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Effectiveness of Elbasvir and Grazoprevir Combination, With or Without Ribavirin, for Treatment-Experienced Patients with Chronic Hepatitis C Infection

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Short Title: EBR/GZR ± RBV in treatment-experienced HCV Patients

Conflicts of interest

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Author contributions

Merck contributed to the trial design, study execution and management, data collection, statistical analyses, and drafting of this paper. Paul Kwo, Paul Stryszak, Frank J. Dutko and Barbara Haber analyzed the data. The sponsor reviewed a penultimate version of the paper. All authors had access to the study data, approved the final paper, and assume full responsibility for the veracity of the data and analyses. The lead/corresponding author had full access to all data and had final responsibility for the decision to submit the manuscript for publication.

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Abbreviations used in this paper: **AEs, adverse events; ART, antiretroviral therapy; CI, confidence interval; EBR, elbasvir; GT, genotype; GZR, grazoprevir; HCV, hepatitis C virus; NGS, next-generation sequencing; PR, peginterferon/ribavirin; RAV, resistance-associated variant; RBV, ribavirin; RT-PCR, reverse transcription polymerase chain reaction; SAEs, serious adverse events; ST, sensitivity threshold.**

Abstract

BACKGROUND & AIMS: Patients infected with hepatitis C virus (HCV) genotype 1, 4, or 6, with or without cirrhosis, previously treated with peg-interferon and ribavirin, are a challenge to treat. We performed a phase 3 randomized controlled open-label trial to assess the effects of 12 or 16 weeks of treatment with once-daily elbasvir (an HCV NS5A inhibitor, 50 mg) and grazoprevir (an HCV NS3/4A protease inhibitor, 100 mg), in a fixed-dose combination tablet, with or without twice-daily ribavirin, in this patient population.

METHODS: We analyzed data from 420 patients (35% with cirrhosis, 64% with a null or partial response to peg-interferon and ribavirin) who were randomly assigned (1:1:1:1) to groups given elbasvir and grazoprevir once daily, with or without twice-daily ribavirin, for 12 or 16 weeks, at 65 study centers in 15 countries in Europe, Asia, and Central and North America. Randomization was stratified by cirrhosis status and type of peg-interferon and ribavirin treatment failure. HCV RNA was measured using COBAS TaqMan v2.0. The primary end point was HCV RNA below 15 IU/mL, 12 weeks after completion of treatment (SVR12). We aimed to determine whether the proportion of patients achieving an SVR12 in any group was was greater than the reference rate (58%).

RESULTS: With 12 weeks of treatment, an SVR12 was achieved by 92.4% of patients given elbasvir and grazoprevir and 94.2% of patients given elbasvir and grazoprevir with ribavirin. With 16 weeks of treatment, an SVR12 was achieved by 92.4% of patients given elbasvir and grazoprevir and 98.1% of patients given elbasvir and grazoprevir with ribavirin. Among patients

treated for 12 weeks without ribavirin, virologic failure occurred in 6.8%, 0%, and 12.5% of patients with HCV genotype 1a, 1b, or 4 infection, respectively. Also among patients given elbasvir and grazoprevir for 12 weeks, virologic failure occurred in 0% of patients infected with HCV genotype 1 and 7.5% infected with HCV genotype 4, respectively, who relapsed after completing peg-interferon and ribavirin or with a null or partial response to peg-interferon and ribavirin. Among patients treated for 16 weeks who received ribavirin, there were no incidences of virologic failure. Common adverse events were fatigue (23.1%), headache (19.8%), and nausea (11.0%).

Conclusions: The combination tablet of elbasvir and grazoprevir, with or without ribavirin, was highly efficacious in inducing an SVR12 in patients with HCV genotype 1, 4, or 6 infection failed by previous treatment with peg-interferon and ribavirin, including patients with cirrhosis and/or a prior null response. The treatment was generally well tolerated. ClinicalTrials.gov no: NCT02105701.

KEY WORDS: Hepatitis C; Randomized; Therapy; C-EDGE Treatment-Experienced

Although significant strides have been made in the treatment of chronic hepatitis C virus (HCV) infection, some patient populations remain difficult to cure. This includes patients with genotype (GT)1 infection who have cirrhosis and prior treatment failures with cirrhosis. In addition, those with HCV GT1a infection are somewhat harder to cure than those with GT1b infection.

Among patients with HCV GT1 infection who failed previous treatment with peginterferon/ribavirin (PR), both 12- and 24-week all-oral, direct-acting antiviral regimens have been studied. In the ION-2 study, SVR12 rates (sustained virologic response 12 weeks after the end of therapy) in treatment-experienced patients with cirrhosis and HCV GT1 infection receiving sofosbuvir/ledipasvir ± RBV were 82-86% in those treated for 12 weeks and 95-100% in those treated for 24 weeks.[1,2] In another study, a paritaprevir-containing 12-week regimen achieved an SVR12 of 87% in patients with cirrhosis and prior null response and 87% in patients with cirrhosis and HCV GT1a infection with a history of prior failure of any type. In contrast, the SVR12 using either regimen for 24 weeks was ≥94%. Most recently, a 12-week regimen of sofosbuvir/velpatasvir has achieved SVR12 rates of 96-100% in treatment-experienced patients with GT1 infection, and has received approval as a 12-week, ribavirin-free treatment option for treatment-naïve, and experienced well-compensated patients with HCV GT1-6 infection, regardless of treatment history.[3,4]

The combination of elbasvir (EBR), a once-daily NS5A inhibitor, and grazoprevir (GZR), a once-daily HCV NS3/4A protease inhibitor, is approved by the United States Food and Drug Administration and Health Canada for the treatment of chronic HCV GT1 or GT4 infection in adults.[5-7] Each of these direct-acting antiviral agents has broad in vitro genotypic activity.[6-10]

Phase 2 and 3 clinical trials evaluated a once daily all-oral regimen of EBR/GZR ± RBV in mono- and HIV co-infected patients with and without cirrhosis, and HCV GT1, 4, or 6 infection.[11-16]

Therapy for HCV infection has focused on regimens that shorten duration without compromising efficacy. Data from the phase 2 C-WORTHY study[13] indicate that an 18-week regimen of EBR/GZR ± RBV may be sufficient to achieve high rates of SVR12 in a previously-treated patient population, including those with cirrhosis. We therefore hypothesized that the combination of EBR/GZR ± RBV could achieve high SVR12 rates when given for only 12–16 weeks which, at the time that the study was designed, would have afforded substantial benefit over the contemporaneous treatment options. At the time of the development of this protocol, this was the first Phase 3 trial to explore a lengthened duration shorter than 24 weeks. The goal of the phase 3 C-EDGE Treatment-Experienced Trial was to assess the need for extended treatment duration (to 16 weeks) and/or addition of ribavirin in patients with chronic HCV GT1, 4, or 6 infections who had failed prior PR therapy.

Materials and Methods

Patients

Male and female adults with HCV GT1, 4, or 6 infection who had failed prior treatment with PR were enrolled. All patients had baseline HCV RNA >10,000 IU/mL. Patients with cirrhosis (as defined according to liver biopsy, FibroScan® >12.5 kPa within 12 months, or FibroSure® >0.75 + APRI >2) or HIV co-infection (either naïve to antiretroviral therapy [ART] or on stable suppressive ART with tenofovir or abacavir and either emtricitabine or lamivudine plus raltegravir, dolutegravir, or rilpivirine) were allowed to enroll. Prior response failure to PR

was defined as null response (<2 $\log_{10}$ IU/mL reduction in HCV RNA at week 12 or <1 $\log_{10}$ IU/mL reduction in HCV RNA at week 4); partial response (>2 $\log_{10}$) reduction in HCV RNA at week 12 but quantifiable HCV RNA at end of treatment); or relapse (undetectable HCV RNA at end of treatment but quantifiable at any time thereafter). Patients with decompensated liver disease, hepatitis B virus coinfection, or previous treatment with a direct acting anti-HCV agent were excluded. Enrollment was constrained to meet the following approximate targets: at least 30% of the participants having cirrhosis and at least 80% with prior partial/null response (collectively termed on-treatment failures) to PR. In the final enrolled population, 35% of patients had cirrhosis, and 64% of patients with prior partial/null response. A complete description of the inclusion/exclusion criteria is listed in the Supplementary Material.

Study Design

This was a phase 3, randomized, parallel-group, multisite, open-label clinical trial of EBR (MK-8742; Merck & Co., Inc., Kenilworth, NJ) + GZR (MK-5172; Merck & Co., Inc.). Patients were randomized (using a central interactive voice responses system or integrated web response system) in a 1:1:1:1 ratio to receive a fixed-dose combination of EBR 50 mg/GZR 100 mg once daily ± RBV twice daily for 12 or 16 weeks, and followed for 24 weeks after cessation of dosing. The randomization schedule was generated by the sponsor using a validated system. Permuted blocks were used for each of the six strata. The randomization schedule was then provided to an independent third-party vendor. The vendor handled the implementation of the schedule, including assigning patients to intervention according to the schedule. Randomization was stratified according to the presence or absence of cirrhosis, and the prior type of treatment

failure to PR (relapse, partial response, or null response). Patients, clinical site, and sponsor personnel were blinded to treatment duration, until week 12 of therapy, at which time additional medication was supplied if patients had been randomized to 16 weeks.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Independent institutional review boards or ethics committees reviewed and approved the protocol and applicable amendments for each institution, and all patients gave written informed consent.

