

# Elbasvir/Grazoprevir and Sofosbuvir for Hepatitis C Virus Genotype 3 Infection With Compensated Cirrhosis: A Randomized Trial

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Many direct-acting antiviral regimens have reduced activity in people with hepatitis C virus (HCV) genotype (GT) 3 infection and cirrhosis. The C-ISLE study assessed the efficacy and safety of elbasvir/grazoprevir (EBR/GZR) plus sofosbuvir (SOF) with and without ribavirin (RBV) in compensated cirrhotic participants with GT3 infection. This was a phase 2, randomized, open-label study. Treatment-naïve participants received EBR/GZR + SOF + RBV for 8 weeks or EBR/GZR + SOF for 12 weeks, and peginterferon/RBV treatment-experienced participants received EBR/GZR + SOF ± RBV for 12 weeks or EBR/GZR + SOF for 16 weeks. The primary endpoint was HCV RNA <15 IU/mL 12 weeks after the end of treatment (sustained virologic response at 12 weeks [SVR12]). Among treatment-naïve participants, SVR12 was 91% (21/23) in those treated with RBV for 8 weeks and 96% (23/24) in those treated for 12 weeks. Among treatment-experienced participants, SVR12 was 94% (17/18) and 100% (17/17) in the 12-week arm, with and without RBV, respectively, and 94% (17/18) in the 16-week arm. Five participants failed to achieve SVR: 2 relapsed (both in the 8-week arm), 1 discontinued due to vomiting/cellulitis (16-week arm), and 2 discontinued (consent withdrawn/lost to follow-up). SVR12 was not affected by the presence of resistance-associated substitutions (RASs). There was no consistent change in insulin resistance, and 5 participants reported serious adverse events (pneumonia, chest pain, opiate overdose, cellulitis, decreased creatinine). High efficacy was demonstrated in participants with HCV GT3 infection and cirrhosis. Treatment beyond 12 weeks was not required, and efficacy was maintained regardless of baseline RASs. **Conclusion:** Data from this study support the use of EBR/GZR plus SOF for 12 weeks without RBV for treatment-naïve and peginterferon/RBV-experienced people with GT3 infection and cirrhosis (ClinicalTrials.gov NCT02601573). (HEPATOLOGY 2018;67:2113-2126)

**H**epatitis C virus (HCV) genotype (GT) 3 has a characteristic profile of pathology, epidemiology, and response to therapy that clearly differentiates it from other HCV subtypes. From a pathologic perspective, it has been shown to possess a direct steatogenic effect that may be associated with accelerated progression of liver fibrosis and reversible

with viral eradication.<sup>(1,2)</sup> From an epidemiologic standpoint, HCV GT3 is the predominant genotype across many countries in Asia, representing 54% of the infections in India and 79% of the infections in Pakistan; each country has 6-7 million adults with HCV infection.<sup>(3)</sup> Countries that have sizable immigrant populations from these Asian countries also have a

*Abbreviations:* AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAA, direct-acting antiviral; EBR, elbasvir; FAS, full analysis set; GT, genotype; GZR, grazoprevir; HCV, hepatitis C virus; HOMA-IR, homeostatic model assessment of insulin resistance; mFAS, modified full analysis set; NS, nonstructural protein; PR, peginterferon/ribavirin; RAS, resistance-associated substitution; RBV, ribavirin; SAE, serious adverse event; SOF, sofosbuvir; SVR, sustained virologic response; SVR12, SVR at 12 weeks; ULN, upper limit of normal.

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high prevalence of GT3 infection, such as the United Kingdom where 44% of HCV infections are attributable to GT3.<sup>(3)</sup>

HCV GT3 is also unique in terms of its response to direct-acting antiviral (DAA) treatment regimens. As the use of DAA regimens has become more commonplace for individuals with HCV infections, it has also become apparent that many currently approved regimens have reduced activity in people with GT3 infection.<sup>(4-6)</sup> The combination of elbasvir (EBR), a once-daily nonstructural protein 5A (NS5A) inhibitor, and grazoprevir (GZR), a once-daily HCV NS3/4A protease inhibitor, has broad *in vitro* genotypic activity and has shown clinical efficacy across a wide cross section of people with HCV GT1 or 4 infection.<sup>(7-10)</sup> Based on the principle that combining DAAs with different mechanisms may allow for shorter treatment durations and provide a higher barrier to resistance, studies have also assessed the combination of EBR/GZR plus the NS5B polymerase inhibitor sofosbuvir (SOF). In the C-SWIFT study, rates of sustained virologic response (SVR) at 12 weeks (SVR12) of 93% (14/15) and 100% (14/14) were attained in participants without cirrhosis but with HCV GT3 infection receiving EBR/GZR

plus SOF for 8 and 12 weeks, respectively, and of 83% (10/12; 1 lost to follow-up and 1 virologic failure) in participants with cirrhosis and GT3 infection treated for 12 weeks.<sup>(11)</sup> The combination of EBR/GZR plus SOF is approved in Canada, New Zealand, Georgia, Mexico, and Egypt for the treatment of GT3 infection. Supported by preliminary data showing high efficacy of EBR/GZR plus SOF in people with HCV GT3 infection, the C-ISLE trial was developed as a regional study of EBR/GZR plus SOF with or without ribavirin (RBV) in participants with compensated cirrhosis and HCV GT3 infection for treatment durations of 8-16 weeks.

## Patients and Methods

### STUDY DESIGN AND PARTICIPANTS

C-ISLE was a phase 2, randomized, parallel-group, open-label clinical study. Treatment-naïve or treatment-experienced, monoinfected or human immunodeficiency virus-coinfected adult participants with chronic HCV GT3 infection, plasma HCV RNA

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$\geq 10,000$  IU/mL, and compensated liver cirrhosis were enrolled (see [Supporting Information](#) for further details). Participants who had previously received DAA therapy, had decompensated liver disease (presence of or history of ascites, esophageal or gastric variceal bleeding, hepatic encephalopathy, or other signs or symptoms of advanced liver disease), were Child-Pugh B or C or had a Child-Turcotte-Pugh score  $>6$ , or had hepatitis B virus coinfection were excluded. Laboratory exclusion criteria included hemoglobin  $<11$  g/dL (women) or  $<12$  g/dL (men), platelets  $<40 \times 10^3/\mu\text{L}$ , albumin  $<3.0$  g/dL, and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels  $>10\times$  the upper limit of normal (ULN).

## RANDOMIZATION AND MASKING

All participants received a fixed-dose combination of EBR 50 mg/GZR 100 mg once daily, plus SOF 400 mg once daily. Participants in arms 1 and 4 also received RBV 800-1,400 mg/day, administered twice daily according to participant body weight at baseline. Treatment-naïve participants were randomized 1:1 to receive EBR/GZR plus SOF plus RBV for 8 weeks or EBR/GZR plus SOF for 12 weeks. Treatment-experienced participants were randomized 1:1:1 to receive EBR/GZR plus SOF with or without RBV for 12 weeks or EBR/GZR plus SOF for 16 weeks. Randomization was performed centrally using an interactive voice response system/integrated web response system. Treatment-experienced participants were stratified based on prior relapse versus nonrelapse (partial response, null response, interferon-intolerant); the number of interferon-intolerant participants was limited to 5 per arm.

