients. The regimen of EBR/GZR + SOF was generally safe and well-tolerated. Re-treatment of the patients who failed short-duration therapy was successfully achieved through extended treatment duration and the addition of ribavirin.

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Figure Legends

FIG. 1. Patient disposition.

FIG 2. SVR12 (primary efficacy endpoint) for patients with HCV GT1 and 3 infection receiving EBR/GZR + SOF, and for patients with HCV GT1 infection undergoing re-treatment with EBR/GZR + SOF and ribavirin (full analysis set).

FIG 3. Prevalence of NS5A and NS3 resistance-associated variants and impact on SVR12 in patients undergoing re-treatment.

TABLE 1. Patient Demographics

	GT1				GT3			GT1
	No Cirrhosis		Cirrhosis		No Cirrhosis		Cirrhosis	Retreatment
	4 Weeks (n = 31)	6 Weeks (n = 30)	6 Weeks (n = 20)	8 Weeks (n = 21)	8 Weeks (n = 15)	12wk (n = 14)	12wk (n = 12)	12wk (n = 25)
Male, n (%)	20 (65)	19 (63)	13 (65)	13 (62)	11 (73)	8 (57)	10 (83)	22 (88)
Mean age, years (SD)	52.1 (9.7)	51.2 (9.5)	55.7 (7.7)	56.6 (8.8)	51.3 (10.1)	42.2 (11.7)	55.3 (5.3)	54.0 (8.9)
Median age, years (range)	55.0 (23-66)	52.5 (27-64)	55.0 (39-72)	56.0 (39-70)	51.0 (31-69)	42.5 (26-58)	56.0 (45-63)	55.0 (23-66)
Age groups, n (%)								
18-35 years	3 (10)	3 (10)	0 (0)	0 (0)	1 (7)	6 (43)	0 (0)	1 (4.0)
36-50 years	10 (32)	8 (27)	5 (25)	5 (24)	6 (40)	3 (21)	2 (17)	6 (24.0)
51-64 years	17 (55)	19 (63)	13 (65)	12 (57)	7 (47)	5 (36)	10 (83)	17 (68.0)
>64 years	1 (3)	0 (0)	2 (10)	4 (19)	1 (7)	0 (0)	0 (0)	1 (4.0)
Race, n (%)								
White	30 (97)	28 (93)	20 (100)	20 (95)	15 (100)	14 (100)	12 (100)	25 (100)
Black or African American	1 (3)	1 (3)	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Asian	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hispanic or Latino ethnicity, n (%)	9 (29)	14 (47)	13 (65)	10 (48)	6 (40)	8 (57)	6 (50)	11 (44)
IL28B (*IFNL3*), n (%)								

CC	11 (35)	8 (27)	6 (30)	5 (24)	6 (40)	3 (21)	6 (50)	5 (20.0)
Non-CC	20 (65)	22 (73)	14 (70)	16 (76)	9 (60)	11 (79)	6 (50)	20 (80.0)
HCV genotype or subtype, n (%)								
GT1a	26 (84)	26 (87)	16 (80)	16 (76)	0	0	0	22 (88.0)
GT1b	5 (16)	4 (13)	4 (20)	5 (24)	0	0	0	3 (12.0)
GT3	0	0	0	0	15 (100)	14 (100)	12 (100)	0
METAVIR fibrosis stage, n (%)								
F0-F2	27 (87)	26 (87)	0 (0)	0 (0)	14 (93)	11 (79)	0 (0)	19 (76.0)
F3	4 (13)	4 (13)	0 (0)	0 (0)	1 (7)	3 (21)	0 (0)	1 (4.0)
F4	0 (0)	0 (0)	20 (100)	21 (100)	0 (0)	0 (0)	12 (100)	5 (20.0)
Baseline HCV RNA (IU/mL), n (%)								
≤800,000	8 (26)	9 (30)	7 (35)	5 (24)	8 (53)	8 (57)	4 (33)	9 (36.0)
>800,000	23 (74)	21(70)	13 (65)	16 (76)	7 (47)	6 (43)	8 (67)	16 (64.0)
≤2,000,000	13 (42)	17 (57)	12 (60)	11 (52)	9 (60)	11 (79)	7 (58)	NA
>2,000,000	18 (58)	13 (43)	8 (40)	10 (48)	6 (40)	3 (21)	5 (42)	NA
Mean ($\times 10^6$ IU/mL)	3.69	3.09	1.66	2.37	3.29	2.57	2.26	6.19

Abbreviations: NA, not available; SD, standard deviation.

