Elbasvir/Grazoprevir and Sofosbuvir For HCV Genotype 3 Infection with Compensated Cirrhosis: A Randomized Trial

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Abbreviations: AE, adverse event; CI, confidence interval; EBR, elbasvir; FAS, full analysis set; GT, genotype; GZR, grazoprevir; HOMA-IR, homeostatic model assessment of insulin resistance; mFAS, modified full analysis set; PR, peginterferon/ribavirin; RAS, resistance-associated substitution; RBV, ribavirin; SAE, serious adverse event; SOF, sofosbuvir; SVR, sustained virologic response; SVR12, sustained virologic response at 12 weeks; ULN, upper limit of normal.

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Abstract

Many direct-acting antiviral regimens have reduced activity in people with hepatitis C virus (HCV) genotype (GT)3 infection and cirrhosis. The aim of the C-ISLE study was to assess 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-naive participants were randomized to EBR/GZR + SOF + RBV for 8 weeks or EBR/GZR + SOF for 12 weeks and treatment-experienced participants were randomized to EBR/GZR + SOF ± RBV for 12 weeks or EBR/GZR + SOF for 16 weeks. The primary end point was HCV RNA <15 IU/mL 12 weeks after end of treatment (SVR12). Among treatment-naive 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relapsed (both in the 8-week arm); 1 discontinued due to vomiting/cellulitis (16-week arm); and 2 discontinued (consent withdrawn/lost to follow-up).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). *Conclusion:* 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. ClinicalTrials.gov no: NCT02601573.

Hepatitis 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.[1,2] 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 to 7 million adults with HCV infection.[3] Countries that have sizeable immigrant populations from these Asian countries also have a high prevalence of GT3 infection, such as the United Kingdom where 44% of HCV infections are attributable to GT3.[3]

Hepatitis C virus GT3 is also unique in terms of its response to direct-acting antiviral agent treatment regimens. As the use of direct-acting antiviral agent 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.[4] A recent meta-analysis indicates low rates of sustained virologic response (SVR) in people with GT3 infection receiving sofosbuvir (SOF)/ledipasvir, and favors the use of SOF/peginterferon/ribavirin (PR) or SOF/daclatasvir for 12 weeks in this population.[4–7] Furthermore, in participants with HCV GT3 infection receiving SOF/daclatasvir for 12 weeks, rates of SVR at 12 weeks (SVR12) declined markedly in cirrhotic compared with noncirrhotic individuals (63% vs 95%).[6] More recently, the combination of SOF/velpatasvir has been approved as the first all-oral 12-week treatment regimen for compensated cirrhotic and noncirrhotic people with HCV GT3 infection.[8] SVR12 rates of 91% (31/34) and 89% (33/37) were attained in treatment-naive and -experienced cirrhotic participants with HCV GT3 infection, respectively, receiving SOF/velpatasvir for 12 weeks in the ASTRAL-3 study.[9] In the SURVEYOR-II study, SVR12 was achieved by 91%–98% of treatment-naive and -experienced cirrhotic and noncirrhotic participants with HCV GT3 infection receiving glecaprevir/pibrentasvir for 12–16 weeks.[10]

However, regardless of duration or cirrhosis status, there remain some challenges in treating people with GT3 infection. Of the 131 participants enrolled in SURVEYOR-II, 5 experienced virologic failure; 4 relapsed and 1 treatment-experienced cirrhotic participant with baseline viral load >17 million IU/mL experienced on-treatment virologic breakthrough. All 5 participants with virologic failure had treatment-emergent Y93H at the time of virologic failure.[10]

The combination of elbasvir (EBR), a once-daily 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.[11–21] Based on the principle that combining direct-acting antiviral agents 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 SOF. In the phase 2 C-SWIFT study, SVR12 rates of 93% (14/15) and 100% (14/14) were attained in noncirrhotic participants 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 cirrhotic participants with GT3 infection treated for 12 weeks.[22] The combination of EBR/GZR plus SOF is approved in Canada, New Zealand, Georgia, Mexico, and Egypt for the treatment of HCV GT3 infection. Supported by these 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 compensated cirrhotic participants with 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, multisite, open-label clinical study. Adult participants with chronic HCV GT3 infection, plasma HCV RNA ≥10,000 IU/mL, and