## PROCEDURES

HCV genotyping at baseline was performed using the Abbott HCV Real Time Genotype II assay. Blood samples for assessment of HCV RNA were collected at baseline; day 3; treatment weeks 1, 2, 4, 6, 8, 12, and 16 (where applicable according to randomized treatment duration); and 4, 8, 12, and 24 weeks after end of treatment. HCV RNA in plasma was measured using a COBAS AmpliPrep/COBAS TaqMan HCV Test, v2.0, assay with a lower limit of quantitation of 15 IU/mL.

Next-generation sequencing was performed using blood samples collected at baseline from all participants and at the time of virologic failure for

participants with HCV RNA  $>1,000$  IU/mL who met criteria for virologic failure. The limit of minority variant detection in the population was  $>1\%$  of the viral population. Any polymorphisms at the following amino acid positions that have been associated with resistance to DAAs were assessed for prevalence and impact on SVR: NS3 (amino acid positions 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, or 175; among these, only substitutions at positions 56, 156, and 168 tend to confer resistance to GZR), NS5A (amino acids 24, 28, 30, 31, 32, 38, 58, 62, 92, or 93), and NS5B (amino acid positions 96, 142, 159, 282, 289, 316, 320, or 321; among these, only substitutions at positions 28, 30, 31, 62, and 93 tend to confer resistance to EBR).

## OUTCOMES

The primary endpoint was SVR12. SVR12 and associated 95% confidence intervals (CIs) were estimated to assess the consistency of response across various subgroups. Assessment of the impact of resistance-associated substitutions (RASs) on SVR12 was performed in the resistance analysis population, which included all participants who had baseline sequencing available and a treatment outcome of either SVR12 or virologic failure. Safety and tolerability were assessed by clinical review of all relevant parameters, including adverse events (AEs) and laboratory parameters. Selected nonserious and serious AEs (SAEs) were designated as events of clinical interest and included overdose, ALT or AST  $>500$  IU/L, ALT or AST  $>3\times$  baseline and  $>100$  IU/L, alkaline phosphatase  $>3\times$  ULN, estimated glomerular filtration rate  $<50$  mL/minute/1.73 m<sup>2</sup>, and serum creatinine grade 2 or higher ( $>1.3\times$  ULN) and elevated from baseline.

Insulin resistance was calculated using the homeostatic model assessment of insulin resistance (HOMA-IR) at baseline, treatment week 8, and follow-up week 12, applying the following formula:  $\text{HOMA-IR} = [\text{insulin } (\mu\text{IU/mL}) \times \text{glucose } (\text{mg/dL})]/405$ . Based on a previous study,<sup>(12)</sup> a HOMA-IR value of  $\geq 3$  was selected to indicate participants with high insulin resistance.

## STATISTICAL ANALYSIS

There was no formal efficacy hypothesis testing conducted in this study. The target enrollment was 25 participants per treatment arm. Efficacy analyses are presented based on the full analysis set (FAS) population, which includes all participants who received at

least one dose of study treatment. The modified FAS (mFAS) population, which excludes participants who discontinued the study for reasons unrelated to treatment, was prespecified in the protocol as the primary population for efficacy analysis. Two-sided 95% CIs were constructed for the proportion of participants achieving SVR12 for each arm separately using the Clopper-Pearson method. Resistance analyses were conducted in the resistance analysis population, which included all participants with baseline sequencing and an outcome of SVR12 or virologic failure. The all-participants-as-treated population was used for the analysis of safety data. This population consisted of all participants who received at least one dose of study drug. The proportions of participants with AEs of elevated laboratory values that are reported as events of clinical interest or with ALT/AST  $>5\times$  ULN at week 4 or later while on treatment are provided with the corresponding 95% CIs. The percentage of participants with any AE, a drug-related AE, an SAE, or an AE which was both drug-related and serious and who discontinued due to an AE are summarized in the same manner.

## ETHICS

The study was conducted at 14 centers in the United Kingdom 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 participants gave written informed consent. This is a registered clinical trial (<https://clinicaltrials.gov/ct2/show/NCT02601573>), and the study protocol (PN083-02) is available in the [Supporting Information](#). All authors had access to the study data and reviewed and approved the final manuscript.

## Results

In total, 120 participants were screened and 100 were enrolled and randomized to treatment (Fig. 1). Of the 20 participants who did not receive study drug, 19 were not randomized and 1 was randomized in error but did not receive study drug. Of the 19 participants not randomized, 15 were screening failures, 2 withdrew prior to randomization, 1 was lost to follow-up, and 1 had an unknown status. The most common reason for screening failure was failure to meet the criteria for compensated cirrhosis. The first participant started treatment on January 26, 2016, and the final

participant completed 12 weeks of follow-up on October 18, 2016. Three participants discontinued treatment prior to medication completion, 2 of whom were considered discontinuations not related to treatment (1 treatment-naïve participant randomized to 12 weeks of treatment was lost to follow-up after week 2 and 1 treatment-experienced participant randomized to EBR/GZR plus SOF plus RBV for 12 weeks withdrew consent after day 7). A third treatment-experienced participant randomized to EBR/GZR plus SOF for 16 weeks had a drug-related AE of vomiting at day 4 leading to study medication interruption, followed by discontinuation on day 7 when a diagnosis of cellulitis was established.

Participant characteristics were generally well balanced across the treatment arms. The majority of the participants were white (69%) and male (68%) (Table 1). The median age was 53 years; 50% had a non-CC interleukin-28B genotype and 49% had a baseline viral load  $>2,000,000$  IU/mL. Cirrhosis was determined by FibroScan in 84% of participants, with a median FibroScan score of 21.4 (range, 12.6-69.1). The median baseline platelet count was  $138 \times 10^3$  cells/ $\mu$ L (range, 46-396), 24% had a platelet count  $<100 \times 10^3$  cells/ $\mu$ L, and the median albumin level at baseline was 4.1 g/dL (range, 1.0-5.0). The median blood glucose level was 97 mg/dL (range, 53-409), and the median baseline HOMA-IR was 5.57 (range, 0.48-209.21). Twenty-three participants in this study had a medical history of diabetes mellitus.

## SVR

Among treatment-naïve participants in the FAS, SVR12 rates were 91% (21/23) in those receiving EBR/GZR plus SOF plus RBV for 8 weeks and 96% (23/24) in those receiving EBR/GZR plus SOF for 12 weeks (Fig. 2A). Two participants receiving 8 weeks of therapy relapsed, and 1 treatment-naïve participant receiving 12 weeks of therapy was lost to follow-up after treatment week 2.