TABLE 2. SVR12 Rates in Defined Subgroups (full analysis set*)

	GT1				GT3		
	Noncirrhotic 4 Weeks	Noncirrhotic 6 Weeks	Cirrhotic 6 Weeks	Cirrhotic 8 Weeks	Noncirrhotic 8 Weeks	Noncirrhotic 12 Weeks	Cirrhotic 12 Weeks
Gender, n/N (%)							
Male	6/20 (30)	15/19 (79)	9/13 (69)	10/13 (77)	10/11 (91)	8/8 (100)	8/10 (80)
Female	4/11 (36)	11/11 (100)	7/7 (100)	7/8 (88)	4/4 (100)	6/6 (100)	2/2 (100)
IL28B genotype, n/N (%)							
CC	4/11 (36)	8/8 (100)	6/6 (100)	5/5 (100)	6/6 (100)	3/3 (100)	4/6 (67)
Non-CC	6/20 (30)	18/22 (82)	10/14 (71)	12/16 (75)	8/9 (89)	11/11 (100)	6/6 (100)
HCV genotype, n/N (%)							
1a	7/26 (27)	22/26 (85)	13/16 (81)	14/16 (88)	—	—	—
1b	3/5 (60)	4/4 (100)	3/4 (75)	3/5 (60)	—	—	—
3	—	—	—	—	14/15 (93)	14/14 (100)	10/12 (83)
Baseline HCV RNA (IU/mL), n/N (%)							
≤800,000	3/8 (38)	9/9 (100)	6/7 (86)	5/5 (100)	8/8 (100)	8/8 (100)	4/4 (100)
>800,000	7/23 (30)	17/21 (81)	10/13 (77)	12/16 (75)	6/7 (86)	6/6 (100)	6/8 (75)
≤2,000,000	4/13 (31)	17/17 (100)	10/12 (83)	10/11 (91)	9/9 (100)	11/11 (100)	7/7 (100)
>2,000,000	6/18 (33)	9/13 (69)	6/8 (75)	7/10 (70)	5/6 (83)	3/3 (100)	3/5 (60)

Cirrhosis, n/N (%)							
No	10/31 (32)	26/30 (87)	0/0 (0)	0/0 (0)	14/15 (93)	14/14 (100)	0/0 (0)
Yes	0/0 (0)	0/0 (0)	16/20 (80)	17/21 (81)	0/0 (0)	0/0 (0)	10/12 (83)
Baseline RAVs, n/N (%)							
NS3 not detected	4/10 (40)	16/18 (89)		5/5 (100)	0/0 (0)	1/1 (100)	
NS3 detected	6/19 (32)	26/32 (81)		12/13 (92)	12/13 (92)	23/24 (96)	
NS5A not detected	7/23 (30)	40/46 (87)		15/15 (100)	14/15 (93)	21/22 (95)	
NS5A detected	2/6 (33)	2/4 (50)		2/3 (67)	0/0 (0)	3/3 (100)	

*Full analysis set includes all allocated patients who received ≥1 dose of study medication

TABLE 3. Tolerability of EBR/GZR + SOF During the Treatment Phase and First 14 Follow-Up Days