compensated liver cirrhosis were enrolled. Compensated cirrhosis was defined as: a liver biopsy performed prior to day 1 showing METAVIR F4 or its equivalent by noninvasive measures; FibroScan® >12.5 kPa performed within 12 months of day 1; or a FibroTest® (FibroSure®) performed during screening with a score of >0.75 and concurrent aspartate aminotransferase (AST):platelet ratio index (APRI) of >2. Participants were either naive to previous HCV therapy, had intolerance to PR (≥4 weeks of PR and ≤80% of treatment duration), or had documented prior virologic failure to PR, defined as null response (<2 $\log_{10}$ IU/mL reduction in HCV RNA after ≥12 weeks OR <1 $\log_{10}$ IU/mL reduction in HCV RNA after 4 weeks and discontinued therapy prior to treatment week 12), partial response (≥2 $\log_{10}$ IU/mL reduction in HCV RNA after ≥12 weeks of treatment, but not achieving undetectable HCV RNA at end of treatment), or relapse (undetectable HCV RNA at end of treatment, but detectable during follow-up). Participants with HIV co-infection were eligible for enrollment, provided that they were either not receiving antiretroviral therapy with CD4+ T-cell count >500 cells/mm^3 at screening or had well-controlled HIV on antiretroviral therapy (defined as HIV RNA <20 copies/mL for ≥8 weeks prior to the study, no virologic failure within 8 weeks [HIV RNA ≥200 copies/mL], and a CD4+ T-cell count >200 cells/mm^3 at screening). Participants who had previously received direct-acting antiviral agent therapy, with 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), who were Child-Pugh B or C or with a Child-Turcotte-Pugh score >6, or with hepatitis B virus co-infection were excluded. Laboratory exclusion criteria included hemoglobin <11 g/dL (females) or <12 g/dL (males), platelets <40 × 10^3 /μL, albumin <3.0 g/dL, and alanine aminotransferase (ALT) or AST levels >10× upper limit of normal.

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 800–1400 mg/day,

administered twice daily according to participant body weight at baseline. Treatment-naive 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

Hepatitis C virus 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 at 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.

Blood samples for assessment of viral resistance were collected at baseline from all participants, and at the time of virologic failure for participants with HCV RNA >1000 IU/mL who met criteria for virologic failure. Next-generation sequencing was performed at baseline and at the time of virologic failure to detect resistance-associated substitutions (RASs). The limit of minority variant detection in the population was >1% of the viral population. Any polymorphism at the following amino acid positions 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), 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).

OUTCOMES

The primary end point was the proportion of participants achieving a SVR12. Subgroup analyses were conducted for each of the 5 treatment groups. SVR12 rate and associated 95% CIs were estimated to assess the consistency of response across various subgroups. Assessment of the impact of 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× baseline and >100 IU/L; alkaline phosphatase >3× upper limit of normal (ULN); estimated glomerular filtration rate <50 mL/min/1.73 m^2, and serum creatinine grade 2 or higher (>1.3× 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 at follow-up week 12, applying the following formula: HOMA-IR = [insulin (μIU/ml) × glucose (mg/dL)]/405. Based on a previous study designed to determine optimal cutoff HOMA-IR values that could be used to identify individuals at higher cardiometabolic risk within the general adult population,[23] a HOMA-IR value of ≥3 was selected to indicate participants with a 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. This sample size was selected based on the understanding that limited clinical data exist regarding the use of EBR/GZR plus SOF in cirrhotic

people with HCV GT3 infection, and that low efficacy has been reported in cirrhotic participants with GT3 infection receiving other SOF-based regimens.[6,7,24] Hence, the target sample size limits any risk to participants, yet still enables an assessment of each regimen within the context of the chosen participant population. Efficacy analyses are presented based on the full analysis set (FAS) population, which includes all participants who received at least 1 dose of study treatment. The modified full analysis set (mFAS) population, which excludes participants who discontinued from the study for reasons unrelated to treatment, was prespecified in the protocol as the primary population for efficacy analysis; however, for purposes of transparency, efficacy data are shown for all treated participants in both the FAS and mFAS. Two-sided 95% confidence intervals (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 1 dose of study drug. The proportion of participants with AEs of elevated laboratory values that are reported as events of clinical interest is provided with the corresponding 95% CIs. Also, the proportion of participants with ALT/AST >5× ULN at week 4 or later while on treatment is estimated along with the corresponding 95% CIs. In addition, the broad clinical and laboratory AE categories, consisting of 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 (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 participant 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 administrative discontinuations (1 treatment-naive 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 *IL28B* 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 138×10^3 cells/μL (range,

46–396), 24% had a platelet count <100 × 10^3 cells/μL, 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 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.

SUSTAINED VIROLOGIC RESPONSE

Among treatment-naive 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-naive participant receiving 12 weeks of therapy was lost to follow-up after treatment week 2.

Among 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 diagnosis of cellulitis, which were characterized by the investigator as related to study drug. Thus, no treatment-experienced participants experienced virologic failure. In the mFAS population, all treatment-naive and -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).