Among peginterferon/RBV (PR) treatment-experienced participants in the FAS, SVR12 rates were 94% (17/18) and 100% (17/17) in participants receiving 12 weeks of EBR/GZR plus SOF with and without RBV, respectively. One participant receiving EBR/GZR plus SOF plus RBV for 12 weeks withdrew consent after day 7. In the 16-week treatment arm (no RBV), SVR12 was achieved by 94% (17/18) of participants, with 1 participant discontinuing treatment after day 7 due to the AE of vomiting and the

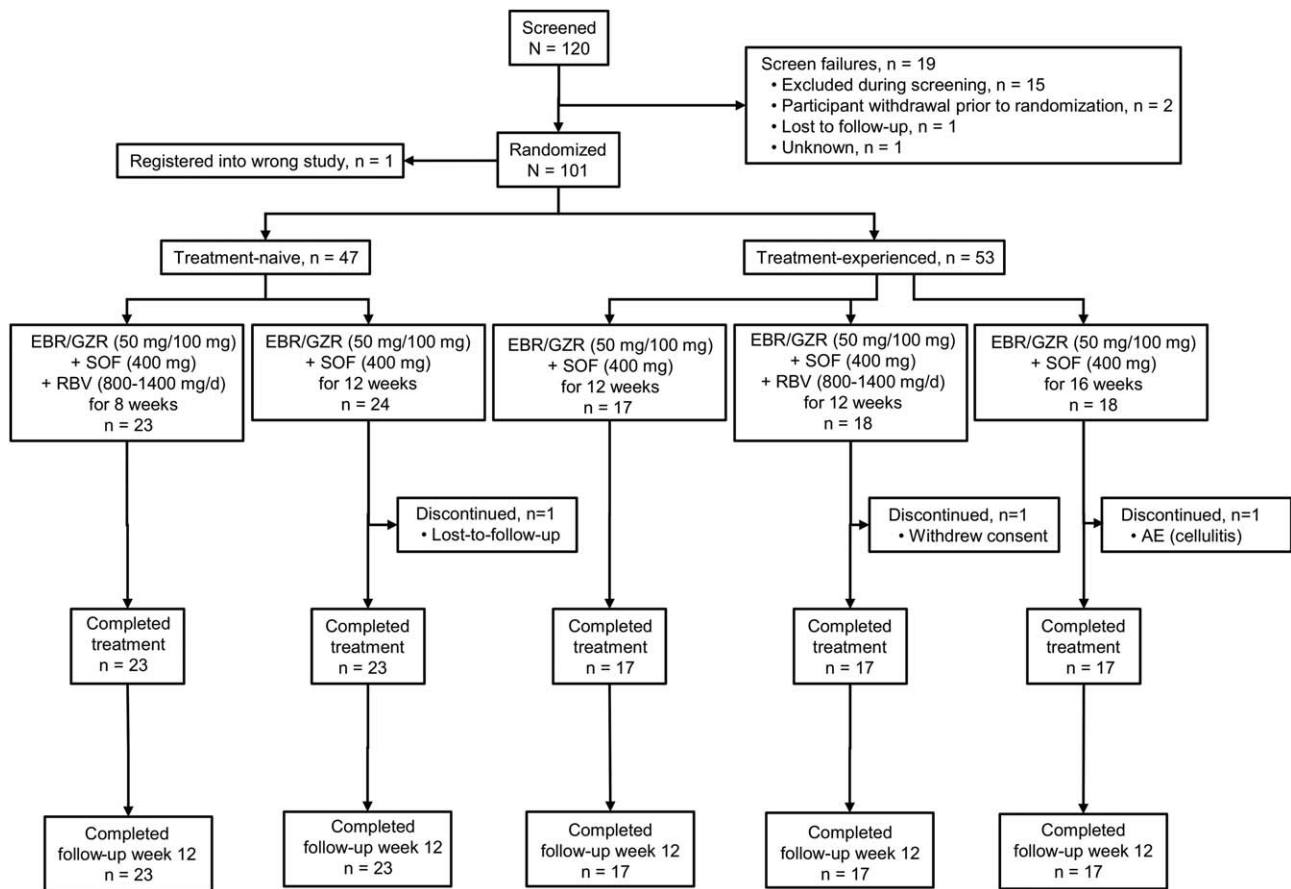


FIG. 1. Participant disposition.

diagnosis of cellulitis, which were characterized by the investigator as related to study drug. Thus, no PR treatment-experienced participants experienced virologic failure. In the mFAS population, all treatment-naive and treatment-experienced participants receiving EBR/GZR plus SOF with or without RBV for 12 weeks achieved SVR12 (Fig. 2B). SVR12 was generally high, regardless of participant characteristics, such as baseline viral load, race, age, treatment duration, and prior treatment response (Fig. 3).

## RASs

A total of 97 participants were included in the resistance analysis population (Fig. 4). Within this population, 90 participants had available sequencing of the NS3 region at baseline, almost all of whom had NS3 RASs at baseline (87/90 [97%]), driven primarily by a V170I polymorphism detected in 86 of 90 (96%) participants. Only 3 participants had no NS3 RASs at

baseline. SVR rates were 97% (85/87) and 100% (3/3) in participants with and without NS3 RASs, respectively, within the resistance analysis population.

All 97 participants in the resistance analysis population had sequences available for NS5A RAS analysis. In total, 50 (52%) participants had detectable NS5A RASs at baseline, and the remaining 47 (48%) participants had no baseline NS5A RASs. Rates of SVR12 were 98% in participants with and without baseline NS5A RASs (49/50 and 46/47, respectively). Five participants had NS5B RASs present at baseline (142S, n = 3; 142T, n = 1; 289Y, n = 1), all of whom achieved SVR12.

Two participants relapsed in this study, both of whom were treatment-naive and receiving 8 weeks of therapy. One relapse participant had wild-type virus at both baseline and time of relapse. This participant had a baseline viral load of 3,779,754 IU/mL, which dropped below the lower limit of quantitation at treatment week 4 and was undetectable at treatment

