# Elbasvir/Grazoprevir Plus Sofosbuvir ± Ribavirin in Treatment-Naive And Treatment-Experienced People With Hepatitis C Virus Genotype 3 Infection and Compensated Cirrhosis: SVR24 Results of the C-ISLE Study

Presented at
The International Liver Congress™ 2017;
April 19-23, 2017;
Amsterdam, The Netherlands

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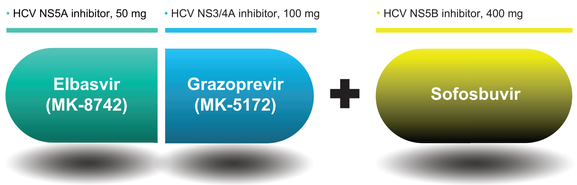
## Background

- Genotype (GT)3 is a common hepatitis C virus (HCV) genotype, accounting for 30% of infections globally[1]
  - GT3 infection is associated with high rates of hepatocellular carcinoma and rapid progression to cirrhosis
- Despite recent advances, HCV GT3 infection and cirrhosis are challenging to treat with all-oral regimens
  - Treatment-experienced people or those with baseline NS5A resistance-associated substitutions (RASs) are particularly challenging
- Elbasvir (EBR) is a once-daily NS5A inhibitor and grazoprevir (GZR) is a once-daily HCV NS3/4A protease inhibitor (**Figure 1**)
  - The combination of EBR and GZR is approved in Europe, the United States, Canada, and other countries worldwide[2]
  - Broad activity vs most HCV genotypes in vitro[3-5]
  - Efficacious in treatment-naive and -experienced people, cirrhotic and noncirrhotic people, HIV/HCV co-infected people, and those with chronic kidney disease[6-9]
- Sofosbuvir (SOF) is an NS5B inhibitor indicated for the treatment of chronic HCV infection as a component of a combination antiviral treatment regimen (**Figure 1**)[10]
- The C-SWIFT study evaluated the safety and efficacy of EBR/GZR + SOF for 4-12 weeks in treatment-naive participants with HCV GT1 or 3 infection[11]
  - High sustained virologic response (SVR) rates (>90%) in HCV GT3-infected, treatment-naive participants receiving EBR/GZR + SOF for 12 weeks
  - Similar efficacy in cirrhotic participants treated for 12 weeks and noncirrhotic participants treated for 8 or 12 weeks

### Figure 1. EBR/GZR plus SOF




## Aim

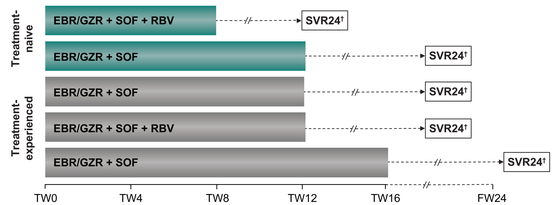
- To evaluate the regimen of EBR/GZR + SOF ± ribavirin (RBV) in cirrhotic participants with HCV GT3 infection for durations ranging from 8-16 weeks