RESISTANCE-ASSOCIATED SUBSTITUTIONS

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%]). 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 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 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 3 RASs were mostly linked within the same virus. All variants were also detected at 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 which 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% who 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.

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 (Fig. 5). 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 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: 3 SAEs (pneumonia, chest pain, opiate overdose) were reported in participants receiving an RBV-containing regimen and 2 (cellulitis and decreased creatinine, both considered as 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 renal-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 3rd 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-naive and -experienced participants, and all participants with the Y93H RASs 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 × 10^6 IU/mL). 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 novel treatment regimen that overcomes the lower efficacy typically observed in cirrhotic participants receiving SOF-based regimens.[5–7] All components of this regimen are currently approved for clinical use, making this a readily available addition to the treatment options for treatment-experienced, cirrhotic people with HCV GT3 infection.

The trial design of the C-ISLE study was based on data from several previous studies. For treatment-naive participants, the 12-week arm was the same as that assessed in the C-SWIFT study,[22] but incorporating a larger sample size. The 8-week arm with RBV was based on data obtained from the ION-2[25] and SIRIUS[26] 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,[27] 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 were negative predictors of response in the phase 3 ASTRAL-3 study, 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 time of failure. Sustained virologic response 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 cirrhotic, treatment-experienced GT3-infected participants. 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[6]; whereas in the BOSON study, 86% (30/35) of cirrhotic, treatment-experienced participants with GT3 infection receiving SOF plus PR for 12 weeks achieved SVR12.[5] In ALLY-3+, SVR12 was 88% (14/16) in treatment-experienced, cirrhotic participants with GT3 infection receiving SOF/daclatasvir plus RBV for 12 weeks and 86% (12/14) in those treated for 16 weeks.[7] More recently, in the SURVEYOR II study, 3 of 4 (75%) treatment-experienced cirrhotic participants with HCV GT3 infection receiving glecaprevir/pibrentasvir for 16 weeks achieved SVR.[28]

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.[2] 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.[29] 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.[30,31] Interestingly, high-molecular-weight adiponectins that help regulate hepatic insulin sensitivity are known to be reduced in people with HCV GT3 infection.[32] 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. Adverse events 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.

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. Finally, 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.

In conclusion, high efficacy was demonstrated in treatment-naive and -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. HOMA-IR remained high during treatment and follow-up but did not appear to impact SVR.

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Author names in bold designate shared co-first authorship.

TABLE 1. Participant Demographics

	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)	Total (N = 100)
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^2	17 (73.9)	18 (75.0)	13 (76.5)	13 (72.2)	11 (61.1)	72 (72.0)
≥30 kg/m^2	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, 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)	4.2 (1.0–5.0)	4.1 (1.1–4.6)	4.0 (1.4–4.9)	4.1 (1.1–4.6)	4.2 (1.1–4.8)	4.1 (1.0–5.0)
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, $\times 10^3$ 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: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; EBR, elbasvir; GZR, grazoprevir; HOMA-IR, homeostatic model assessment of insulin resistance; IFN, interferon; PR, peginterferon/ribavirin; RBV, ribavirin; SOF, sofosbuvir.

TABLE 2. Safety and Adverse Events

	Treatment-naïve		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)
Serious AE, n (%)	0 (0)	0 (0)	1 (5.9)	3 (16.7)	1 (5.6)*
Drug-related serious AE, 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)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EBR, elbasvir; GZR, grazoprevir; RBV, ribavirin; SOF, sofosbuvir; ULN, upper limit of normal.

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

Figure Legends

FIG. 1. Participant disposition. Abbreviations: EBR, elbasvir; GZR, grazoprevir; RBV, ribavirin; SOF, sofosbuvir.

FIG. 2. SVR12 in the full analysis set (A) and the modified full analysis set (B).*mFAS excluded patients who discontinued treatment for reasons unrelated to study medication. Abbreviations: EBR, elbasvir; GZR, grazoprevir; mFAS, modified full analysis set; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virologic response at 12 weeks.

FIG. 3. Subgroup analyses: SVR12 in the mFAS population. *Confidence interval based on Clopper-Pearson method. Abbreviations: BMI, body mass index, CI, confidence interval; mFAS, modified full analysis set; SVR12, sustained virologic response at 12 weeks.

FIG. 4. Resistance-associated substitutions: prevalence and impact on SVR12. Resistance was assessed by next-generation sequencing with 15% sensitivity threshold; only includes participants with a virologic outcome. Abbreviations: RAS, resistance-associated substitution; SVR12, sustained virologic response at 12 weeks.

FIG. 5. Impact of treatment on insulin resistance. *HOMA-IR values >3.0 were considered as highly insulin resistant. Abbreviation: HOMA-IR, homeostatic model assessment of insulin resistance.