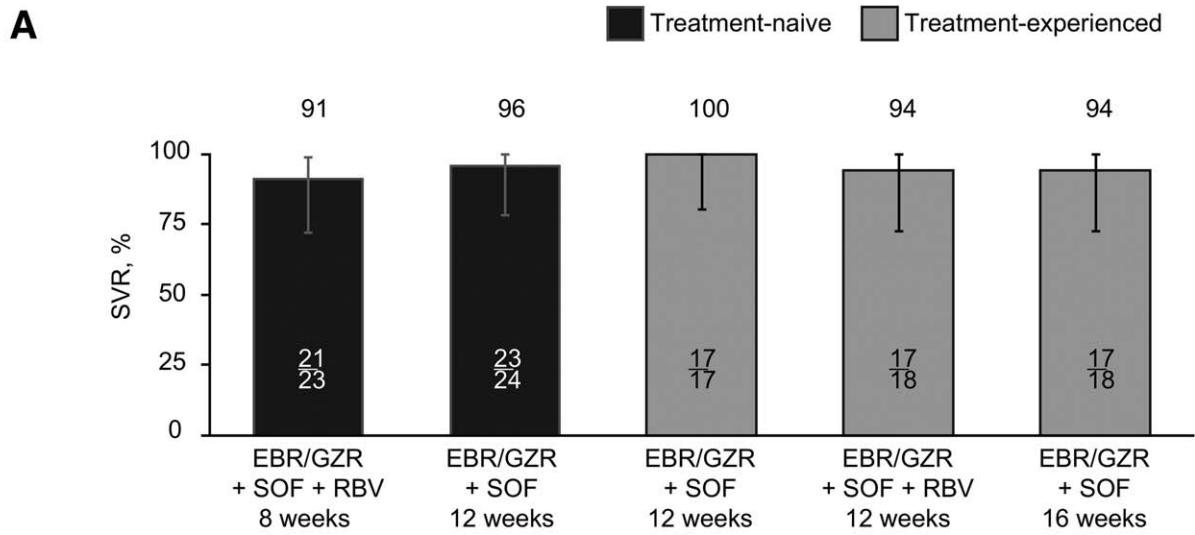
TABLE 1. Participant Demographics

	Treatment-naive		Treatment-experienced			Total (N = 100)
	EBR/GZR + SOF + RBV for 8 weeks (n = 23)	EBR/GZR + SOF for 12 weeks (n = 24)	EBR/GZR + SOF for 12 weeks (n = 17)	EBR/GZR + SOF + RBV for 12 weeks (n = 18)	EBR/GZR + SOF for 16 weeks (n = 18)	
Sex, n (%)						
Male	13 (56.5)	17 (70.8)	11 (64.7)	12 (66.7)	15 (83.3)	68 (68.0)
Female	10 (43.5)	7 (29.2)	6 (35.3)	6 (33.3)	3 (16.7)	32 (32.0)
Race, n (%)						
White	16 (69.6)	19 (79.2)	13 (76.5)	9 (50.0)	12 (66.7)	69 (69.0)
Asian	6 (26.1)	4 (16.7)	4 (23.5)	9 (50.0)	6 (33.3)	29 (29.0)
Other	1 (4.3)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)
Age, years, median (range)	51 (37-68)	48 (32-64)	58.0 (48-68)	56.0 (38-70)	53.0 (43-66)	53 (32-70)
BMI, n (%)						
<30 kg/m <sup>2</sup>	17 (73.9)	18 (75.0)	13 (76.5)	13 (72.2)	11 (61.1)	72 (72.0)
≥30 kg/m <sup>2</sup>	6 (26.1)	6 (25.0)	4 (23.5)	5 (27.8)	7 (38.9)	28 (28.0)
Prior treatment history, n (%)						
Treatment-naive	23 (100.0)	24 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	47 (47.0)
IFN-intolerant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (1.0)
PR null responder	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (1.0)
PR relapser	0 (0.0)	0 (0.0)	17 (100.0)	17 (94.4)	17 (94.4)	51 (51.0)
Baseline viral load, n (%)						
≤2,000,000 IU/mL	12 (52.2)	10 (41.7)	10 (58.8)	8 (44.4)	11 (61.1)	51 (51.0)
>2,000,000 IU/mL	11 (47.8)	14 (58.3)	7 (41.2)	10 (55.6)	7 (38.9)	49 (49.0)
IL28B genotype, n (%)						
CC	14 (60.9)	16 (66.7)	6 (35.3)	7 (38.9)	7 (38.9)	50 (50.0)
Non-CC	9 (39.1)	8 (33.3)	11 (64.7)	11 (61.1)	11 (61.1)	50 (50.0)
Cirrhosis diagnosis, n (%)						
Biopsy	4 (17.4)	3 (12.5)	3 (17.6)	3 (16.7)	3 (16.7)	16 (16.0)
FibroScan	19 (82.6)	21 (87.5)	14 (82.4)	15 (83.3)	15 (83.3)	84 (84.0)
FibroScan result, kPa, median (range)	21.5 (13.3-49.1)	21.8 (13.1-44.3)	21.1 (13.8-69.1)	20.9 (13.8-53.2)	21.1 (12.6-53.3)	21.4 (12.6-69.1)
ALT, IU/L, median (range)	89 (30-389)	97 (33-320)	82 (21-294)	93 (29-174)	106 (28-265)	94 (21-389)
AST, IU/L, median (range)	81 (35-286)	93 (55-272)	96 (24-148)	77 (23-173)	77 (44-203)	85 (23-286)
Bilirubin, mg/dL, median (range)	0.6 (0.2-3.8)	0.6 (0.3-1.5)	0.7 (0.3-1.6)	0.5 (0.2-1.1)	0.6 (0.2-1.5)	0.6 (0.2-3.8)
Albumin, g/dL, median (range)	4.3 (3.6-5.1)	4.4 (3.6-4.9)	4.1 (3.4-4.9)	4.2 (3.6-4.7)	4.2 (3.3-4.8)	4.2 (3.3-5.1)
Hemoglobin, g/dL, median (range)	14.5 (11.3-16.1)	15.0 (12.8-17.3)	14.4 (11.5-16.6)	14.3 (11.5-18.5)	14.7 (12.7-16.9)	14.6 (11.3-18.5)
Platelets, ×10 <sup>3</sup> cells/μL, median (range)	134 (76-205)	144 (60-227)	119 (78-396)	173 (62-313)	133 (46-298)	138 (46-396)
Glucose, mg/dL, median (range)	94 (70-269)	96 (53-409)	106 (80-295)	98 (61-347)	106 (85-354)	97 (53-409)
HOMA-IR, median (range)	4.4 (0.48-48.9)	5.3 (1.4-89.7)	5.6 (2.1-30.4)	8.8 (3.0-84.4)	10.9 (1.5-209.2)	5.6 (0.5-209.2)
Insulin, μIU/mL, median (range)	17.7 (2.8-196.1)	21.3 (7.1-192.3)	15.7 (8.2-101.9)	36.3 (11.5-195.4)	26.9 (7.3-495.5)	21.0 (2.8-495.5)