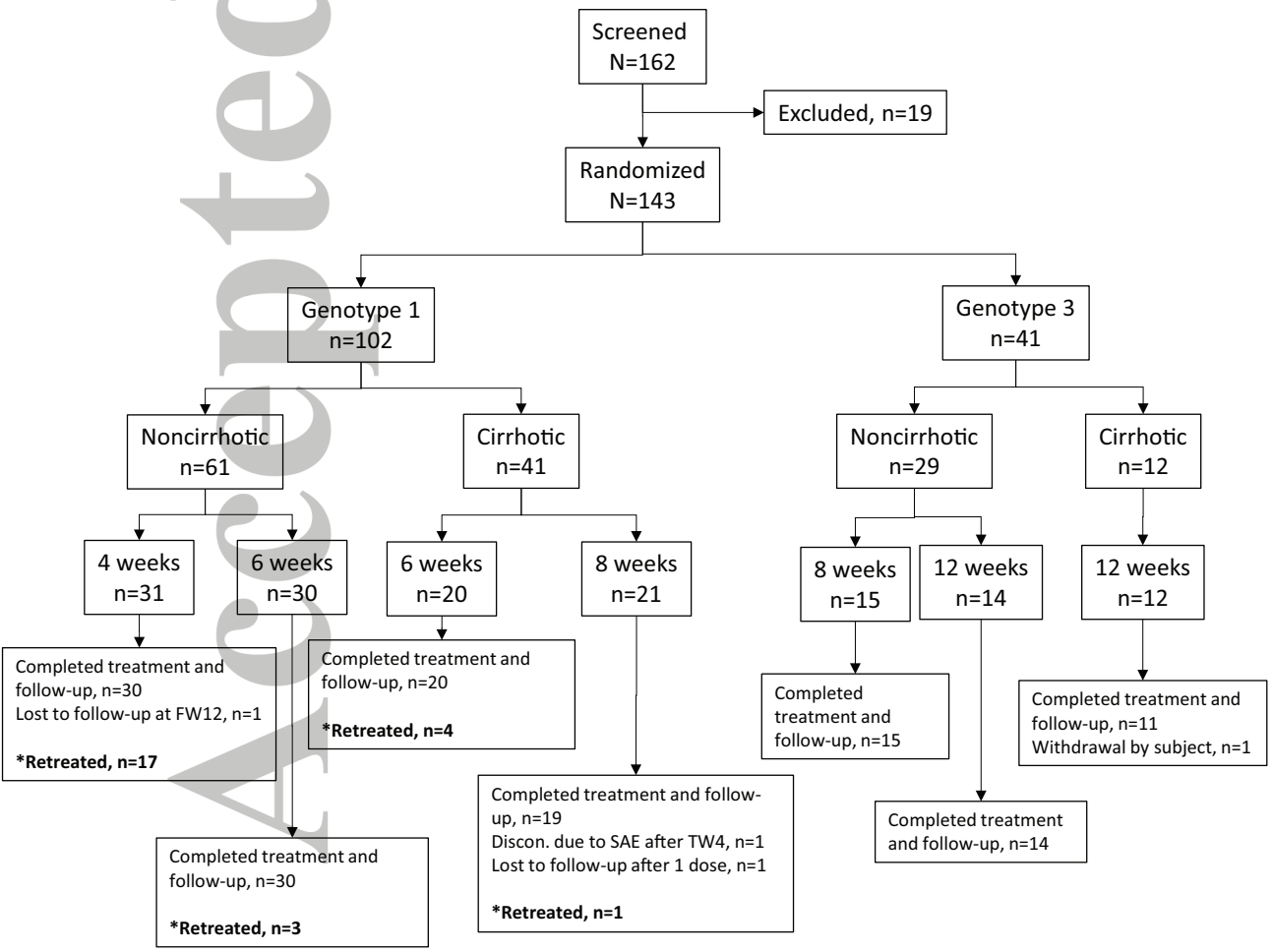
	GT1				Genotype 3		
	No Cirrhosis		Cirrhosis		No Cirrhosis		Cirrhosis
	4 Weeks (n = 31)	6 Weeks (n = 30)	6 Weeks (n = 20)	8 Weeks (n = 21)	8 Weeks (n = 15)	12 Weeks (n = 14)	12 Weeks (n = 12)
Serious AE, n (%)	0 (0)	0 (0)	0 (0)	1 (5)*	0 (0)	0 (0)	0 (0)
Drug-related AE, n (%)	2 (6)	1 (3)	2 (10)	2 (10)	1 (7)	1 (7)	3 (25)
Death, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Discontinued due to AE, n (%)	0 (0)	0 (0)	0 (0)	1 (5)*	0 (0)	0 (0)	0 (0)
Hemoglobin <10 g/dL, n (%)	1 (3)	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)
Total bilirubin >5× baseline, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Late ALT/AST >5× ULN, n (%)[†]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Most common drug-related AEs, n (%)[‡]							
Headache	1 (3)	0 (0)	1 (5)	1 (5)	1 (7)	0 (0)	1 (8)
Fatigue	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (8)
Nausea	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)	1 (7)	1 (8)

*Pneumonia on day 40 of treatment which led to discontinuation of therapy. Serious AE was judged by the study investigator to be unrelated to study medication.