Figure 1.

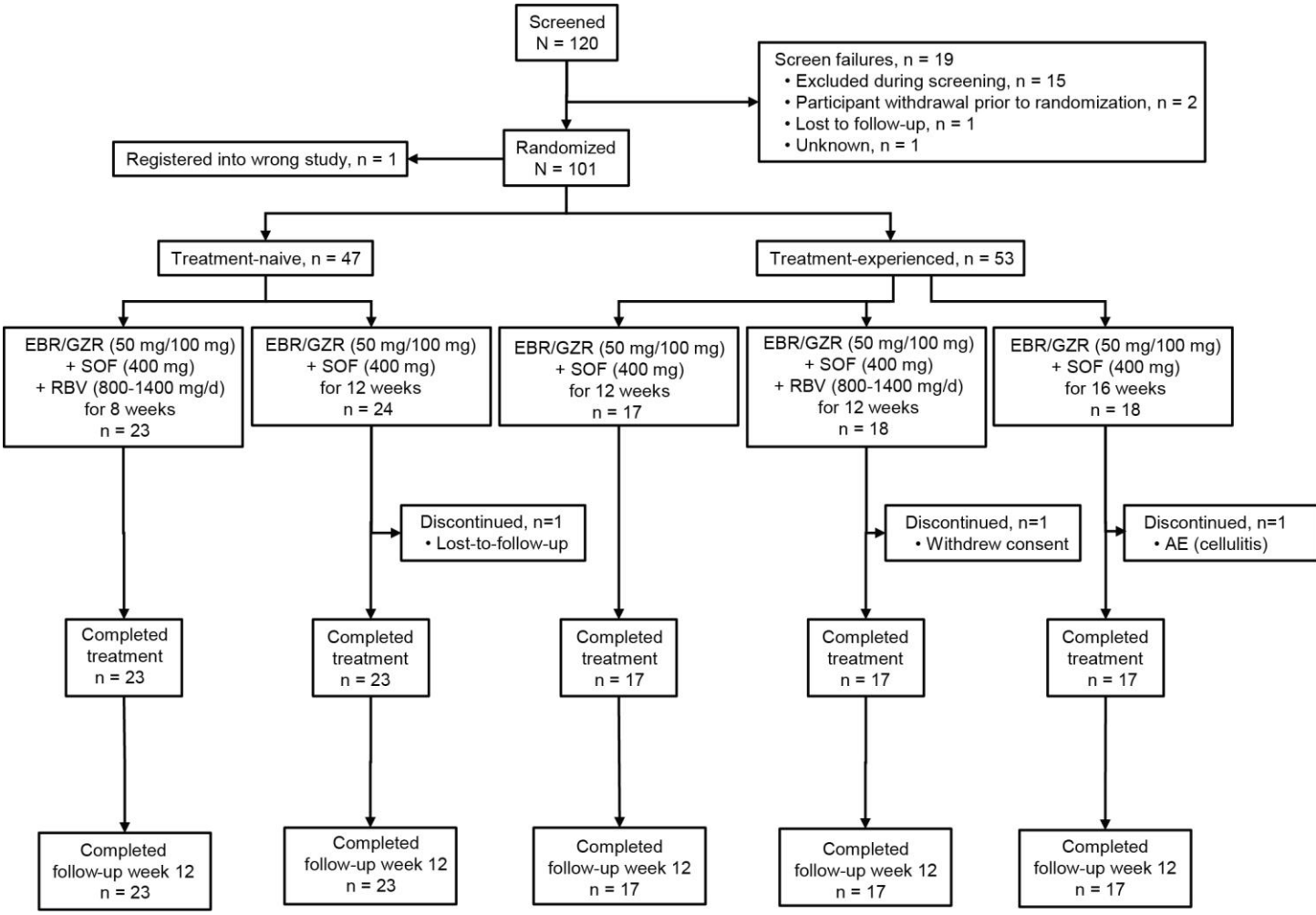
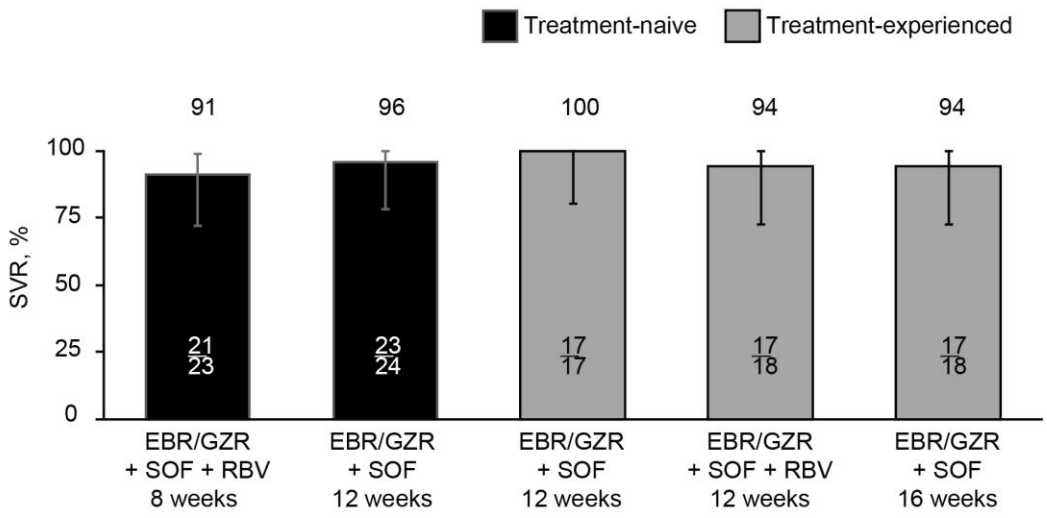