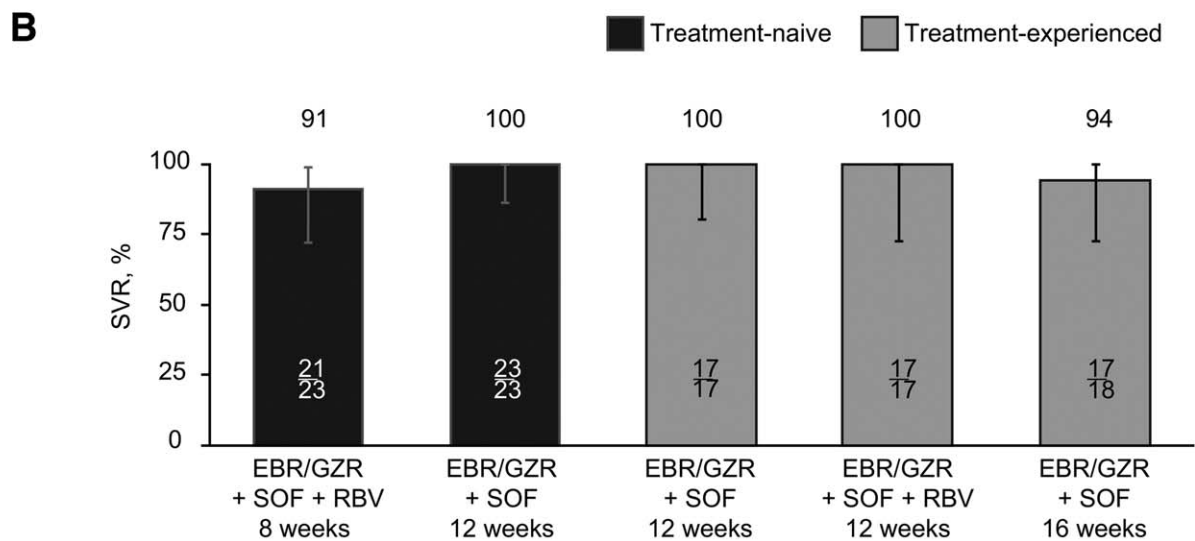
Abbreviations: BMI, body mass index; IFN, interferon; IL, interleukin.

week 6. During follow-up, HCV RNA was 8,933 IU/mL at follow-up week 8, confirmed as 23,013 IU/mL 10 days later. The second relapse participant had Y93H, P58S, and S62T present at baseline in 44%, 99%, and 62% of the viral population, respectively, suggesting that these three RASs were mostly linked within the same virus genome. All variants were also detected at the time of virologic failure. This participant had a baseline viral load of 5,141,616 IU/mL, HCV RNA below the lower limit of quantitation at treatment week 6, and undetectable HCV RNA at treatment week 8. HCV RNA levels were 147,166 IU/mL and 4,864,183 IU/mL at follow-up weeks 4 and 24, respectively.

The resistance analysis population included a total of 9 participants with the Y93H substitution at baseline, of whom 4 had Y93H detected as 11%-87% of the total viral population and 5 had Y93H comprising 1%-7% of the total viral population. Of the 4 participants with Y93H present in ≥11% of the total viral population, only 1 who received 8 weeks of therapy relapsed. The other 3 participants with the baseline Y93H variant ≥11% were treated for ≥12 weeks, and all those with Y93H present at 1%-7%, achieved SVR12, regardless of prior treatment history or prevalence of Y93H. Full details for the 9 participants with Y93H detected at baseline are provided in [Supporting Table S1](#).



Relapse	2	0	0	0	0
Discontinued due to AE	0	0	0	0	1
Nonvirologic failure	0	1	0	1	0



Relapse	2	0	0	0	0
Discontinued due to AE	0	0	0	0	1
Excluded from mFAS analysis*	0	1	0	1	0

**FIG. 2.** SVR12 in the FAS (A) and the mFAS (B). \*mFAS excluded patients who discontinued treatment for reasons unrelated to study medication.