Study Assessments

Plasma HCV RNA concentrations were measured by the COBAS® AmpliPrep/COBAS® TaqMan® HCV test, v2.0 (Roche Molecular Diagnostics, Branchburg, NJ) with a lower limit of quantitation of 15 IU/mL. Specimens for HCV RNA measurements were collected at screening, baseline, treatment weeks 1, 2, 4, 6, 8, 10, and 12 (treatment weeks 14 and 16 if in the 16-week arms), and follow-up weeks 4, 8, 12, and 24.

Population sequencing and next-generation sequencing (NGS) were performed at baseline and at the time of virologic failure to detect RAVs. The specific NS5A loci evaluated included any polymorphism at amino acid positions 28, 30, 31, and 93. These particular amino acids were evaluated based on data from the EBR/GZR phase 2/3 clinical programs, which indicate that only polymorphisms at these 4 positions impact the efficacy of EBR/GZR. For population sequencing of NS3 and NS5A RAVs, HCV RNA was reverse-transcribed and amplified using reverse transcription polymerase chain reaction (RT-PCR) followed by population (Sanger) sequencing of the NS3 and NS5A genes on an ABI Sequencer from samples with RNA levels of

≥1000 IU/mL. The limit of minority variant detection in the population was >25% of the viral population.[17] For NGS of NS5A RAVs, HCV RNA was reverse-transcribed and amplified using RT-PCR followed by library preparation, amplification using Nextera XT, and sequencing of the NS5A gene (llumina, MiSeq). Data QC analysis and variant calling were performed using data with Q score >30. NGS data were analyzed at 1% and 15% levels of sensitivity for variant detection.

Endpoints and Statistical Analysis

The primary objectives were to evaluate: 1) the efficacy of EBR/GZR (± RBV), defined as the proportion of patients achieving SVR12 (HCV RNA <15 IU/mL 12 weeks after cessation of all therapy); and 2) EBR/GZR safety and tolerability. Virologic failures were categorized as breakthrough viremia (confirmed HCV RNA ≥15 IU/mL during treatment after previously being below 15 IU/mL), rebound (defined as a confirmed >1 $\log_{10}$ IU/mL increase in HCV RNA from nadir while on treatment), and relapse (confirmed HCV RNA level ≥15 IU/mL subsequent to cessation of study therapy after becoming <15 IU/mL at the end of treatment). Confirmation was determined by a separate blood sample within 2 weeks of the first sample. Intermittent missing HCV RNA values were imputed as the worst of the 2 adjacent values. Non-intermittent missing HCV RNA values were considered as treatment failures.

This study was designed to randomize 400 patients into four arms in a 1:1:1:1 ratio. There was 99% power to demonstrate the primary hypothesis that the proportion of subjects in at least one of the arms would have an SVR12 rate superior to 58% at an overall α level of 0.05. The historical SVR12 reference rate of 58% is based on response rates from a previous study of

treatment experienced patients receiving simeprevir plus PR[18], and adjusted according to the constrained enrollment goals of patients with prior null/partial response (complete details are included in the protocol, located in the *Supplementary Materials*). This power calculation was based on the assumption of an underlying response rate of at least 80% in the treatment arms.

The primary efficacy and safety analyses were performed on the full analysis set (FAS), which included all patients receiving at least 1 dose of the study treatment. Hypothesis tests were conducted using a one-sided exact test for a binomial proportion. The within-group 95% confidence intervals (CIs) on the proportions of interest were computed by the Clopper-Pearson method, while the Miettinen-Nurminen method was used for between-pooled-group comparisons.[19] Multiplicity was controlled by using two sets of tests. First, the 12-week treatment arms were compared against the historical reference rate of 58% using a closed testing procedure. The 12-week arm with RBV was tested first at a one-sided alpha level of 0.0125. Only if superiority relative to the historical reference rate was found, the 12-week arm without RBV was tested at a one-sided alpha level of 0.0125. Second, the 16-week treatment arms were compared against the historical reference rate also using a closed testing procedure. The 16-week arm with RBV was tested first at a one-sided alpha level of 0.0125. Only if superiority relative to the historical reference rate was found, the 16-week arm without RBV was tested at a one-sided alpha level of 0.0125. Secondary efficacy analyses were considered as supportive, hypothesis-generating estimations. A per-protocol analysis, which focused on virologic failures and excluded patients who discontinued treatment for administrative reasons, was conducted in predefined patient subgroups (sex, GT, *IL28B* genotype, baseline viral load, presence of cirrhosis, prior treatment response, and HIV coinfection).

Assessment of the impact of RAVs on SVR12 was performed in the resistance analysis population, which included all patients who had baseline sequencing available and a treatment outcome of either SVR12 or virologic failure.

The frequencies of serious adverse events (SAEs) that occurred at any time during the study, and other adverse events (AEs) that occurred up to 14 days after cessation of treatment, were calculated. Investigators assessed the relationship of each AE or SAE to study therapy; AEs and SAEs were regarded as drug-related if judged as being at least possibly related to study drug by the investigator.

Role of Funding Source

Merck Sharp & Dohme Corp contributed to trial management, data collection and statistical analyses, and the writing and review of this manuscript. All authors had access to the data, reviewed and approved the final manuscript, and take full responsibility for the accuracy of the data and statistical analysis. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

Results

The study was performed at 65 study centers in 15 countries across Europe, Asia, and Central and North America. In total, 482 patients were screened and 420 were enrolled and randomized to treatment (Figure 1). Of the 62 patients not randomized, 3 patients withdrew prior to randomization and 59 patients were screen failures (i.e., did not meet inclusion criteria). The most common reasons for screen failure were exclusionary laboratory values

(13.8%), no protocol-specified prior treatment status (10.3%), failure to meet protocol definitions of chronic HCV GT1, 4, or 6 infection (8.6%); and lack of informed consent (8.6%). The first patient started treatment on June 11, 2014 and the final patient completed 12 weeks of follow-up on March 13, 2015. Twelve patients were excluded from the per-protocol population (EBR/GZR for 12 weeks, n = 3 [consent withdrawn, n = 2; death, n = 1]; EBR/GZR + RBV for 12 weeks, n = 3 [no documentation regarding prior treatment failure, n = 2; ascites, n = 1]; EBR/GZR for 16 weeks, n = 1 [non–medication-related noncompliance]; EBR/GZR + RBV for 16 weeks, n = 5 [lost to follow-up, n = 2; illegal drug use, n = 1; prohibited medication, n = 1; noncompliance due to AE, n = 1]).

The proportions of patients with various demographic characteristics were similarly distributed across the treatment arms. The majority of the patients were white (68%) and male (65%). The median age was 55 years (range, 19–77 years); 14% were ≥65 years of age and 79% had a non-CC *IL28B* genotype (Table 1). Overall, 49% had HCV RNA >2,000,000 IU/mL. The proportion of patients with prior relapse, partial response, or null response was similar across all 4 treatment arms. Five percent of patients were HIV coinfected, 35% had cirrhosis, and 64% had prior partial/null response. Patient demographics according to HCV genotype are presented in Supplementary Table 1.

Sustained Virologic Response

The SVR rates were 92.4% (95% CI: 85.5, 96.7) in the 12-week EBR/GZR arm, 94.2% (95% CI: 87.9, 97.9) in the 12-week EBR/GZR + RBV arm, 92.4% (95% CI: 85.5, 96.7) in the 16-week EBR/GZR arm, and 98.1% (95% CI: 92.0, 99.4) in the 16-week EBR/GZR + RBV arm (Figure 2). The

SVR12 rate in each group was statistically superior to the historical reference rate of 58% ($p < .001$ for each comparison based on a one-sided exact test for a binomial proportion). Pooling across treatment durations, the difference in SVR12 between the patients who received RBV and those who did not was 3.8% (95% CI: -0.7%, 8.7%). Pooling arms with and without RBV, the difference in SVR12s between patients who received 16 weeks of treatment and those who received 12 weeks of treatment was 2.0% (95% CI: −2.6%, 6.8%).

Overall, 19/420 (4.5%) patients experienced virologic failure (16 relapses, 2 rebound, and 1 breakthrough). None of the patients in the 16-week EBR/GZR + RBV arm experienced virologic failure. In the 12-week (no RBV) arm, virologic failure occurred in 6.8%, 0%, and 12.5% of G1a-, 1b-, or 4-infected patients, respectively. There were no dose modifications following virologic failure in either of the 12-week treatment arms. There was little difference in relapse rates between RBV- and non-RBV-containing 12 week arms (5.8% vs 5.7%, respectively). 3.8% of patients relapsed in the non-RBV-containing 16 week arm.