Screened
N = 120
Screen failures, n = 19
• Excluded during screening, n = 15
• Participant withdrawal prior to randomization, n = 2
• Lost to follow-up, n = 1
• Unknown, n = 1
Registered into wrong study, n = 1
Randomized
N = 101
Treatment-naive, n = 47
Treatment-experienced, n = 53
EBR/GZR (50 mg/100 mg) + SOF (400 mg) + RBV (800-1400 mg/d) for 8 weeks n = 23
EBR/GZR (50 mg/100 mg) + SOF (400 mg) for 12 weeks n = 24
EBR/GZR (50 mg/100 mg) + SOF (400 mg) for 12 weeks n = 17
EBR/GZR (50 mg/100 mg) + SOF (400 mg) + RBV (800-1400 mg/d) for 12 weeks n = 18
EBR/GZR (50 mg/100 mg) + SOF (400 mg) for 16 weeks n = 18
Discontinued, n=1
• Lost-to-follow-up
Discontinued, n=1
• Withdrew consent
Discontinued, n=1
• AE (cellulitis)
Completed treatment n = 23
Completed treatment n = 23
Completed treatment n = 17
Completed treatment n = 17
Completed treatment n = 17
Completed follow-up week 12 n = 23
Completed follow-up week 12 n = 23
Completed follow-up week 12 n = 17
Completed follow-up week 12 n = 17
Completed follow-up week 12 n = 17

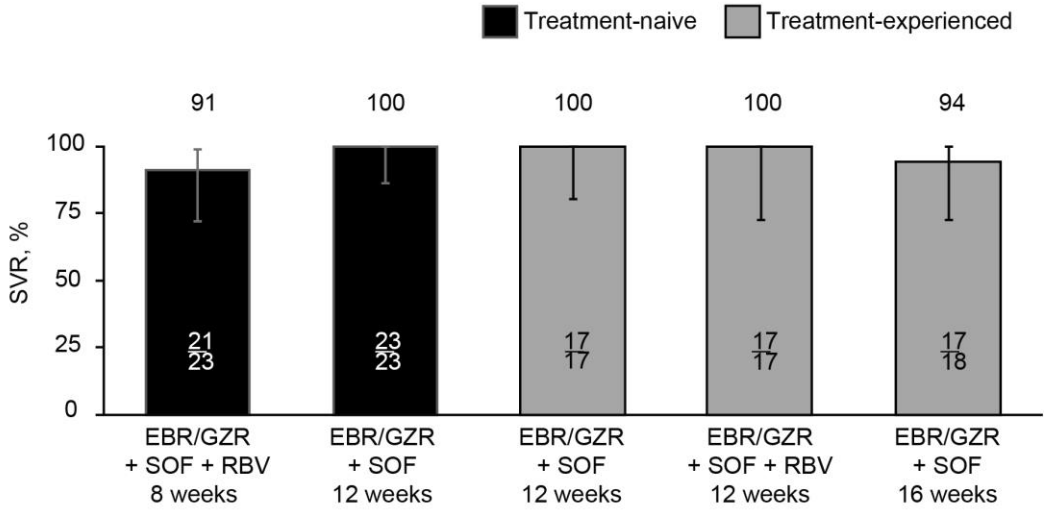
Figure 2.

A



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

B



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

Figure 3.