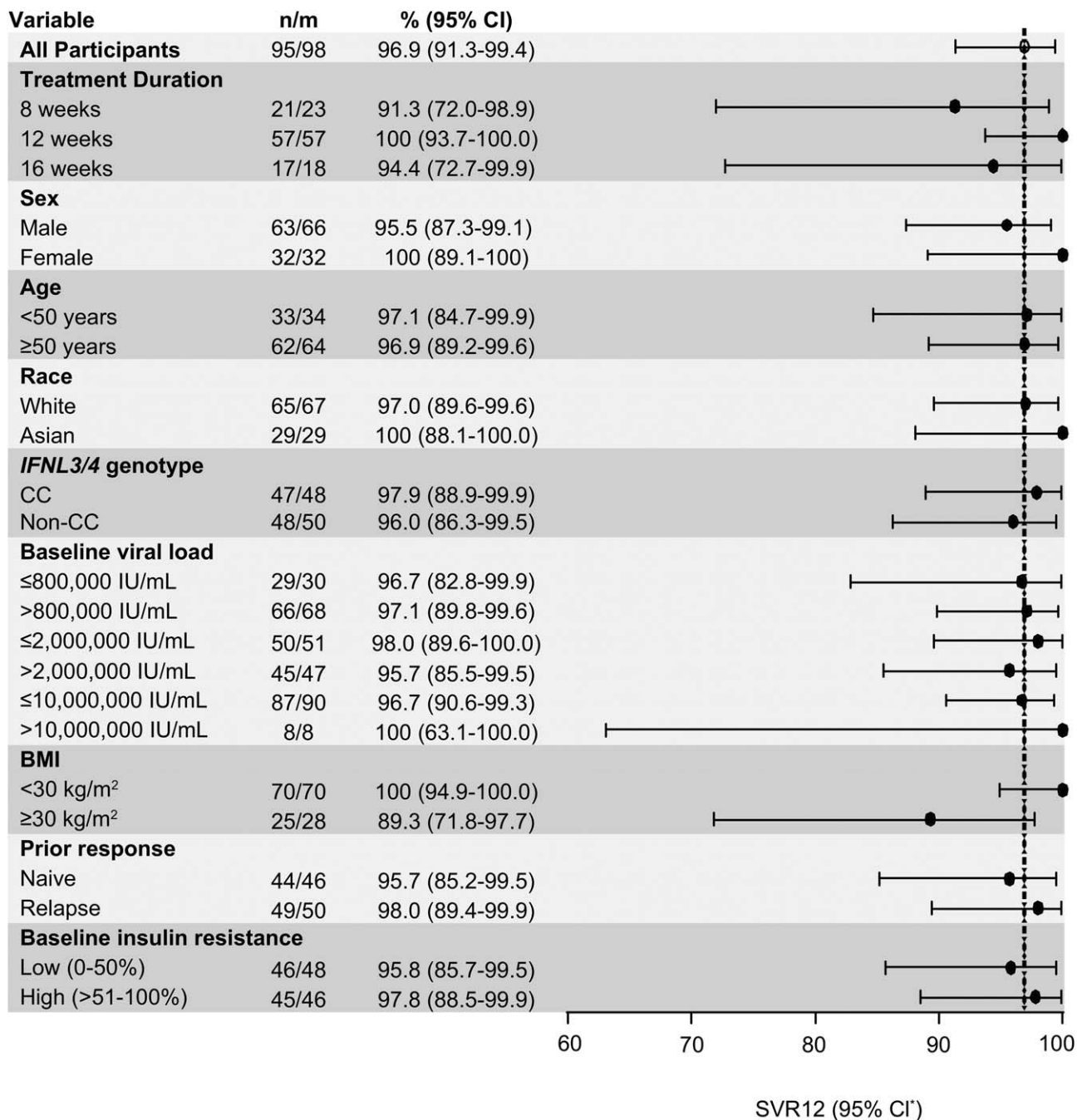


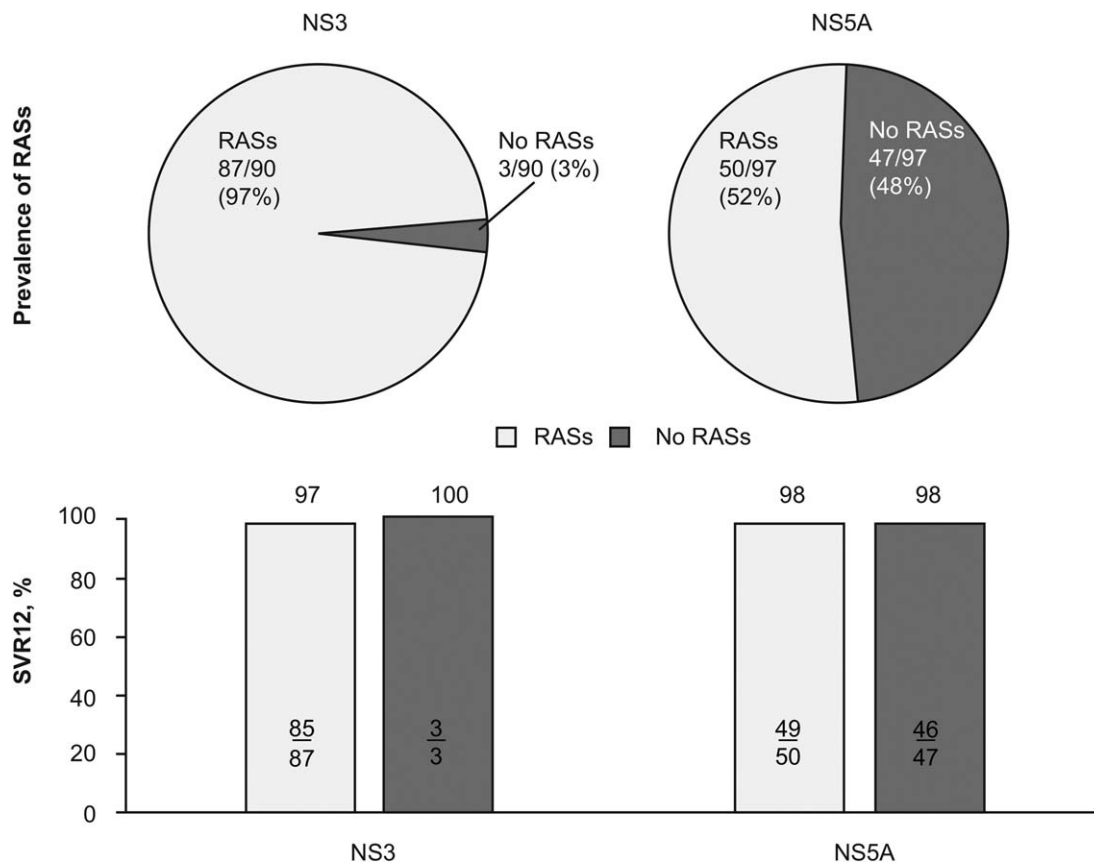
FIG. 3. Subgroup analyses: SVR12 in the mFAS population. \*Confidence interval based on Clopper-Pearson method. Abbreviations: BMI, body mass index; IFN, interferon.

### IMPACT ON INSULIN RESISTANCE

There was no consistent change in HOMA-IR during treatment or follow-up. Among all participants, median HOMA-IR values were 5.57 (range,

0.48-209.21) at baseline, 5.27 (range, 0.75-173.84) at treatment week 8, and 5.52 (range, 1.10-163.83) at follow-up week 12. A HOMA-IR level of ≥3 was arbitrarily used as an indication of participants who were highly insulin-resistant. The proportion of participants with HOMA-IR ≥3 remained consistent





**FIG. 4.** RASs: prevalence and impact on SVR12. Resistance was assessed by next-generation sequencing with a 15% sensitivity threshold; only participants with a virologic outcome are included. The NS3 substitutions and the number of participants (in parentheses) in whom they were detected included V170I (86), T54S (1), V55I (1), V107I (2), R155K (1), V158I (1), and **Q168K/R** (5). The NS5A substitutions and the number of participants (in parentheses) in whom they were detected included L24A/T (2), M28V (4), A30F/K/L/S/T/V (12), **L31M** (4), P58A/S (3), S62A/K/L/T/V (38), and **Y93H** (3). Substitutions in bold are known to confer resistance to EBR or GZR.

throughout the study: 81% (77/95), 83% (70/84), and 77% (66/86) of participants at baseline, treatment week 8, and follow-up week 12, respectively.

Both relapse participants had mean baseline HOMA-IR values of 4.51, which were below the baseline mean of 8.50 for those who achieved SVR. Furthermore, the mean change in HOMA-IR from baseline to follow-up week 12 was  $-1.50$  (improving from 4.51 at baseline to 3.02 at follow-up week 12) in the 2 participants with virologic failure. Neither participant had a history of diabetes.

## TOLERABILITY

The most common AEs were fatigue ( $n = 36$ , 36%), headache ( $n = 35$ , 35%), and nausea ( $n = 19$ , 19%) (Table 2). The majority of AEs were of mild or

moderate severity. When considering only those participants treated for 12 weeks, fatigue (56% [10/18] versus 34% [14/41]), nausea (33% [6/18] versus 15% [6/41]), and headache (61% [11/18] versus 29% [12/41]) occurred at a numerically higher rate in participants receiving RBV compared with those not receiving RBV. Rash (17% [3/18] versus 5% [2/41]), pruritus (28% [5/18] versus 5% [2/41]), and abdominal pain (22% [4/18] versus 7% [3/41]) were also more common among participants treated for 12 weeks receiving RBV compared with those receiving the RBV-free regimen.

There were no SAEs reported among treatment-naive participants. Five treatment-experienced participants reported SAEs: three SAEs (pneumonia, chest pain, opiate overdose) were reported in participants receiving an RBV-containing regimen, and two