Subgroup Analysis

A per-protocol analysis, which focuses on virologic failures, was conducted to evaluate the efficacy of EBR/GZR among subgroups of patients in the study (Figure 3). Across arms, 207/218 (95.0%), 143/145 (98.6%), 32/36 (88.9%), and 5/6 (83.3%) of GT1a, 1b, 4, and 6-infected patients, respectively, achieved SVR12. Overall, the SVR12 rate was 93.8% (135/144) in patients with cirrhosis and 96.6% (255/264) in patients without cirrhosis. Across all treatment arms, SVR12 was achieved by 98% (202/207) of patients with baseline viral load ≤2,000,000

IU/mL and 94% (188/201) of those with baseline viral load >2,000,000 IU/mL. Among those who received the 12-week regimen, SVR12 rates were highest among GT1b-infected patients (34/34, 100%), those with prior PR relapse (35/35, 100%), or those with partial response (17/18, 94.4%). Efficacy among GT1a-infected patients (55/59, 93.2%) and those with prior null response (45/49, 91.8%) were lower. SVR12 rates were 100% for all patients who received EBR/GZR + RBV for 16 weeks, including patients with G1a infection and prior null response (20/20), patients with baseline NS3 RAVs (37/37), and patients with NS5A baseline RAVs (6/6).

Resistance-Associated Variants

In patients infected with HCV GT1, the presence of NS3 RAVs at baseline did not reduce SVR12 rates. The prevalence of baseline NS3 RAVs was 33.2% (123/370), based on population sequencing, and the SVR12 rates were 97.2% (240/247) and 94.3% (115/122) in patients without baseline NS3 RAVs or with NS3 RAVs, respectively (Supplementary Table 2). The slightly higher rate of virologic failure among patients with baseline NS3 RAVs is likely explained by the co-existence of baseline NS5A RAVs in these patients. Of the 14 GT1 virologic failures, 12 had baseline NS5A RAVs, and of the 2 failures who were wild-type for NS5A, only 1 had a baseline NS3 RAV (Supplementary Table 3).

Population sequencing (with a sensitivity threshold [ST] of approximately 25%) and NGS (with an ST of 1% and 15%) were used to analyze the impact of NS5A RAVs at positions 28, 30, 31, and 93 on SVR (Table 2). Regardless of RAV detection method (NGS 1% or 15% ST or population sequencing 25% ST), SVR was >98% in patients designated as having no baseline RAVs. SVR rates were also universally high in patients with HCV GT1b infection, regardless of

the absence or presence of NS5A baseline RAVs. RAVs also had no discernable impact on rates of SVR12 among patients with HCV GT4 or GT6 infection, although the number of patients with these genotypes was low (Supplementary Table 4).

In patients with GT1a infection across the 4 arms, increasing assay sensitivity was associated with an increase in the number of patients classified as having baseline RAVs, as expected (Table 2). Population sequencing (25% ST) and NGS (15% ST) yielded identical estimates of the proportion of patients with baseline RAVs (13.9% [31/223] and 13.9% [31/223]), consistent with the broadly similar sensitivity of these 2 assays, whereas an increase in assay sensitivity (NGS 1%) was associated with an increased proportion of patients considered to have NS5A RAVs at baseline (24% [53/223]). Thus, in the GT1a-infected population, the NGS 1% assay identified an additional 22 patients with baseline NS5A RAVs who were considered as having no baseline RAVs when using the lower-sensitivity assays. SVR rates among GT1a-infected patients with baseline RAVs were: population sequencing, 68% (21/31); NGS (15% ST), 68% (21/31); and NGS (1% ST), 81% (43/53) (Figure 4). It is apparent from these data that the same 10 virologic failures are identified by all 3 assays as having baseline NS5A RAVs, and that increasing assay sensitivity does not identify additional virologic failures with baseline RAVs. SVR was achieved by all 22 patients identified as having baseline RAVs using NGS 1% ST who were not identified as having baseline RAVs using the lower-sensitivity assays. Thus, the lower-sensitivity assays (population sequencing and NGS 15%) offer the highest precision in identifying patients with baseline RAVs at risk of virologic failure.

Assessment of the impact of baseline NS5A RAVs in patients with GT1a infection was also conducted according to randomized treatment arm (Table 2). Rates of SVR12 varied by

treatment arm, ranging from 40% to 100% in patients with RAVs according to NGS 15% and from 50% to 100% in those with RAVs according to population sequencing. The low numbers of patients with RAVs within each treatment arm likely contributes to the wide variation in these response rates. GT1a-infected patients with baseline RAVs were most likely to experience virologic failure if treated for 12 weeks: 7 of the 10 GT1a-infected patients with baseline NS5A RAVs who experienced virologic failure received a 12-week treatment regimen. SVR was 100% in all 6 patients with baseline RAVs who were treated with EBR/GZR + RBV for 16 weeks (2/6 of these patients had cirrhosis; Supplementary Table 5). Among GT1a-infected patients who did not have baseline NS5A RAVs at positions 28, 30, 31, or 93 using population sequencing, a 12-week regimen of EBR/GZR resulted in high SVR12 rates in all patients (49/50, 98%) and in the subgroups with cirrhosis (18/18, 100%) and prior null response (24/25, 96%).

Tolerability

The most common AEs observed were fatigue (23.1%), headache (19.8%), nausea (11.0%), and accidental overdose (7.9%) (Table 3). The majority of AEs were of mild or moderate severity. SAEs occurred in 3.1% of patients, and the frequencies were similar across the 4 treatment arms. Discontinuations due to AEs occurred in 1.7% of patients, most often in the treatment arm that received 16 weeks of treatment with EBR/GZR + RBV (n = 5). However, none of the discontinuations were attributed to the study drugs. Hemoglobin levels ≤9.9 g/dL occurred in 31/210 (14.8%) of patients in the RBV-containing arms and no patients (0/210) in the RBV-free groups. Hemoglobin decreases were managed by dose reductions of RBV. No discontinuations were due to anemia. Grade 3 or 4 elevations of bilirubin occurred in 7% of

patients in the RBV-containing arms and <1% of patients in the RBV-free groups. These bilirubin elevations typically occurred during the first 4 weeks of treatment, were often associated with decreases in hemoglobin, and were unrelated to alanine aminotransferase (ALT) elevation. Four patients (1.0%) had late elevations of ALT or aspartate aminotransferase (>5× upper limit of normal), but these elevations were transient and did not require interruption or discontinuation of EBR/GZR. All ALT elevations returned to baseline after study medication was discontinued and all subjects with an ALT elevation >5x ULN achieved SVR.

Discussion

This phase 3 trial examined the EBR/GZR fixed-dose combination in the treatment of prior PR treatment failures for durations of 12 or 16 weeks ± RBV. Overall SVR rates ranged from 92% with 12 weeks of EBR/GZR without RBV to 97% with 16 weeks of EBR/GZR with RBV. Across all treatment arms, SVR12 was achieved by 98% of patients with baseline viral load ≤2,000,000 IU/mL. The overall virologic failure rate was 3.8%. Subgroup analysis demonstrated 100% SVR rates for a 12 week RBV-free regimen for patients with HCV GT1b infection regardless of past treatment history and 100% SVR rates for patients with a history of prior relapse regardless of genotype. No virologic failures were seen among patient treated for 16 weeks of EBR/GZR with RBV.

Among HCV GT1a-infected patients, efficacy was lowest in the EBR/GZR (−RBV) 12-week arm and highest in the EBR/GZR (+RBV) 16-week arm. Baseline testing for NS5A RAVs at positions 28, 30, 31, and 93 using population sequencing was highly effective in predicting the success of the 12-week regimen. In the 12-week (−RBV) arm, virologic failures occurred in 40%

and 2% of GT1a-infected patients with or without baseline RAVs, respectively. All patients with such RAVs who received a regimen of EBR/GZR + RBV for 16 weeks achieved SVR12 (6/6, 100%). Among HCV G1b-infected patients, 98.6% (145/157) achieved SVR regardless of duration or the presence of RBV. SVR was 89% in patients with HCV GT4 infection (n = 36). Among GT4-infected patients, a longer duration of therapy with EBR/GZR + RBV was associated with higher efficacy compared with arms that did not include RBV or were of shorter duration. The combination of EBR/GZR was generally safe and well tolerated, and serious AEs were rare.

The fixed-dose combination of EBR/GZR ± RBV achieved high SVR12 rates in important patient subpopulations, including those with null response, blacks/African Americans, and patients with cirrhosis (although it should also be noted that a FibroScan score of 12.5kPa identifies well-compensated patients with a relatively early stage of cirrhosis). SVR12 rates were also high in patients with HIV/HCV coinfection; however, these response rates should be viewed with some caution because only 21 coinfected patients were included in this study. For patients with HCV GT1b infection, the presence of any of these predictors of poor response did not adversely impact SVR rates. Blacks/African Americans consisted of 17% (70/408) of the per-protocol study population and overall SVR12 in blacks/African Americans was 99% (69/70). In patients with prior PR null response, 16 weeks of treatment with EBR/GZR + RBV resulted in no virologic failures. These observations parallel data from the C-WORTHY study, where SVR rates of 100% (33/33) were reported in patients with prior PR null response when retreated with EBR/GZR + RBV for 18 weeks.[14]