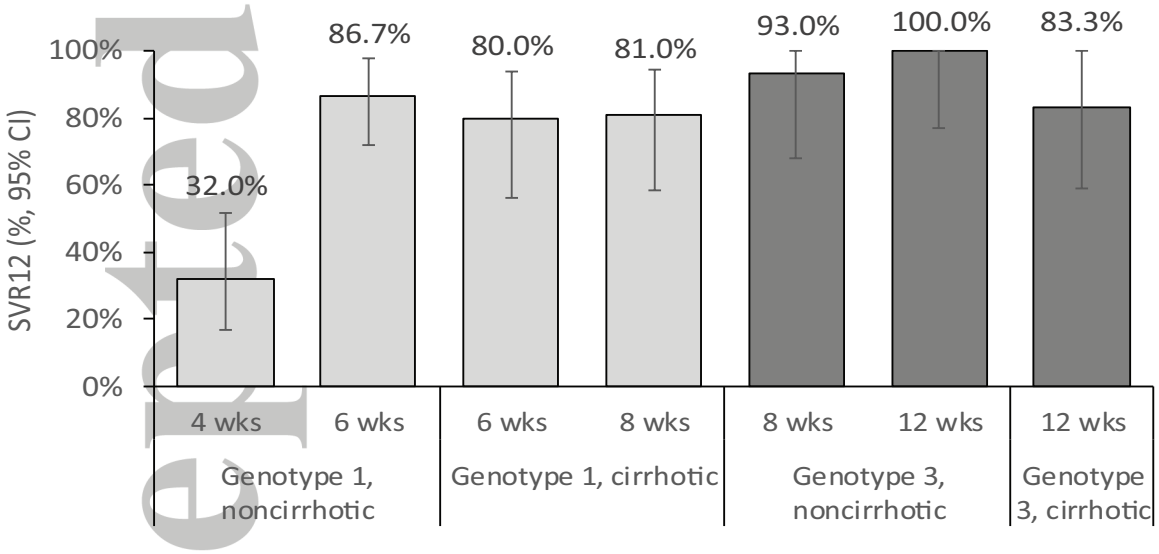
[†]Late ALT/AST >5× ULN: elevations after treatment week 4 in ALT or AST >5× ULN.

‡Most common AEs were defined as those in >2% of patients overall.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.



Twenty-five patients with HCV GT1 infection underwent retreatment with sofosbuvir plus EBR/GZR + SOF and ribavirin for 12 weeks. Twenty-three patients completed retreatment and 12 weeks of follow-up and 2 patients were lost to follow-up (at treatment week 4 and follow-up day 3).