TABLE 2. Safety and AEs

	Treatment-naive		Treatment-experienced		
	EBR/GZR + SOF + RBV for 8 weeks (n = 23)	EBR/GZR + SOF for 12 weeks (n = 24)	EBR/GZR + SOF for 12 weeks (n = 17)	EBR/GZR + SOF + RBV for 12 weeks (n = 18)	EBR/GZR + SOF for 16 weeks (n = 18)
Any AE, n (%)	20 (87.0)	21 (87.5)	14 (82.4)	17 (94.4)	17 (94.4)
Fatigue	6 (26.1)	8 (33.3)	6 (35.3)	10 (55.6)	6 (33.3)
Nausea	4 (17.4)	3 (12.5)	3 (17.6)	6 (33.3)	3 (16.7)
Diarrhea	1 (4.3)	3 (12.5)	3 (17.6)	2 (11.1)	3 (16.7)
Headache	5 (21.7)	7 (29.2)	5 (29.4)	11 (61.1)	7 (38.9)
Rash	3 (13.0)	1 (4.2)	1 (5.9)	3 (16.7)	1 (5.6)
Drug-related AE, n (%)	14 (60.9)	13 (54.2)	5 (29.4)	15 (83.3)	11 (61.1)
SAE, n (%)	0 (0)	0 (0)	1 (5.9)	3 (16.7)	1 (5.6)*
Drug-related SAE, n (%)	0 (0)	0 (0)	0 (0)	1 (5.6)	1 (5.6)
Discontinuation due to an AE, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.6)*
Deaths, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ALT, n (%)					
1.1-2.5× baseline	1 (4.3)	0 (0)	0 (0)	2 (11.1)	1 (5.6)
>2.5× baseline	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
>5.0× baseline	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AST, n (%)					
1.1-2.5× baseline	1 (4.3)	1 (4.2)	1 (5.9)	2 (11.1)	0 (0)
>2.5× baseline	1 (4.3)	0 (0)	0 (0)	0 (0)	0 (0)
>5.0× baseline	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ALT/AST >5× ULN, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bilirubin, n (%)					
>1.1-1.5× baseline	4 (17.4)	1 (4.2)	3 (17.6)	5 (27.8)	2 (11.1)
>1.6-2.5× baseline	4 (17.4)	0 (0)	2 (11.8)	1 (5.6)	2 (11.1)
>2.6-5.0× baseline	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hemoglobin <10 g/dL, n (%)	0 (0)	0 (0)	1 (5.9)	2 (11.1)	0 (0)

\*One treatment-experienced participant receiving 16 weeks of therapy experienced an SAE of vomiting followed by treatment discontinuation several days later when a diagnosis of cellulitis was made.

(cellulitis and decreased creatinine, both considered drug-related by the investigator) were reported in participants receiving EBR/GZR plus SOF. One participant discontinued treatment from the 16-week treatment arm due to an SAE of cellulitis. This participant had study medication interrupted following an SAE of vomiting on day 4, and then on day 7 the participant had medication discontinued following a diagnosis of cellulitis.

Three participants had on-treatment hemoglobin levels <10 g/dL, 2 of whom were receiving RBV and required RBV dose reduction. The participant with hemoglobin <10 g/dL who was not receiving an RBV-containing regimen also had an SAE of pneumonia. There were no ALT/AST elevations >5× ULN and no bilirubin elevations >2.6× baseline values.

Events of clinical interest were reported by 7 participants. Six participants took accidental overdoses: all were the result of participant error, none resulted in an AE, and all were addressed through participant education. One treatment-experienced participant receiving

EBR/GZR plus SOF plus RBV for 12 weeks experienced an SAE which met the criteria for a kidney-related event of clinical interest. This participant had a drug-related SAE of decreased creatinine clearance beginning on day 8 of treatment. It was severe in intensity and had a duration of approximately 1 week. The event resolved with continued treatment, and no action was taken by the investigator.

## Discussion

People with HCV GT3 infection and cirrhosis who have failed previous treatment attempts are generally regarded as one of the most difficult-to-treat populations with HCV infection. Additional treatment options are therefore required for this population, and increasing the barrier to resistance through the introduction of a third mechanistically distinct antiviral agent represents a rational solution to overcoming resistance-associated failure. Adopting this approach, data from the present study indicate that a

combination of EBR/GZR plus the NS5B polymerase inhibitor SOF for 12 weeks results in SVR rates of 96%-100%, with no participant receiving this regimen experiencing virologic failure. Efficacy was high in both treatment-naïve and treatment-experienced participants, and all participants with the Y93H RAS at baseline who received at least 12 weeks of EBR/GZR plus SOF achieved SVR. Two participants receiving 8 weeks of therapy failed to achieve SVR: both were male with a high baseline viral load ( $3.8$  and  $5.1 \times 10^6$  IU/mL), and no treatment-emergent NS3, NS5A, or NS5B RASs were detected. A nonimpactful baseline NS3 V170I polymorphism was detected in both participants, and baseline NS5A P58S, S62T, and Y93H were detected in one participant, with only Y93H conferring resistance to EBR. Insulin resistance did not appear to be a causal factor associated with relapse in these participants. The combination of EBR/GZR and SOF therefore represents a treatment regimen that overcomes the lower efficacy typically observed in participants with cirrhosis receiving SOF-based regimens.<sup>(4-6)</sup> All components of this regimen are currently approved for clinical use, making this a readily available addition to the treatment options for treatment-experienced patients with cirrhosis and with HCV GT3 infection.

The trial design of the C-ISLE study was based on data from several previous studies. For treatment-naïve participants, the 12-week arm was the same as that assessed in the C-SWIFT study<sup>(11)</sup> but incorporating a larger sample size. The 8-week arm with RBV was based on data obtained from the ION-2<sup>(13)</sup> and SIR-IUS<sup>(14)</sup> studies, which demonstrated that lower SVR rates following shorter-duration treatment could be improved by either extending duration or adding RBV. In the C-EDGE Treatment-Experienced study,<sup>(15)</sup> efficacy did not vary according to the presence or absence of cirrhosis, but SVR12 did vary according to certain baseline characteristics. For example, participants with GT1b infection or who had previously relapsed following a PR regimen achieved SVR12 rates >95% with a 12-week regimen of EBR/GZR plus RBV, regardless of cirrhosis. Participants with GT1a infection and baseline RASs benefited most from an extended treatment duration. Therefore, treatment with EBR/GZR plus SOF with and without RBV for 12 weeks was studied, with an RBV-free 16-week arm also included to assess the impact of extended therapy in the absence of RBV.

Treatment options for people with GT3 infection include SOF plus peginterferon and/or RBV or SOF

plus daclatasvir in regions where daclatasvir is available. Treatment options have recently increased for this population with the approval of a 12-week regimen of SOF plus velpatasvir for people with HCV GT3 infection, including those with both cirrhosis and treatment experience. However, the presence of both cirrhosis and prior treatment with a PR regimen was a negative predictor of response in the phase 3 ASTRAL-3 study,<sup>(16)</sup> and among participants with both characteristics, SVR12 rates with SOF/velpatasvir for 12 weeks were 89% (33/37). Furthermore, of the 11 participants who relapsed in this study, 10 had the Y93H RAS at the time of failure. SVR was 88% among GT3-infected participants with NS5A RAS at baseline compared with 97% in those who did not and fell to 84% (21/25) in participants with the Y93H variant at baseline. Other studies have shown variable response rates in treatment-experienced, GT3-infected participants with cirrhosis. In ALLY-3, SVR12 was achieved by 69% (9/13) of treatment-experienced participants with GT3 infection and compensated cirrhosis receiving SOF/daclatasvir for 12 weeks,<sup>(5)</sup> whereas in the BOSON study, 86% (30/35) of treatment-experienced participants with cirrhosis and GT3 infection receiving SOF plus PR for 12 weeks achieved SVR12.<sup>(4)</sup> In ALLY-3+, SVR12 was 88% (14/16) in treatment-experienced participants with cirrhosis and GT3 infection receiving SOF/daclatasvir plus RBV for 12 weeks and 86% (12/14) in those treated for 16 weeks.<sup>(6)</sup> More recently, in the SURVEYOR II study, 3 of 4 (75%) treatment-experienced participants with cirrhosis and HCV GT3 infection receiving glecaprevir/pibrentasvir for 16 weeks achieved SVR.<sup>(17)</sup>