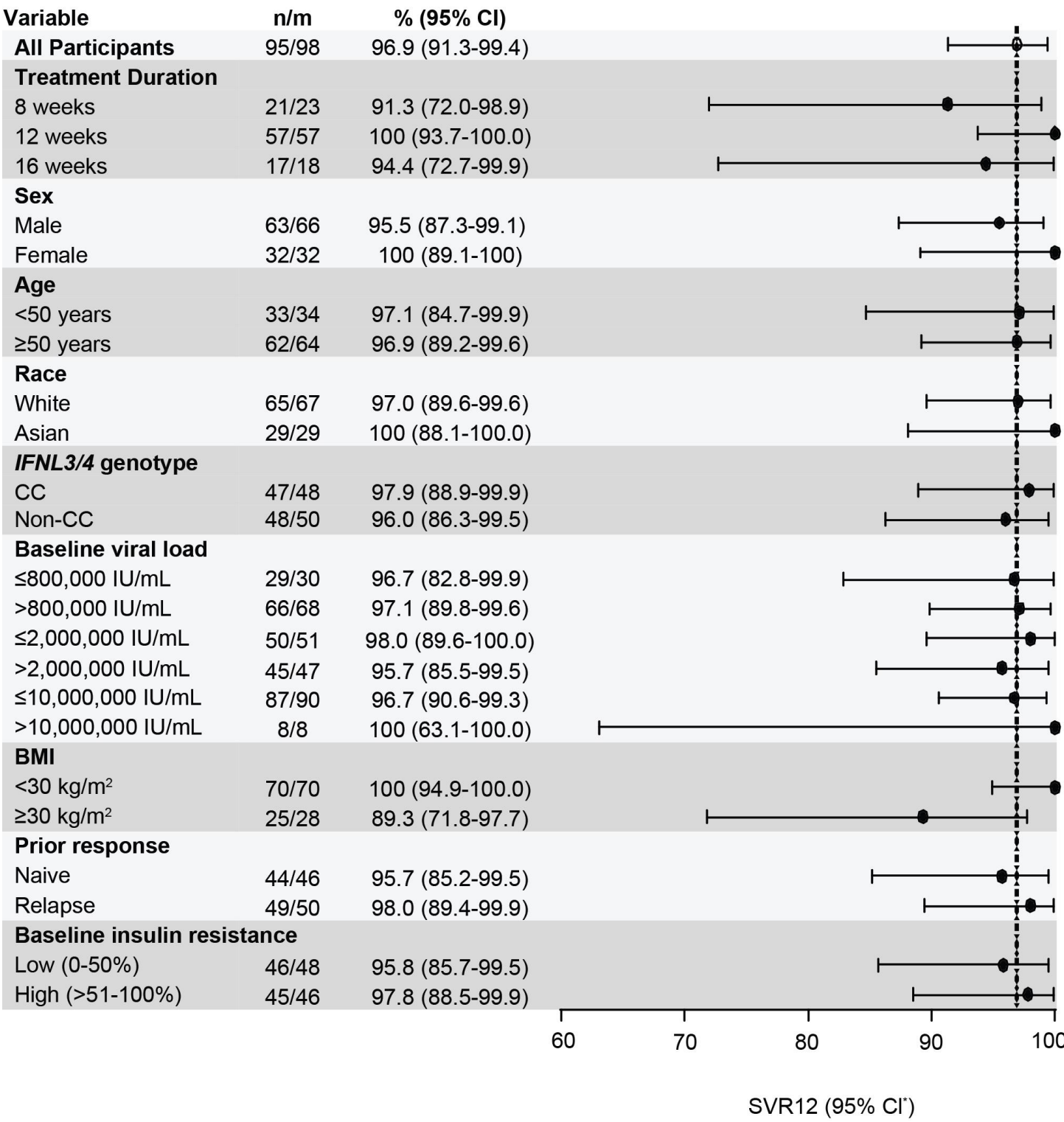

Variable
n/m
% (95% CI)
All Participants 95/98 96.9 (91.3-99.4)
Treatment Duration
8 weeks 21/23 91.3 (72.0-98.9)
12 weeks 57/57 100 (93.7-100.0)
16 weeks 17/18 94.4 (72.7-99.9)
Sex
Male 63/66 95.5 (87.3-99.1)
Female 32/32 100 (89.1-100)
Age
<50 years 33/34 97.1 (84.7-99.9)
≥50 years 62/64 96.9 (89.2-99.6)
Race
White 65/67 97.0 (89.6-99.6)
Asian 29/29 100 (88.1-100.0)
IFNL3/4 genotype
CC 47/48 97.9 (88.9-99.9)
Non-CC 48/50 96.0 (86.3-99.5)
Baseline viral load
≤800,000 IU/mL 29/30 96.7 (82.8-99.9)
>800,000 IU/mL 66/68 97.1 (89.8-99.6)
≤2,000,000 IU/mL 50/51 98.0 (89.6-100.0)
>2,000,000 IU/mL 45/47 95.7 (85.5-99.5)
≤10,000,000 IU/mL 87/90 96.7 (90.6-99.3)
>10,000,000 IU/mL 8/8 100 (63.1-100.0)
BMI
<30 kg/m2 70/70 100 (94.9-100.0)
≥30 kg/m2 25/28 89.3 (71.8-97.7)
Prior response
Naive 44/46 95.7 (85.2-99.5)
Relapse 49/50 98.0 (89.4-99.9)
Baseline insulin resistance
Low (0-50%) 46/48 95.8 (85.7-99.5)
High (>51-100%) 45/46 97.8 (88.5-99.9)
60
70
80
90
100
SVR12 (95% CI*)

Figure 4.