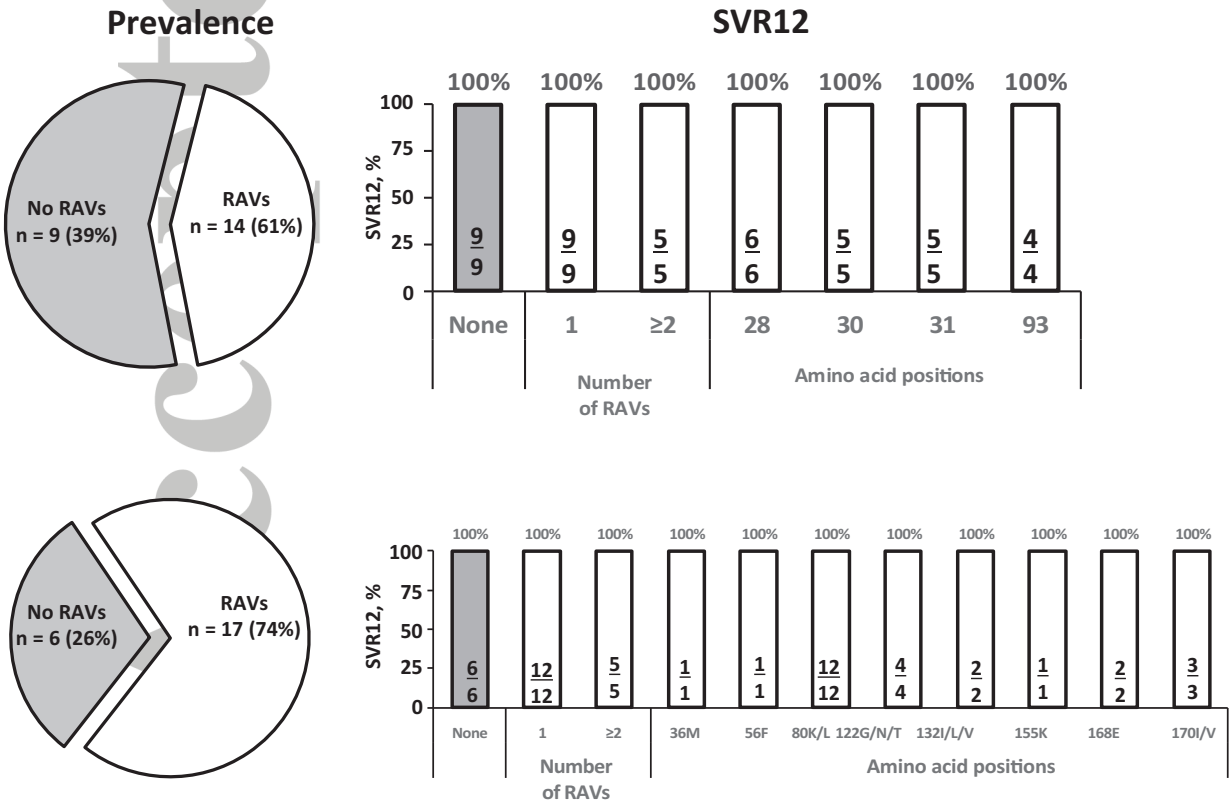


Total Patients	**31**	**30**	**20**	**21**	**15**	**14**	**12**
	10	26	16	17	14	14	10
Non-virologic failure	1	0	0	1	0	0	1
Breakthrough	0	0	0	0	0	0	0
Relapse	20	4	4	2	1	0	1
Reinfection	0	0	0	1*	0	0	0

[a]*Genotyping of plasma samples taken at the time of virologic failure indicated that one of the cirrhotic patients with HCV GT1 infection treated for 8 weeks had HCV GT2 present at time of failure. This patient was reclassified as a reinfection.*

Nonvirologic failures:

- *GT1 noncirrhotic 4 weeks: 1 patient lost to follow-up*
- *GT1 cirrhotic 8 weeks: 1 patient lost to follow up, 1 patient discontinued due to serious AE*
- *GT3 cirrhotic 12 weeks: 1 patient withdrew due to work schedule unrelated to AE*



[a]*Next-generation sequencing 1% sensitivity threshold (population sequencing data used for 1 patient who had a Y93N NS5A RAV). NS5A RAVs: any variant at amino acid positions 28, 30, 31, and 93. NS3 RAVs: any variant at amino acid positions 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170 and 175.*

Supporting Information

SUPPORTING TABLE S1. On-treatment Results with HCV GT1 (per-protocol population)

		% (n/m) of Patients With HCV RNA <15 IU/mL					
Patients	Treatment	Treatment Week 4	End of Treatment (EOT)	2 Weeks after EOT	4 Weeks after EOT	8 Weeks after EOT	12 Weeks after EOT (SVR12)
Noncirrhotic	4 weeks	81 (25/31)	81 (25/31)	100 (31/31)	39 (12/31)	39 (12/31)	33 (10/30)
Noncirrhotic	6 weeks	82 (23/28)	96 (27/28)	100 (28/28)	89 (25/28)	89 (25/28)	89 (25/28)
Cirrhotic	6 weeks	85 (17/20)	100 (20/20)	100 (20/20)	80 (16/20)	80 (16/20)	80 (16/20)
Cirrhotic	8 weeks	89 (17/19)	100 (19/19)	100 (19/19)	89 (17/19)	89 (17/19)	89 (17/19)

SUPPORTING TABLE S2: Impact of Baseline RAVs on Efficacy in Patients With HCV GT1 Infection