Recent data suggest that some naturally occurring HCV polymorphisms that reduce in vitro activity of direct-acting antiviral agents may affect SVR12 rates, depending on the

combination of antiviral drugs. For example, the presence of the naturally occurring Q80K polymorphism in NS3 at baseline reduced the SVR12 rate in HCV GT1a-infected patients treated with simeprevir and PR (and in patients with cirrhosis treated for 12 weeks with simeprevir and sofosbuvir) but did not reduce the SVR12 rate in patients without cirrhosis treated with simeprevir and sofosbuvir.[20-23] In this study, there was a high prevalence of NS3 baseline polymorphisms in the HCV GT1a-infected population, but their presence did not reduce SVR12 rates using EBR/GZR, indicating that EBR/GZR overcomes these resistance polymorphisms. Recent data suggest that the presence of NS5A polymorphisms conferring >100-fold resistance to ledipasvir, while uncommon, reduced the SVR12 rate in patients with cirrhosis treated with sofosbuvir/ledipasvir for either 12 or 24 weeks.[24] In GT1a patients with cirrhosis treated with sofosbuvir/ledipasvir, only 85% achieved SVR among those with baseline NS5A RAVS compared with 98% in those without.[24]

We found the highest precision in detecting clinically relevant baseline NS5A RAVs was obtained when using population sequencing or NGS with a 15% ST to detect RAVs at 4 positions: 28, 30, 31, and 93. Increasing assay sensitivity served to increase the number of patients categorized as having a baseline RAV, but failed to identify any additional patients with treatment failure. Thus, when calculating rates of virologic failure, the numerator (number of patients with failure) remained constant across all evaluations while the denominator (number of patients with baseline RAVs) increased as the assay sensitivity was increased. The use of population sequencing or NGS (15% ST) to detect NS5A RAVs represents the most specific and sensitive test for patients with NS5A RAVs who go on to fail virologically with EBR/GZR. Commercially available NS5A assays utilizing population sequencing or NGS (15% ST) at amino

acid positions 28, 30, 31, and 93 are available in the United States. Use of these assays in patients with HCV GT1a infection can help maximize rates of SVR12. Among patients without RAVs as defined by these tests, the present study indicates that SVR12 rates of ≈99% are attainable. Data from the present study suggest that 14% of patients with prior non-response and GT1a infection will show presence of baseline RAVs, which appear to be overcome through extending treatment duration to 16 weeks and the inclusion of RBV. These outcomes are consistent regardless of other baseline factors such as cirrhosis, prior treatment failure type, and baseline viral load, thus indicating that NS5A RAV testing alone can be used to define the optimal dosing regimen for patients with GT1a infection being considered for EBR/GZR therapy. Therefore, testing for NS5A RAV among GT1a infected patients can be used to identify the subset of patients who can benefit from the addition of ribavirin and extension of treatment to 16 weeks.[5]

The recent approval of a 12-week regimen of sofosbuvir/velpatasvir in the US and Europe for compensated patients with HCV infection, regardless of genotype or response to prior therapy represents another milestone in the treatment of HCV infection.[4,25] This regimen provides a shorter duration alternative to the 24-week regimens of sofosbuvir/ledipasvir, sofosbuvir + simeprevir, or paritaprevir/ritonavir/ombitasvir + dasabuvir + RBV in treatment-experienced patients with cirrhosis. Paritaprevir/ritonavir/ombitasvir + dasabuvir (without ribavirin) can also be administered for 12 weeks in treatment-experienced cirrhotic patients with HCV GT1b infection. EBR/GZR is also available as a 12-week treatment option for most compensated patients with HCV genotypes 1 and 4, regardless, of cirrhosis status or prior treatment response, but with the need to extend treatment duration and add ribavirin for

patients with HCV GT1a infection and baseline NS5A RAVs. In the present study, HCV GT1a-infected patients with prior PR partial or null responses achieved SVR rates of 100% with no virologic failures when receiving 16 weeks of treatment with EBR/GZR + RBV. While the sample size is small, combination therapy using EBR/GZR + RBV for 16 weeks also achieved high SVR12 rates in prior PR treatment failures with HCV GT4 or 6 infection.

In this study, there was a notable adverse impact of ribavirin therapy on safety events. Drug-related AEs were higher among patients receiving ribavirin with both 12- (64% vs 39%) and 16-week (76% vs 44%) treatment regimens. Similarly, approximately 5% of patients in each of the ribavirin-containing arms reported a grade 3/4 hemoglobin decline, compared with no patients in the ribavirin-free arms. AEs commonly associated with ribavirin such as fatigue, nausea, and anemia were all reported at higher rates in the ribavirin treatment arms. Given the lack of any incremental improvement in SVR12 associated with ribavirin therapy with either 12- or 16-week treatment arms, a regimen consisting of EBR/GZR alone for 12 weeks appears appropriate for most treatment-experienced patients with chronic HCV infection, the only exception being a subset of GT1a-infected patients. Longer duration, 16 weeks, with the addition of RBV can benefit either GT1a-infected patients with baseline NS5A RAVs or alternatively, if RAV testing is not available, 16 weeks + RBV can effectively treat prior null or partial responders with HCV GT1a infection.

Initial results from the ongoing C-CREST-1 and 2 trials, confirm the efficacy and safety of a 3-drug combination of grazoprevir and the NS5B polymerase inhibitor MK-3682 with either elbasvir or the NS5A inhibitor Ruzasvir (MK-8408) in GT1-, 2- and 3-infected treatment naïve patients without cirrhosis.[26] These findings support further evaluation of this regimen among a

more diverse population of HCV-infected patients, including those with additional genotypes, cirrhosis, prior treatment and those with HIV/HCV-co-infection.

There are several limitations to the present study. Because of the open-label nature of treatment, patients were aware of their ribavirin allocation. Further, the historical reference rate was based on a 48-week study of a PR-based treatment regimen. Although, this represented the best available control rate at the time this study was designed, more recent studies have since been published that have yielded higher rates of SVR. The sample size within certain of the predefined patient subgroups, most notably the HIV/HCV coinfected group, was small; thus, limiting the conclusions that can be drawn for these patient groups. Finally, treatment durations of 24-weeks were not considered appropriate for this study due to earlier data that high rates of SVR could be achieved with treatment durations <24 weeks.[13]

In conclusion, the C-EDGE TE study demonstrated that treatment with EBR/GZR-containing regimens was highly effective in the treatment of GT1-, 4-, or 6-infected patients who failed prior PR therapy. Importantly, there was no difference in response rates between patients with and without cirrhosis, irrespective of therapy duration and with or without the addition of ribavirin. Virologic failure was observed in 5.8% of patients treated with a 12-week regimen of EBR/GZR. To maximize SVR rates, HCV GT1a- or 4-infected patients with a prior history of null or partial response to peginterferon/RBV therapy may benefit from the addition of RBV and extension of therapy to 16 weeks. Alternatively, baseline RAV testing of HCV GT1a-infected patients may be used to identify the small subset of patients who can benefit from the addition of RBV and extension of therapy to 16 weeks.

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Figure Legends

Figure 1. Patient flow diagram. *One patient had missing data for status at the end of the treatment phase; this patient completed the study but was counted as having neither discontinued treatment nor completed treatment (status of "Status Not Recorded"). **One patient had a status that is not recorded; this patient missed the follow-up week 12 visit due to relocation but may not be completely lost to follow-up.

Figure 2. Rates of SVR12 after end of treatment (primary efficacy; full analysis set [FAS] analysis). The SVR12 rates (% of patients with HCV RNA <15 IU/mL at 12 weeks after the end of treatment) for all patients who received at least 1 dose of study medication (FAS analysis) is shown for each arm of the study, with 95% CIs determined with the Clopper-Pearson method. The number of patients with virologic breakthrough (confirmed HCV RNA ≥15 IU/mL during treatment after previously being below 15 IU/mL), virologic rebound (defined as a confirmed >1 $\log_{10}$ IU/mL increase in HCV RNA from nadir while on treatment), and virologic relapse (confirmed HCV RNA level ≥15 IU/mL subsequent to cessation of study therapy after becoming <15 IU/mL at the end of treatment), and the number of patients who were lost to follow-up or discontinued early due to reasons other than virologic failure, are shown in the table. Confirmation was determined by a separate blood sample within 2 weeks of the first sample. *LTFU/early DC, lost to follow-up/early discontinuation due to reasons other than virologic failure.

Figure 3. SVR12 rates by subgroup analysis (per-protocol analysis). The SVR12 rates (HCV RNA <15 IU/mL at follow-up week 12) are shown by subgroups in a per-protocol analysis. The per-protocol analysis excluded 12 patients who discontinued for administrative reasons (EBR/GZR for 12 weeks: withdrew consent [n = 2], death 22 days after discontinuing study medication, considered unlikely to be related to study medication by the investigator [n = 1]; EBR/GZR + RBV for 12 weeks: no documentation for prior treatment failure classification [n = 2], prohibited prior medical condition [ascites] [n = 1]; EBR/GZR for 16 weeks: non–medication-related nonadherence with study drug [n = 1]; EBR/GZR + RBV for 16 weeks: lost to follow-up [n = 2], illegal drug user [n = 1], prohibited medication [n =1], nonadherence due to AE [n = 1]).

Figure 4. Efficacy of EBR/GZR in HCV GT1a-infected patients with or without baseline NS5A RAVs and prevalence of baseline NS5A RAVs at positions 28, 30, 31, and 93, based on population sequencing (sensitivity threshold 25%) and NGS (sensitivity threshold 15% and 1%) (all treatment arms combined). RAVs were assessed as any polymorphism at amino acids 28, 30, 31, and 93 loci within the NS5A region.