## Participants and Methods

### Study Design

- C-ISLE (NCT02601573; Protocol PN083-02) was a randomized, open-label, UK-based clinical trial in HCV GT3-infected participants with compensated cirrhosis (**Figure 2**)
- Adults with chronic HCV GT3 infection were included
  - Compensated liver cirrhosis defined by liver biopsy (METAVIR F4) or transient elastography (>12.5 kPa)
  - Treatment-naive, experienced to peginterferon/RBV, monoinfected or HIV co-infected
- All participants received EBR 50 mg/GZR 100 mg + SOF (400 mg as per prescribing information) ± RBV 800-1400 mg/day
  - Treatment-naive participants were treated for 8 or 12 weeks
  - Treatment-experienced participants were treated for 12 or 16 weeks
    - Randomization of treatment-experienced participants was stratified based on prior relapse vs nonrelapse (partial, null, interferon-intolerant)
  - Target enrollment was 25 participants per arm
  - The primary endpoint was SVR 12 weeks after completion of therapy (SVR12, HCV RNA <15 IU/mL [cobas® TaqMan® v2.0])
    - SVR 24 weeks after completion of therapy (SVR24) was assessed as a secondary endpoint
    - SVR12 data were presented at The Liver Meeting® 2016[12]; this presentation provides the final SVR24 data
- Efficacy analysis population
  - Full analysis set (FAS) included all participants who received ≥1 dose of study drug
  - Modified FAS (mFAS) excluded participants who discontinued for reasons unrelated to the treatment regimen, including discontinuation for non–drug-related AEs
- Resistance analysis was performed using next-generation sequencing: detection limit for variants of ≈1% or ≈15% prevalence
  - Resistance analysis population included all participants who had baseline sequencing available and a treatment outcome of either SVR12 or virologic failure
  - NS3 polymorphisms at positions 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, or 175
  - NS5A polymorphisms at positions 24, 28, 30, 31, 32, 38, 58, 62, 92, or 93
  - NS5B polymorphisms at positions 96, 142, 159, 282, 289, 316, 320, or 321

### Figure 2. Study design




FW, follow-up week; TW, treatment week.
†The primary endpoint was HCV RNA <15 IU/mL at FW12 (SVR12). SVR24 was assessed as a secondary endpoint.

## Results

### Demographics and Characteristics

- 100 participants with HCV GT3 infection and compensated cirrhosis were enrolled (**Table 1**)

### Table 1. Participant demographics

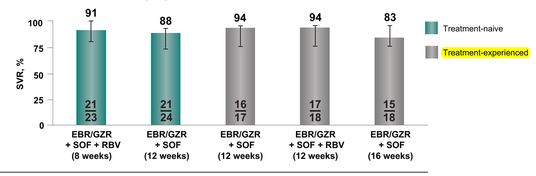
| | Cirrhotic GT3-infected participants (n = 100) |
|---|---|
| Male, n (%) | 68 (68) |
| Race, n (%) | |
| Asian | 29 (29) |
| White | 69 (69) |
| Other | 2 (2) |
| Age, years, mean (SD) | 53.4 (8.7) |
| BMI ≥30 kg/m$^2$, n (%) | 28 (28) |
| Cirrhosis diagnosis method | |
| Liver biopsy, n (%) | 16 (16) |
| FibroScan®, n (%) | 84 (84) |
| FibroScan® score, kPa, mean (SD) | 25.4 (12.1) |
| Prior treatment history, n (%) | |
| Naive | 47 (47) |
| PR-experienced | 53 (53) |
| HCV RNA $\log_{10}$, IU/mL, mean (SD) | 6.2 (0.7) |
| *IL28B* CC, n (%) | 50 (50) |
| Albumin, g/dL, mean (SD) | 3.6 (1.2) |
| ALT IU/L, median (range) | 94 (21-389) |
| Total bilirubin, mg/dL, mean (SD) | 0.7 (0.4) |
| Platelets × 10$^3$ cells/μL, median (range) | 138 (46-396) |
| Platelet count <100 × 10$^3$ cells/μL, n (%) | 24 (24) |

ALT, alanine aminotransferase; BMI, body mass index; PR, peginterferon/ribavirin; SD, standard deviation.

### Virologic Response

- In the FAS, SVR24 was achieved by 91% and 88% of treatment-naive participants treated for 8 and 12 weeks, respectively (**Figure 3**)
- SVR24 was achieved by 94%, 94% and 83% of treatment-experienced participants treated for 12 or 16 weeks
  - Two participants experienced virologic failure, both relapses in the 8-week treatment arm, with virologic recurrence prior to follow-up week (FW)12. There were no virologic failures after FW12
  - One participant discontinued treatment due to the drug-related adverse event (AE) of cellulitis
  - Seven participants were lost to follow-up: 2 prior to FW12 and 5 between FW12 and FW24