	Prevalence [n/m (%)]	SVR12 [n/m (%)]	
Gene or Duration of Treatment	Baseline RAVs	Patients Without Baseline RAVs	Patients With Baseline RAVs
NS3	65/98 (66%)	25/33 (76%)	44/64 (69%)
4 -week duration	19/29 (66%)	4/10 (40%)	6/19 (32%)
6-week duration	32/50 (64%)	16/18 (89%)	26/32 (81%)
8-week duration	14/19 (74%)	5/5 (100%)	12/13 (92%)
All GT1a pooled	56/81 (69.1%)	22/29 (75.9%)	34/52 (65.4%)
All GT1b pooled	13/16 (81.3%)	3/4 (75.0%)	10/12 (83.3%)
NS5A	13/98 (13%)	62/84 (74%)	6/13 (46%)
4-week duration	6/29 (21%)	7/23 (30%)	2/6 (33%)
6-week duration	4/50 (8%)	40/46 (87%)	2/4 (50%)
8-week duration	3/19 (16%)	15/15 (100%)	2/3 (67%)
All GT1a pooled	55/81 (67.9%)	50/69 (72.5%)	5/12 (41.7%)
All GT1b pooled	13/16 (81.3%)	12/15 (80.0%)	1/1 (100.0%)

Population sequencing was performed and analyzed for the presence of any polymorphism compared with the reference sequence in the NS3 (amino acid positions 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, and 175), NS5A (amino acid positions 28, 30, 3,1 and 93), and NS5B (amino acid positions 96, 142, 159, 282, 289, 316, 320, and 321) gene regions. No RAVs were detected in the NS5B region.

SUPPORTING TABLE S3. Impact of NS3 RAVs in Selected Patient Groups

Population	Virologic Failures/ Patients in RAP* [X/Y], (%)	Number of Sequences Available [m]	Number of Patients With RAVs		Treatment-emergent NS3 RAVs (Number of Patients With Variants Detected)
			NS3 RAVs Not Detected [n], (n/m) (%)	NS3 RAVs Detected [n], (n/m) (%)	
Overall	29/98 (29.6)	28	26 (92.9)	2 (7.1)	Q80K (1), D168E (1)
By Genotype and Subtypes					
GT1a	26/82 (31.7)	25	23 (92.0)	2 (8.0)	Q80K (1), D168E (1)
GT1b	3/16 (18.8)	3	3 (100.0)	0 (0.0)	-
By Virologic Failure Category					
Relapse	29/98 (29.6)	28	26 (92.9)	2 (7.1)	Q80K (1), D168E (1)
By Treatment Duration					
4 weeks	20/30 (66.7)	19	17 (89.5)	2 (10.5)	Q80K (1), D168E (1)
6 weeks	8/50 (16.0)	8	8 (100.0)	0 (0.0%)	-
8 weeks	1/18 (5.6)	1	1 (100.0)	0 (0.0%)	-
By Cirrhosis Status					
Cirrhotic	5/38 (13.2)	5	5 (100.0)	0 (0.0%)	-
Noncirrhotic	24/60 (40.0)	23	21 (91.3)	2 (8.7%)	Q80K (1), D168E (1)

The following RAV(s) within NS3 were selected for reporting: 36*, 54*, 55*, 56*, 80*, 107*, 122*, 132*, 155*, 156*, 158*, 168*, 170*, and 175*, where * denotes any polymorphism

compared with the reference sequence at these positions. The resistance-analysis population (RAP) included all patients with baseline resistance data and a virologic outcome of either SVR or relapse.

X, number of virologic failures in the RAP; Y, number of patients who received study therapy in the RAP; m, number of patients who received study therapy and had samples sequenced for RAVs; n, number of patients who had the specified RAV(s) detected.

-, no RAV detected.

*One patient with GT1b infection at baseline but detected with GT2b virus at relapse was excluded from the post-baseline analysis.

SUPPORTING TABLE S4. Impact of NS5A RAVs in Selected Patient Groups

Population	Virologic Failures/ Patients in RAP* [X/Y], (%)	Number of Sequences Available [m]	Number of Patients With RAVs		Treatment-emergent NS5A RAVs (Number of Patients With Variants Detected)
			NS5A RAVs Not Detected [n], (n/m) (%)	NS5A RAVs Detected [n], (n/m) (%)	
Overall	29/98 (29.6)	28	17 (58.6)	12 (41.4)	M28A/T/V (5), Q30L/R (6), L31M (1), Y93C/H/N (3)
By Genotype and Subtypes					
GT1a	26/82 (31.7)	26	14 (53.8)	12 (46.2)	M28A/T/V (5), Q30L/R (6), L31M (1), Y93C/H/N (3)
GT1b	3/16 (18.8)	3	3 (100.0)	0 (0.0)	-
By Virologic Failure Category					
Relapse	29/98 (29.6)	29	17 (58.6)	12 (41.4)	M28A/T/V (5), Q30L/R (6), L31M (1), Y93C/H/N (3)
By Treatment Duration					
4 weeks	20/30 (66.7)	20	12 (60.0)	8 (40.0)	M28A (1), Q30L/R (6),