New combinations were evaluated to determine if they improve efficacy in people with HCV GT3 and cirrhosis. The triple combination of SOF/velpatasvir and the pangenotypic NS3/4 protease inhibitor voxilaprevir was among the first therapies to demonstrate SVR12 >90% after 8 weeks of treatment in treatment-naïve participants with GT3 infection and cirrhosis (94% [17/18]).<sup>(18)</sup> In a combined cohort of treatment-experienced participants with and without cirrhosis, SVR12 after 12 weeks of SOF/velpatasvir/voxilaprevir was 95%-96% (74/78 and 52/54, respectively)<sup>(19)</sup>; in participants with HCV GT3 infection and cirrhosis enrolled in the POLARIS-1 study, SVR12 was 93% (52/56).<sup>(19)</sup> The 12-week duration of this combination was subsequently approved for people with HCV GT3 infection with or without cirrhosis who are treatment-experienced. The pangenotypic combination of glecaprevir/pibrentasvir was also evaluated. In

the SURVEYOR II study, 3 of 4 (75%) treatment-experienced participants with cirrhosis and HCV GT3 infection receiving glecaprevir/pibrentasvir for 16 weeks achieved SVR.<sup>(17)</sup> In part 3 of this study, 96% (45/47) of treatment-experienced participants with cirrhosis and HCV GT3 infection achieved SVR12 after 16 weeks.<sup>(20)</sup> Therefore, the 16-week regimen of this combination was recently approved for treatment-experienced people with HCV GT3 infection and compensated cirrhosis. Though participant characteristics and treatment length differ among the studies, the SVR12 rates achieved by SOF/velpatasvir/voxilaprevir and glecaprevir/pibrentasvir in treatment-experienced participants with HCV GT3 infection and cirrhosis are similar to those achieved with EBR/GZR/SOF.

There is a well-documented association between HCV infection and insulin resistance, but the causality, and hence pathology, linking HCV infection with insulin control is poorly understood, although it seems clear that genotype-specific differences exist.<sup>(2)</sup> In a large study of interferon-based therapy, viral clearance was associated with a reduction in the proportion of participants with insulin resistance among those with HCV GT1 infection but not those with HCV GT2 or 3 infection.<sup>(21)</sup> In people with GT3 infection, high viral load is known to exert direct steatogenic effects that are reversible with virologic eradication, although this may not contribute directly to insulin resistance or progression of liver fibrosis.<sup>(22,23)</sup> Interestingly, high-molecular weight adiponectins that help regulate hepatic insulin sensitivity are known to be reduced in people with HCV GT3 infection.<sup>(24)</sup> Regardless of the underlying pathology, data from the present study agree with previous reports indicating that viral clearance in people with HCV GT3 infection does not improve insulin resistance.

The addition of SOF to the EBR/GZR combination was generally well tolerated in the present study. AEs such as fatigue and rash were notably more frequent in participants receiving an RBV-containing regimen, and 2 of the 3 participants with hemoglobin levels <10 g/dL were also receiving RBV. There were no ALT/AST elevations >5× ULN and no bilirubin elevations >2.6× baseline values.

It is unclear how results from the present study may apply to other patient groups. This study did not enroll participants who did not have cirrhosis, so it does not provide data regarding the safety and efficacy of this regimen in people with GT3 infection and less advanced liver disease. However, in the C-SWIFT study, SVR12 rates of 93% (14/15) and 100% (14/14)

were achieved in participants who did not have cirrhosis but who did have HCV GT3 infection and were receiving EBR/GZR + SOF for 8 or 12 weeks, respectively.<sup>(11)</sup> A conservative estimate of the efficacy associated with a 12-week regimen (gained from pooling the 8-week and 12-week treatment arms) suggests an SVR rate of ≈97% (28/29) in participants without cirrhosis but with HCV GT3 infection. The study also did not address the efficacy of EBR/GZR + SOF in people with GT3 infection and cirrhosis who have previously failed SOF/RBV or daclatasvir/SOF ± RBV. Participants with prior DAA failure were excluded from the present study, and therefore care should be exercised in extrapolating the findings of the current study to this population.

This was a single-arm study with no comparator treatment arm, and therefore indirect comparisons with other treatments should be made with caution. Most participants also had well-compensated cirrhosis, so these data should not be extrapolated to participants with decompensated disease. There was no formal efficacy hypothesis testing conducted in this study; therefore, comparisons between treatment arms were not prespecified or powered for statistical comparison. Most participants in this study had liver cirrhosis defined by the noninvasive FibroScan test. In total, 84 of 100 participants were evaluated by FibroScan, with a median score of 21.4 kPa; no participants had a FibroScan score <12.6 kPa. Based on previously reported validation studies,<sup>(25)</sup> most of the participants in the current study had FibroScan scores consistent with METAVIR F4. Furthermore, the use of GZR in this regimen precludes its use in patients with Child-Pugh B or C liver disease, for which GZR is contraindicated. This study enrolled participants exclusively at UK clinical centers, so this should be accounted for when extrapolating these findings to people from other geographic regions. Finally, the importance of GZR in this three-drug regimen is unclear. While EBR and SOF are considered pangenotypic agents, GZR has lower efficacy in people with GT3 infection compared with other genotypes. In the C-WORTHY part D study, SVR rates were 45% in participants with GT3 infection receiving EBR/GZR for 12 weeks.<sup>(26)</sup> In the context of the present study, we cannot comment on whether SVR rates would be attained in participants receiving only SOF plus EBR as this was not considered within our study design and EBR is not available as a single entity. We believe that the inclusion of GZR within this regimen as a third mechanistically distinct antiviral agent reinforces a high barrier to

resistance and helps mitigate the possibility of virologic escape. Furthermore, for countries where the cost of SOF is a concern, generic SOF could be combined with EBR/GZR; but clinicians will need to take account of local regulations before this can be considered, and the authors wish to clarify that they are not advocating such an approach.

In conclusion, high efficacy was demonstrated in treatment-naïve and PR treatment-experienced participants with HCV GT3 infection and cirrhosis, with SVR12 rates of 100% achieved in participants receiving EBR/GZR plus SOF with or without RBV for 12 weeks. Extended-duration treatment beyond 12 weeks was not required, and high efficacy was maintained regardless of presence of baseline NS5A RASs or addition of RBV. Data from this study support the use of EBR/GZR plus SOF for 12 weeks without RBV for treatment-naïve and PR-experienced people with HCV GT3 infection and cirrhosis. HOMA-IR remained high during treatment and follow-up but did not appear to impact SVR.

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## Supporting Information

Additional Supporting Information may be found at [onlinelibrary.wiley.com/doi/10.1002/hep.29852/supinfo](http://onlinelibrary.wiley.com/doi/10.1002/hep.29852/supinfo).