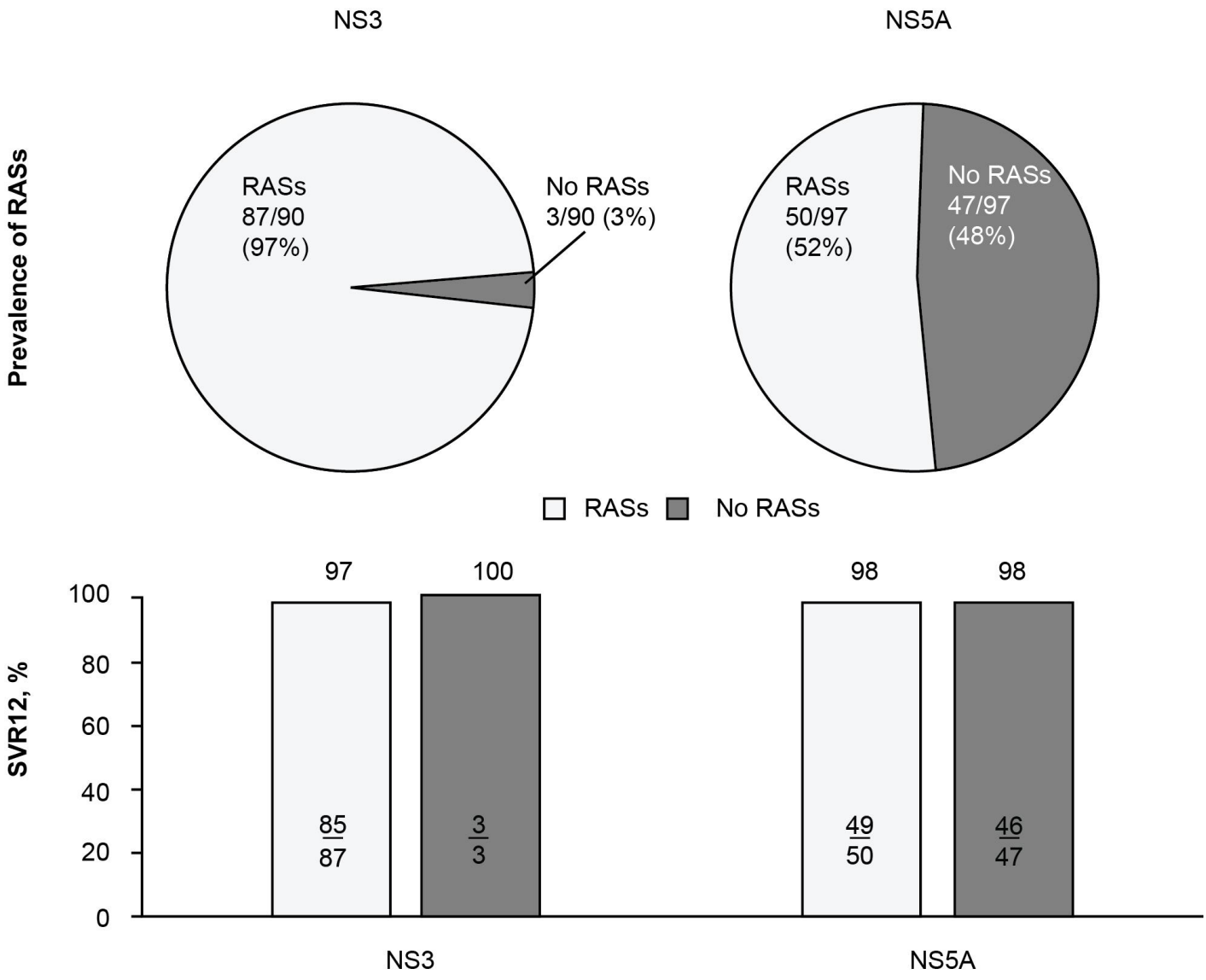
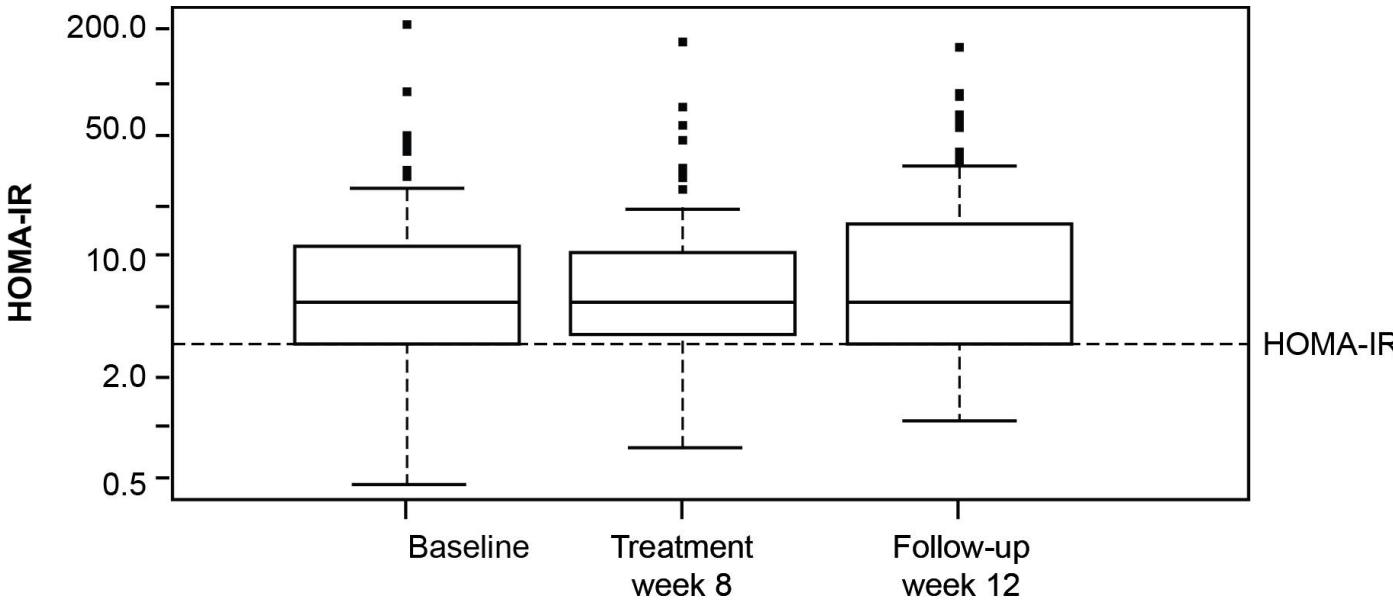