					L31M (1), Y93H/N (2)
6 weeks	8/50 (16.0)	8	5 (62.5)	3 (37.5%)	M28A/T/V (3), Y93C (1)
8 weeks	1/18 (5.6)	1	0 (0)	0 (0.0%)	M28V (1)
By Cirrhosis Status					
Cirrhotic	5/38 (13.2)	5	2 (40.0)	3 (60.0%)	M28A/T/V (3), Y93C (1)
Noncirrhotic	24/60 (40.0)	24	15 (62.5)	9 (37.5%)	M28A/V (2), Q30L/R (6), L31M (1), Y93H/N (2)

The following NS5A RAV(s) were selected for reporting: 28*, 30*, 31*, and 93*, where * denotes any polymorphism compared with the reference sequence at these positions.

X, number of virologic failures in the RAP; Y, number of patients who received study therapy in the RAP; m, number of patients who received study therapy and had samples sequenced for RAVs; n, number of patients who had the specified RAV(s) detected.

-, no RAV detected.

*One patient with GT1b infection at baseline but detected with GT2b virus at relapse was excluded from the post-baseline analysis.

SUPPORTING TABLE 5. Impact of Baseline NS3 RAVs on Efficacy in GT3-infected Patients

	SVR12		
Population	Overall Efficacy in Patients With Sequence in RAP	NS3 RAVs Not Detected	NS3 RAVs Detected
Overall GT3 in RAP	36/38 (94.7%)	1/1 (100%)	35/37 (94.6%)
By Treatment Duration			
8 weeks	12/13 (92.3%)	0/0 (n/a)	12/13 (92.3%)
12 weeks	24/25 (96.0%)	1/1 (100%)	23/24 (95.8%)

Population sequencing was performed and analyzed for the presence of any polymorphism compared with the reference sequence in the NS3 gene at amino acid positions 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, and 175. The resistance-analysis population (RAP) included all patients with baseline resistance data and a virologic outcome of either SVR or relapse.

SVR12, number of SVR patients/number of patients in each category.

SUPPORTING TABLE 6. Impact of Baseline NS5A RAVs on the Efficacy in GT3-infected Patients

	SVR12		
Population	Overall Efficacy in Patients With Sequence in RAP	NS3 RAVs Not Detected	NS3 RAVs Detected
Overall GT3 in RAP	38/40 (95.0%)	35/37 (94.6%)	3/3 (100.0%)
By Treatment Duration			
8 weeks	14/15 (93.3%)	14/15 (93.3%)	0/0 (NA)
12 weeks	24/25 (96.0%)	21/22 (95.5%)	3/3 (100.0%)

Population sequencing was performed and analyzed for the presence of any polymorphism compared with the reference sequence in the NS5A gene at amino acid positions 28, 30, 31, and 93.

SVR12, number of SVR patients with RAV selected/number of patients with RAV selected in each category.

SUPPORTING TABLE 7. Presence of RAVs Among Patients Undergoing Re-treatment With EBR/GZR + SOF + RBV for 12 Weeks According to Differing Assay Sensitivity

	Next-generation sequencing (1% sensitivity threshold) N = 23	Population sequencing (≈20% sensitivity threshold) N = 23
NS5A RAVs		
No RAV	9 (39%)	14 (61%)
Any RAV	14 (61%)	9 (39%)
AA28	6	4
AA30	5	4
AA31	5	1
AA93	4	3
1 RAV	9 (39%)	6 (26%)
≥2 RAVs	5 (22%)	3 (13%)
NS3 RAVs		
No RAV	6 (26)	7 (30)
Any RAV	17 (74)	16 (70)
AA36	1	1
AA56	1	1
AA80	12	11
AA122	4	4
AA132	2	2
AA155	1	0
AA168	2	2
AA170	3	2
1 RAV	12 (52)	11 (48)
≥2 RAVs	5 (22)	5 (22)