Table 1. Demographics

	12 weeks		16 weeks		Total
	No RBV n = 105	+ RBV n = 104	No RBV n = 105	+ RBV n = 106	N = 420
Male, n (%)	66 (63)	72 (69)	69 (66)	64 (60)	271 (65)
Age, *y*, median, (range)	56 (25, 76)	56 (23, 75)	55 (31, 73)	55 (19, 77)	55 (19, 77)
18–35 *y*, n (%)	6 (6)	3 (3)	4 (4)	4 (4)	17 (4)
36–50 *y*, n (%)	16 (15)	22 (21)	26 (25)	25 (24)	89 (21)
51–64 *y*, n (%)	66 (63)	67 (64)	59 (56)	65 (61)	257 (61)
≥65 *y*, n (%)	17 (16)	12 (12)	16 (15)	12 (11)	57 (14)
Race, n (%)					
Caucasian	66 (63)	70 (67)	72 (69)	78 (74)	286 (68)
African American	23 (22)	24 (23)	9 (9)	15 (14)	71 (17)
Asian	15 (14)	9 (9)	22 (21)	10 (9)	56 (13)
Other	1 (1)	1 (1)	2 (2)	3 (3)	7 (2)
Ethnicity, Hispanic or Latino, n (%)	8 (8)	11 (11)	11 (10)	9 (8)	39 (9)
HCV genotype or subtype, n (%)					
GT1a	61 (58)	60 (58)	48 (46)	58 (55)	227 (54)

GT1b	34 (32)	29 (28)	48 (46)	36 (34)	147 (35)
GT1 other	1 (1)	0 (0)	0 (0)	2 (2)	3 (1)
GT4	9 (9)	15 (14)	5 (5)	8 (8)	37 (9)
GT6	0 (0)	0 (0)	4 (4)	2 (2)	6 (1)
Baseline HCV RNA, *IU/mL*, n (%)					
≤2,000,000	54 (51)	52 (50)	48 (46)	59 (56)	213 (51)
>2,000,000	51 (49)	52 (50)	57 (54)	47 (44)	207 (49)
≤10,000,000	96 (91)	100 (96)	102 (97)	104 (98)	402 (96)
>10,000,000	9 (9)	4 (4)	3 (3)	2 (2)	18 (4)
Mean (SD)	3.6×10^6 (4.7×10^6)	3.1×10^6 (3.8×10^6)	3.3×10^6 (3.9×10^6)	2.9×10^6 (3.5×10^6)	3.2×10^6 (4.0×10^6)
IL28B genotype, n (%)					
CC	20 (19)	16 (15)	28 (27)	21 (20)	85 (20)
Non-CC	84 (80)	86 (83)	77 (73)	85 (80)	332 (79)
Missing	1 (1)	2 (2)	0 (0)	0 (0)	3 (1)
HIV co-infection, n (%)	6 (6)	5 (5)	6 (6)	4 (4)	21 (5)
Hepatic fibrosis stage, n (%)					
Metavir F0-F2	49 (47)	55 (53)	55 (52)	56 (53)	215 (51)
Metavir F3	19 (18)	14 (13)	12 (11)	13 (12)	58 (14)

Metavir F4	37 (35)	35 (34)	38 (36)	37 (35)	147 (35)
Cirrhosis diagnosis method*, n (%)					
Biopsy	18 (17.1)	8 (7.7)	10 (9.5)	14 (13.2)	50 (11.9)
FibroSure	0 (0)	5 (4.8)	2 (1.9)	2 (1.9)	9 (2.1)
FibroScan	19 (18.1)	22 (21.2)	26 (24.8)	21 (19.8)	88 (21.0)
FibroScan score†, kPa,	[n=50]	[n=53]	[n=67]	[n=51]	[n=221]
Mean (SD)	15.21 (11.543)	14.27 (9.51)	14.18 (12.52)	14.54 (11.40)	14.52 (11.30)
Median (range)	11.70 (2.9-53.3)	10.20 (4.9-41.0)	9.10 (4.3-67.8)	10.40 (3.8-54.2)	10.40 (2.9-67.8)
Baseline platelet count					
Mean, cells/µL (SD)	167.12 (58.46)	174.96 (60.41)	171.16 (60.76)	179.04 (72.50)	173.08 (63.24)
<100 x 10^3 cells/ µL, n (%)	15 (14.3)	14 (13.5)	11 (10.5)	8 (7.5)	48 (11.4)
Baseline serum albumin					
Mean, g/dL (SD)	4.29 (0.35)	4.32 (0.34)	4.34 (0.28)	4.21 (0.42)	4.29 (0.35)
<3.5 g/dL, n (%)	1 (1.0)	2 (1.9)	0 (0)	6 (5.7)	9 (2.1)
Prior treatment					

response, n (%)					
Prior null	49 (47)	44 (42)	46 (44)	43 (41)	182 (43)
Prior partial response	21 (20)	22 (21)	21 (20)	23 (22)	87 (21)
Prior relapse	35 (33)	38 (37)	38 (36)	40 (38)	151 (36)
Patients with Cirrhosis	n = 37	n = 35	n = 38	n = 37	n = 147
Age, *y*, median, (range)	56 (39, 75)	57 (23, 75)	58 (37, 72)	56 (19, 72)	57 (19,75)
Baseline platelet count, mean (SD)	121.14 (47.15)	128.18 (54.35)	136.68 (57.30)	126.59 (50.70)	128.21 (52.27)
Baseline serum albumin, mean (SD)	4.09 (0.37)	4.11 (0.33)	4.25 (0.30)	3.92 (0.43)	4.09 (0.38)

*Method used for diagnosis in 147 patients with cirrhosis.

n, the number of patients with the baseline characteristic and the % of patients in each group with that baseline characteristic. Baseline results were determined on day 1; SD, standard deviation.

Table 2. SVR12 in Patients With HCV GT1 Infection, With or Without NS5A RAVs at Amino Acid Positions 28, 30, 31, and 93 by Population Sequencing (25% sensitivity threshold) and Next-generation Sequencing (15% and 1% sensitivity thresholds)[a]

	Sustained virologic response		
HCV genotype/regimen	Patients without baseline NS5A RAVs [n/N (%)]	Patients with baseline NS5A RAVs [m/M (%)]	All patients [t/T (%)]
POPULATION SEQUENCING 25% SENSITIVITY THRESHOLD			
Overall GT1a	190/192 (99.0%)	21/31 (67.7%)	211/223 (94.6%)
12 weeks (− RBV)	49/50 (98.0%)	6/10 (60.0%)	55/60 (91.7%)
12 weeks (+ RBV)	50/51 (98.0%)	6/9 (66.7%)	56/60 (93.3%)
16 weeks (− RBV)	42/42 (100.0%)	3/6 (50.0%)	45/48 (93.8%)
16 weeks (+ RBV)	49/49 (100.0%)	6/6 (100.0%)	55/55 (100.0%)
Overall GT1b	117/117 (100.0%)	28/30 (93.3%)	145/147 (98.6%)
12 weeks (− RBV)	30/30 (100.0%)	4/4 (100.0%)	34/34 (100.0%)
12 weeks (+ RBV)	24/24 (100.0%)	4/5 (80.0%)	28/29 (96.6%)
16 weeks (− RBV)	35/35 (100.0%)	11/12 (91.7%)	46/47 (97.9%)
16 weeks (+ RBV)	28/28 (100.0%)	9/9 (100.0%)	37/37 (100.0%)
NGS 15% SENSITIVITY THRESHOLD			
Overall GT1a	190/192 (99.0%)	21/31 (67.7%)	211/223 (94.6%)
12 weeks (− RBV)	48/49 (98.0%)	7/11 (63.6%)	55/60 (91.7%)
12 weeks (+ RBV)	50/51 (98.0%)	6/9 (66.7%)	56/60 (91.7%)

16 weeks (− RBV)	43/43 (100.0%)	2/5 (40.0%)	45/48 (93.8%)
16 weeks (+ RBV)	49/49 (100.0%)	6/6 (100.0%)	55/55 (100.0%)
Overall G1b	39/40 (97.5%)	9/10 (90.0%)	48/50 (96.0%)
12 weeks (− RBV)	11/11 (100.0%)	2/2 (100.0%)	13/13 (100.0%)
12 weeks (+ RBV)	9/10 (90.0%)	1/1 (100.0%)	10/11 (90.9%)
16 weeks (− RBV)	11/11 (100.0%)	3/4 (75.0%)	14/15 (93.3%)
16 weeks (+ RBV)	8/8 (100.0%)	3/3 (100.0%)	11/11 (100.0%)
NGS 1% SENSITIVITY THRESHOLD			
Overall GT1a	168/170 (98.8%)	43/53 (81.1%)	211/223 (94.6%)
12 weeks (− RBV)	41/42 (97.6%)	14/18 (77.8%)	55/60 (91.7%)
12 weeks (+ RBV)	45/46 (97.8%)	11/14 (78.6%)	56/60 (93.3%)
16 weeks (− RBV)	40/40 (100.0%)	5/8 (62.5%)	45/48 (93.8%)
16 weeks (+ RBV)	42/42 (100%)	13/13 (100.0%)	55/55 (100.0%)
Overall GT1b	36/36 (100.0%)	12/14 (85.7%)	48/50 (96.0%)
12 weeks (− RBV)	11/11 (100.0%)	2/2 (100.0%)	13/13 (100.0%)
12 weeks (+ RBV)	8/8 (100.0%)	2/3 (66.7%)	10/11 (90.9%)
16 weeks (− RBV)	11/11 (100.0%)	3/4 (75.0%)	14/15 (93.3%)
16 weeks (+ RBV)	6/6 (100.0%)	5/5 (100.0%)	11/11 (100.0%)

m, number of patients with baseline NS5A RAVs who achieved SVR12; M, number of patients with baseline NS5A RAVs; n, number of patients without baseline NS5A RAVs who achieved SVR12; N, number of patients without baseline NS5A RAVs; t, total number of patients in treatment arm who achieved SVR12; T, total number of patients in treatment arm.