NS3
NS5A
Prevalence of RASs
RASs
87/90
(97%)
No RASs
3/90 (3%)
RASs
50/97
(52%)
No RASs
47/97
(48%)
RASs
No RASs
SVR12, %
100
80
60
40
20
0
97
100
98
98
85
87
3
3
49
50
46
47
NS3
NS5A

Figure 5.



HOMA-IR, median (range)	5.57 (0.48–209.21)	5.27 (0.75–173.84)	5.52 (1.10–163.83)

Supporting Documents

SUPPLEMENTARY TABLE S1. Participants With Y93H Variants Detectable at Baseline

Patient #	Treatment history	Treatment	Y93H in viral population, %	Other NS5A RASs	Treatment outcome
1	TN	EBR/GZR + SOF + RBV for 8 weeks	1	A30V (2%)	SVR12
2	TN	EBR/GZR + SOF for 12 weeks	87	A30L (7%); A30S (5%) A30V (2%); S62T (90%) S621T (62%)	SVR12
3	TN	EBR/GZR + SOF + RBV for 8 weeks	44	P58S (99%); S62A (3%) S62T (62%)	Relapse
4	TN	EBR/GZR + SOF for 12 weeks	11	A30M (14%)	SVR12
5	TE	EBR/GZR + SOF + RBV for 12 weeks	1	A30V (1%)	SVR12
6	TE	EBR/GZR + SOF for 12 weeks	2	S62T (99%)	SVR12
7	TE	EBR/GZR + SOF + RBV for 12 weeks	28	A30F (17%); A30V (75%) S62T (11%); S62L (7%)	SVR12

8	TE	EBR/GZR + SOF for 16 weeks	7	P58H (1%); P58T (1%)	SVR12
9	TE	EBR/GZR + SOF + RBV for 12 weeks	2	P58T (1%)	SVR12

Abbreviations: EBR, elbasvir; GZR, grazoprevir; RAS, resistance-associated substitution; RBV, ribavirin; SOF, sofosbuvir; SVR12; sustained virologic response at 12 weeks; TE, treatment-experienced; TN, treatment-naive.