[a]Assessed in the resistance analysis population, which includes all patients who have baseline sequencing available and a treatment outcome of either SVR12 achieved or virologic failure.

Table 3. Tolerability

	12 weeks		16 weeks		
	No RBV n = 105	+ RBV n = 104	No RBV n = 105	+ RBV n = 106	Total N=420
Serious adverse event, n (%)	4 (3.8)[a]	3 (2.9)[b]	3 (2.9)[c]	4 (3.8)[d]	14 (3.3)
Drug-related adverse event, n (%)	41 (39.0)	67 (64.4)	46 (43.8)	81 (76.4)	235 (56.0)
Death, n (%)	0	0	0	0	0
Discontinued study medication due to adverse event, n (%)	1 (1.0)[e]	1 (1.0)[f]	0	5 (4.7)[g]	7 (1.7)
Discontinued study medication due to drug-related adverse event, n (%)	0	1 (1.0)[h]	0	2 (1.9)[i]	3 (0.7)
Hemoglobin, n (%)					
Grade 1 (10.0–10.9 *g/dL*)	3 (2.9)	20 (19.2)	1 (1.0)	15 (14.2)	39 (9.3)
Grade 2 (9.0–9.9 *g/dL*)	0	4 (3.8)	0	17 (16.0)	21 (5.0)
Grade 3 (7.0–8.9 *g/dL*)	0	5 (4.8)	0	4 (3.8)	9 (2.1)
Grade 4 (<7.0 *g/dL*)	0	0	0	1 (0.9)	1 (0.2)
Total bilirubin >5× baseline, n (%)	0	0	0	0	0

Late ALT/AST >5× ULN[j], n (%)	0	1 (1.0)	3 (2.9)	0	4 (1.0)
Most common AEs[k], n (%)					
Fatigue	20 (19.0)	28 (26.9)	17 (16.2)	32 (30.2)	97 (23.1)
Headache	22 (21.0)	21 (20.2)	20 (19.0)	20 (18.9)	83 (19.8)
Nausea	9 (8.6)	15 (14.4)	4 (3.8)	18 (17.0)	46 (11.0)
Accidental overdose	3 (2.9)	15 (14.4)	1 (1.0)	14 (13.2)	33 (7.9)
Insomnia	5 (4.8)	11 (10.6)	6 (5.7)	10 (9.4)	32 (7.6)
Anemia	0 (0.0)	12 (11.5)	0 (0.0)	17 (16.0)	29 (6.9)
Pruritus	1 (1.0)	11 (10.6)	5 (4.8)	11 (10.4)	28 (6.7)

The tolerability analyses were performed on all randomized patients who received at least one dose of study medication. Adverse events and discontinuations are reported for the treatment period and the first 14 days of follow-up. The frequencies for laboratory values (hemoglobin, bilirubin, late ALT/AST elevations) are the lowest values while on treatment or the first 14 days of follow-up.

AST, aspartate aminotransferase; ULN, upper limit of normal.

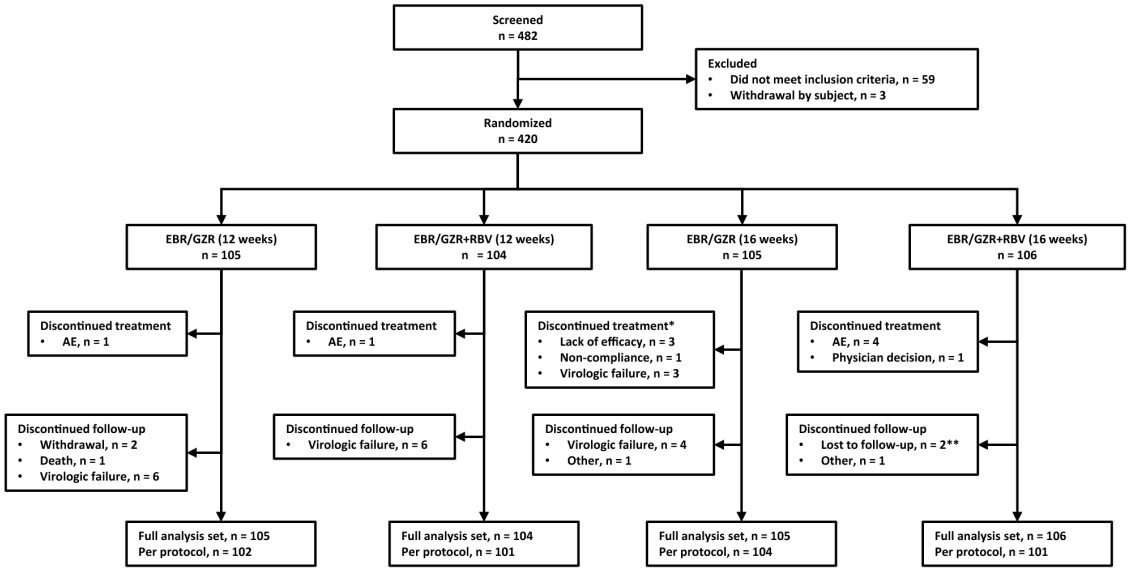
Serious adverse events: [a]Unstable angina/coronary artery disease; hip fracture; sudden hearing loss; ascites; [b]Abdominal pain/transient ischemic attack; infectious colitis; uterine polyp; [c]Overdose; lymphocytosis; loss of consciousness; [d]Tibia fracture; rib fracture; anemia; colitis/gastrointestinal inflammation.

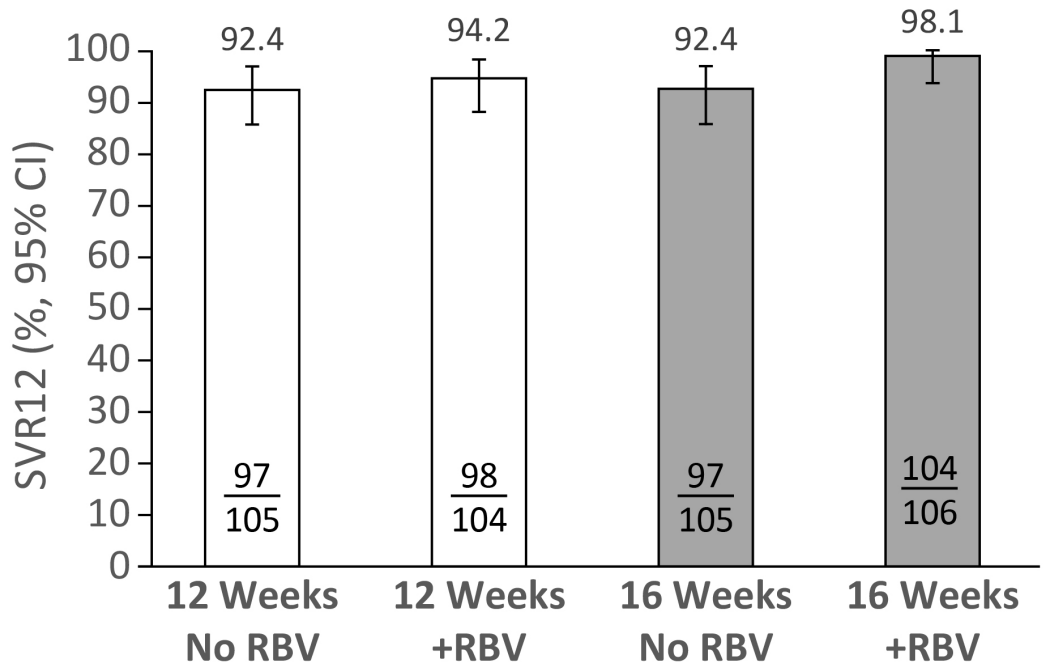
Discontinued medications due to AE: [e]Ascites; [f]Emotional lability day 35; [g]Portal vein thrombosis; palpitations; colonic angioedema; drug abuse; suicidal ideation.

Discontinued medications due to drug-related adverse event: [h]Emotional lability day 35; [i]Palpitations, suicidal ideation.

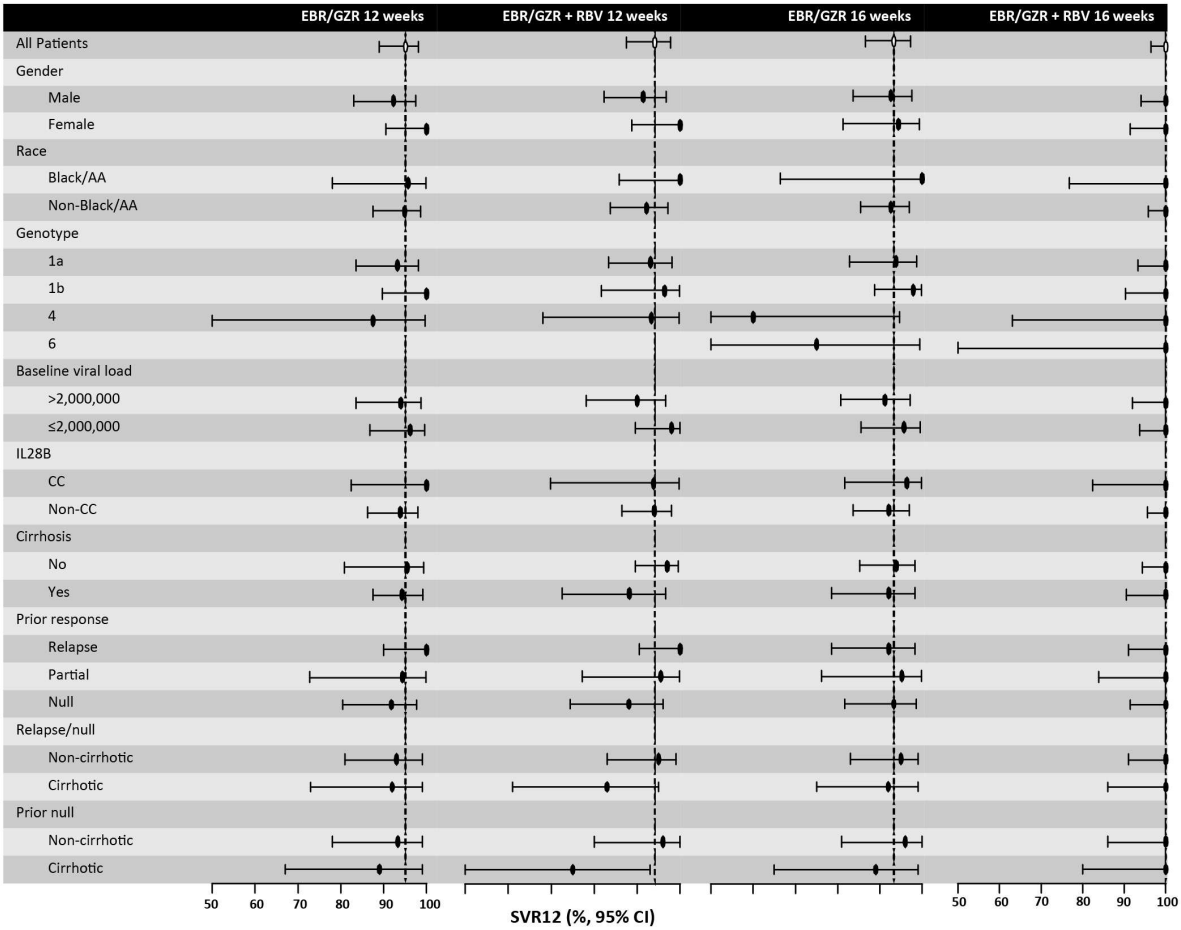
[j]Late ALT or AST > 5× ULN after treatment week 4 after normalization of ALT and AST values.

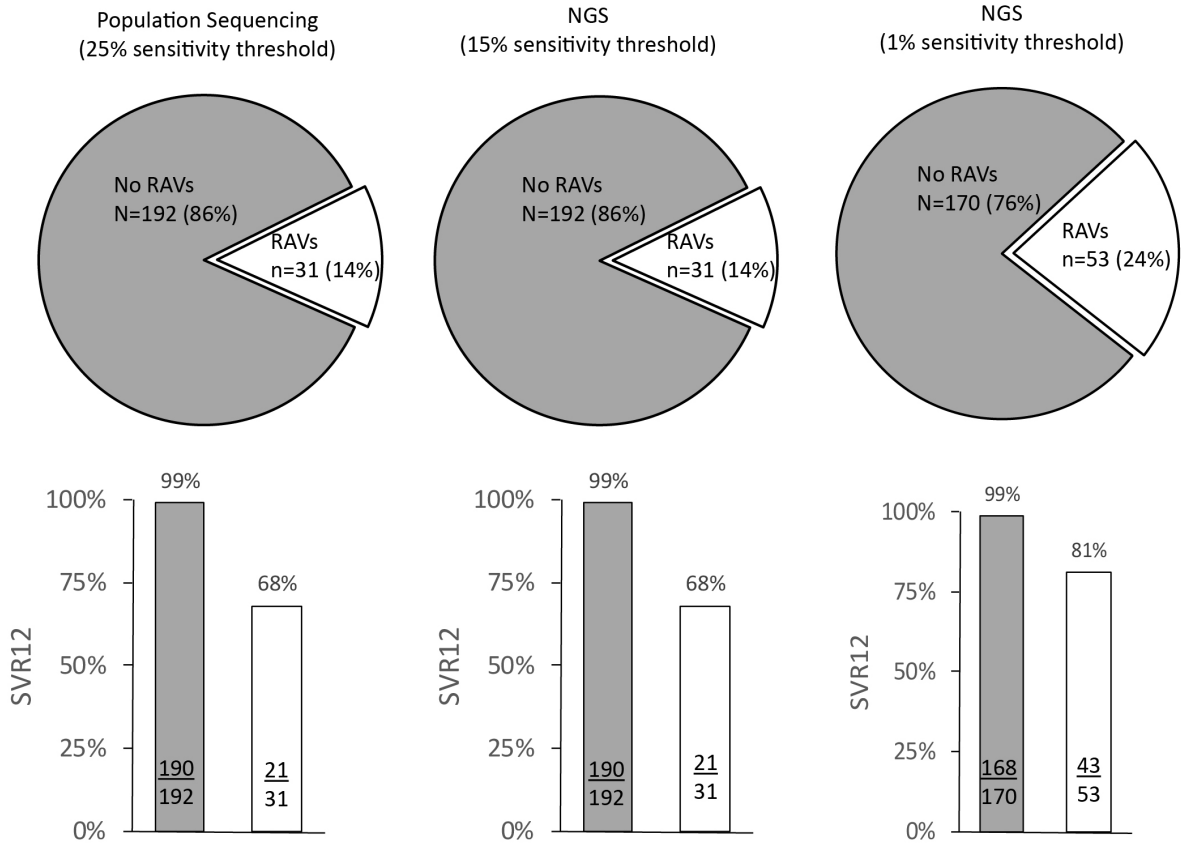
[k]Most common = overall frequency >10% in any group.





Break-through	0	0	1	0
Rebound	0	0	2	0
Relapse	6	6	4	0
LTFU/ Early DC*	2	0	1	2





Supplementary Materials

Supplementary Table 1. Patient demographics by HCV genotype

	HCV G1a (n = 227)	HCV G1b + other (n = 150)	HCV G4 (n = 37)	HCV G6 (n = 6)
Age, y, median (range)	57 (19 – 73)	56.0 (23-77)	51 (31-75)	58 (36-63)
Race				
Hispanic/Latino	22 (9.7)	13 (8.7)	4 (10.8)	0 (0.0)
Not Hispanic/Latino	204 (89.9)	137 (91.3)	32 (86.5)	6 (100.0)
Race, n (%)				
White	159 (70.0)	93 (62.0)	34 (91.9)	0 (0.0)
Black/African American	48 (21.1)	20 (13.3)	3 (8.11	0 (0.0)
Asian	14 (6.2)	36 (24.0)	0 (0.0)	6 (100)
Multiple	6 (2.6)	1 (0.7)	0 (0.0)	0 (0.0)
Cirrhosis, n (%)				
Yes	77 (33.9)	50 (33.3)	17 (46.0)	3 (50.0)
No	150 (66.1)	100 (66.7)	20 (54.0)	3 (50.0)
Baseline platelet count, mean (SD)	176.5 (63.5)	171.8 (60.0)	158.5 (74.9	165.3 (53.3)
Baseline serum albumin, mean (SD)	4.28 (0.36)	4.31 (0.33)	4.28 (0.45)	4.23 (0.35)
Baseline HCV RNA, mean (SD)	3.36×10^6 (4.11×10^6)	2.90×10^6 (3.20×10^6)	2.95×10^6 (4.59×10^6)	7.62×10^6 (9.66×10^6)
IL28B genotype, n (%)				
CC	40 (17.7)	38 (25.3)	4 (10.8)	4 (66.7)
nonCC	186 (82.3)	112 (74.7)	33 (89.2)	2 (33.3)

Supplementary Table 2. Impact of Baseline NS3 Variants on Efficacy by Ribavirin and Treatment Duration in GT1-infected Patients, as Measured by SVR12[a]

Population	SVR12 in all patients[b]	SVR12 in patients with NS3 variants not detectable	SVR12 in patients with NS3 variants detected
Overall GT1 in RAV	356/370 (96.2%)	240/247 (97.2%)	116/123 (94.3%)
Without RBV/12 Weeks	89/94 (94.7%)	57/59 (96.6%)	32/35 (91.4%)
With RBV/12 Weeks	84/89 (94.4%)	58/62 (93.5%)	26/27 (96.3%)
Without RBV/16 Weeks	91/95 (95.8%)	70/71 (98.6%)	21/24 (87.5%)
With RBV/16 Weeks	92/92 (100%)	55/55 (100%)	37/37 (100%)
Overall GT1a in RAV	211/223 (94.6%)	107/112 (95.5%)	104/111 (93.7%)
Without RBV/12 Weeks	55/60 (91.7%)	27/29 (93.1%)	28/31 (90.3%)
With RBV/12	56/60 (93.3%)	33/36 (91.7%)	23/24 (95.8%)

Weeks			
Without RBV/16 Weeks	45/48 (93.8%)	26/26 (100%)	19/22 (86.4%)
With RBV/16 Weeks	55/55 (100%)	21/21 (100%)	34/34 (100%)
Overall GT1b in RAV	144/146 (98.6%)	133/135 (98.5%)	11/11 (100%)
Without RBV/12 Weeks	34/34 (100%)	30/30 (100%)	4/4 (100%)
With RBV/12 Weeks	28/29 (96.6%)	25/26 (96.2%)	3/3 (100%)
Without RBV/16 Weeks	46/47 (97.9%)	44/45 (97.8%)	2/2 (100%)
With RBV/16 Weeks	36/36 (100%)	34/34 (100%)	2/2 (100%)
Overall GT1 other in RAV	1/1 (100%)	ND	1/1 (100%)
Without RBV/12 Weeks	ND	ND	ND

With RBV/12 Weeks	ND	ND	ND
Without RBV/16 Weeks	ND	ND	ND
With RBV/16 Weeks	1/1 (100%)	ND	1/1 (100%)

RAVs assessed by population sequencing; limit of detection approximately 25%. The complete NS3 genes were amplified from samples with RNA levels of 1000 IU/mL or greater by using reverse transcription polymerase chain reaction. Resultant amino acid sequences were compared with wild-type GT1a (H77; accession number NC004102) or GT1b (Con1; AJ238799) reference sequences. To assess the effect of baseline NS3 variants, specific amino acid loci prone to selection by early generation NS3/4A protease inhibitors (positions 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, and 175) were studied in replicon cell lines encoding mutations in a GT1a backbone.

ND, not determined.

[a]SVR12 = number of patients with HCV RNA <15 IU/mL at 12 weeks after end of treatment/total number of patients in each category.

[b]Resistance analysis population excluded patients who discontinued for administrative reasons or did not have sequence data.

Supplementary Table 3. RAVs in Patients With HCV GT1a and GT1b Infection and Virologic Failure

					NS3 RAVs			NS5A RAVs		
SUBJID	Genotype	Cirrhosis status	Response to prior therapy	VF category*	At baseline	At failure	At FW24	At baseline	At failure	At FW24
680801	1a	Cirrhosis	Null response	Relapse	Q80K	(Q80K), A156T, D168A	(Q80K)	L31M	Q30R, (L31M)	Q30R, (L31M)
680811	1a	Cirrhosis	Null response	Relapse	Q80K	Y56H, (Q80K), R155I/R, D168V	Y56H, (Q80K)	Y93Y/N	(Y93N)	(Y93N)
682036	1a	Non-cirrhotic	Null response	Relapse	WT	V107I	V107I	WT	Q30H, Y93H	Q30H, Y93H
680817	1a	Cirrhosis	Null	Relapse	WT	WT	WT	L31L/M	Q30R,	Q30R,

			response						(L31M)	(L31M)
682060	1a	Non-cirrhotic	Null response	Relapse	WT	A156T/A	WT	L31L/M	Q30R, (L31M)	Q30R, (L31M)
680819	1a	Cirrhosis	Null response	Relapse	I170I/V	R155K/R	WT	L31M	Q30R, (L31M)	Q30R, (L31M)
682090	1a	Non-cirrhotic	Null response	Relapse	Q80K	(Q80K), D168Y	(Q80K)	WT	Q30R, Y93H	Q30R, Y93Y/H
681264	1a	Non-cirrhotic	Partial response	Relapse	Q80K	(Q80K), D168A	(Q80K)	L31L/I/M	Q30R, (L31M)	Q30R, (L31M)
681637	1a	Non-cirrhotic	Partial response	Relapse	WT	WT	WT	Y93N	M28T, Y93S	M28T, Y93S
680432	1a	Cirrhotic	Partial response	Relapse	WT	A156T, V158A	n/a	Q30H	(Q30H)	n/a

681624	1a	Non-cirrhotic	Partial response	Relapse	Q80K	V36L, (Q80K), D168A	V36L, (Q80K)	Q30H	M28T, (Q30H)	M28T, ((Q30H)
681655	1a	Non-cirrhotic	Partial response	Relapse	I170V	A156T, (I170V)	(I170V)	M28T	(M28T), Q30R	(M28T), Q30R
681205	1b	Non-cirrhotic	Relapse	Relapse	WT	WT	WT	Y93H	L28M, (Y93H)	L28M, (Y93H)
680835	1b	Cirrhosis	Null response	Relapse	WT	WT	WT	L31I/M	(L31M), Y93H	(L31M), Y93H

FW, follow-up week; N/A, no sequence available; VF, virologic failure; WT, wild-type.

*Virologic failure category refers to outcome of treatment in present study.

[a]Five patients with HCV GT4 or GT6 infection had VF. These patients are not listed.

[b]Baseline RAVs that persist through VF are indicated in parentheses.

Supplementary Table 4. SVR in Patients With HCV GT4 or GT6 infection, With Or Without NS5A RAVs at Amino Acid Positions 28, 30, 31, and 93 by Population Sequencing (25% Sensitivity Threshold) and Next-generation Sequencing (15% and 1% Sensitivity Thresholds)[a]

	SVR		
HCV genotype/regimen	Patients without baseline NS5A RAVs [n/N (%)]	Patients with baseline NS5A RAVs [m/M (%)]	All patients [t/T (%)]
POPULATION SEQUENCING 25% SENSITIVITY THRESHOLD			
GT4	27/29 (93.1%)	5/7 (71.4%)	32/36 (88.9%)
12 weeks (− RBV)	6/7 (85.7%)	1/1 (100.0%)	7/8 (87.5%)
12 weeks (+ RBV)	11/12 (91.7%)	3/3 (100.0%)	14/15 (93.3%)
16 weeks (− RBV)	3/3 (100.0%)	0/2 (0.0%)	3/5 (60.0%)
16 weeks (+ RBV)	7/7 (100%)	1/1 (100.0%)	8/8 (100.0%)
GT6	2/2 (100.0%)	2/2 (100.0%)	4/4 (100.0%)
12 weeks (− RBV)	ND	ND	ND
12 weeks (+ RBV)	ND	ND	ND
16 weeks (− RBV)	1/1 (100.0%)	1/1 (100.0%)	2/2 (100.0%)
16 weeks (+ RBV)	1/1 (100.0%)	1/1 (100.0%)	2/2 (100.0%)
NGS 15% SENSITIVITY THRESHOLD			
GT4	27/29 (93.1%)	5/7 (71.4%)	32/36 (88.9%)
12 weeks (− RBV)	6/7 (85.7%)	1/1 (100.0%)	7/8 (87.5%)

12 weeks (+ RBV)	11/12 (91.7%)	3/3 (100.0%)	14/15 (93.3%)
16 weeks (− RBV)	3/3 (100.0%)	0/2 (0.0%)	3/5 (60.0%)
16 weeks (+ RBV)	7/7 (100.0%)	1/1 (100.0%)	8/8 (100.0%)
GT6			
12 weeks (− RBV)			
12 weeks (+ RBV)			
16 weeks (− RBV)			
16 weeks (+ RBV)			
NGS 1% SENSITIVITY THRESHOLD			
GT4	25/27 (92.6%)	7/9 (77.8%)	32/36 (88.9%)
12 weeks (− RBV)	4/5 (80.0%)	3/3 (100.0%)	7/8 (87.5%)
12 weeks (+ RBV)	11/12 (91.7%)	3/3 (100.0%)	14/15 (93.3%)
16 weeks (− RBV)	3/3 (100.0%)	0/2 (00%)	3/5 (60.0%)
16 weeks (+ RBV)	7/7 (100.0%)	1/1 (100.0%)	8/8 (100.0%)
GT6			
12 weeks (− RBV)			
12 weeks (+ RBV)			
16 weeks (− RBV)			
16 weeks (+ RBV)			

m, number of patients with baseline NS5A RAVs who achieved SVR12; M, number of patients with baseline NS5A RAVs; n, number of patients without baseline NS5A RAVs who achieved

SVR12; N, number of patients without baseline NS5A RAVs; t, total number of patients in treatment arm who achieved SVR12; T, total number of patients in treatment arm.

[a]Assessed in the resistance analysis population, which includes all patients who have baseline sequencing available and a treatment outcome of either SVR12 or virologic failure.

Supplementary Table 5. Patient characteristics of patients with NS5A RAVs at baseline receiving EBR/GZR+RBV for 16 weeks

Patient number	RAV	Age	Gender	Prior Response	Cirrhosis Status
1	031M	57	M	Relapser	Cirrhotic
2	028V	59	M	Relapser	Cirrhotic
3	031M	72	M	Relapser	Non-Cirrhotic
4	028M/V	67	M	Relapser	Non-Cirrhotic
5	093C	56	F	Relapser	Non-Cirrhotic
6	030H, 093H	62	M	Null Responder	Non-Cirrhotic