### Figure 3. SVR24 in the FAS population

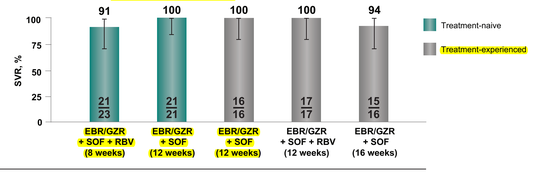



| | | | | | |
|---|---|---|---|---|---|
| **Relapse** | | | | | |
| EOT to FW12 | 2 | 0 | 0 | 0 | 0 |
| FW12 to FW24 | 0 | 0 | 0 | 0 | 0 |
| **Nonvirologic failure†** | | | | | |
| Prior to FW12 | 0 | 1 | 0 | 1 | 1‡ |
| FW12 to FW24 | 0 | 2 | 1 | 0 | 2 |

EOT, end of treatment.
†All lost to follow-up or consent withdrawn, except 1 participant‡ who discontinued treatment due to a drug-related AE.

- In the mFAS, SVR24 was achieved by 100% of treatment-naive and -experienced participants receiving EBR/GZR + SOF for 12 weeks (**Figure 4**)

### Figure 4. SVR24 in the mFAS population




| | | | | | |
|---|---|---|---|---|---|
| **Relapse** | | | | | |
| EOT to FW12 | 2 | 0 | 0 | 0 | 0 |
| FW12 to FW24 | 0 | 0 | 0 | 0 | 0 |
| **Discontinued due to AE** | 0 | 0 | 0 | 0 | 1 |
| **Excluded from mFAS analysis†** | 0 | 3 | 1 | 1 | 2 |

†All lost to follow-up or consent withdrawn.

- Two participants relapsed (**Table 2**)
  - At baseline, participant 1 had Y93H, P58S, and S62T present in 44%, 99% and 62% of the viral population, suggesting these 3 RASs were linked within the same virus

### Table 2. Relapse participants

| Participant | Treatment history | Treatment regimen | Time of relapse | NS5A RAVs | |
|---|---|---|---|---|---|
| | | | | Baseline | Failure |
| 1 | Naive | EBR/GZR + SOF + RBV (8 weeks) | FW4 | Y93H, P58S, S62T | P58S, S62T |
| 2 | Naive | EBR/GZR + SOF + RBV (8 weeks) | FW8 | WT | WT |

### Nonvirologic Failures

- Eight participants had nonvirologic failure (**Table 3**)

### Table 3. Nonvirologic failures

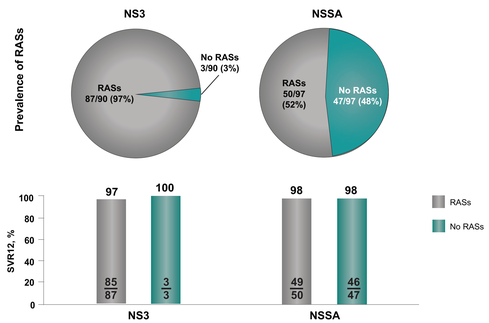
| Participant | Treatment history | Treatment regimen | Reason for discontinuation |
|---|---|---|---|
| Prior to FW12 | | | |
| 1 | Naive | EBR/GZR + SOF (12 weeks) | LTFU after TW2 |
| 2 | Experienced | EBR/GZR + SOF + RBV (12 weeks) | Withdrew consent after day 7 |
| 3 | Experienced | EBR/GZR + SOF (16 weeks) | Discontinued after day 7 due to cellulitis |
| Between FW12 and FW24 | | | |
| 4 | Naive | EBR/GZR + SOF (12 weeks) | LTFU/withdrew consent |
| 5 | Naive | EBR/GZR + SOF (12 weeks) | LTFU/withdrew consent |
| 6 | Experienced | EBR/GZR + SOF (12 weeks) | LTFU/withdrew consent |
| 7 | Experienced | EBR/GZR + SOF (16 weeks) | LTFU/withdrew consent |
| 8 | Experienced | EBR/GZR + SOF (16 weeks) | LTFU/withdrew consent |

LTFU, lost to follow-up.

### Resistance analyses

- The presence of baseline NS3 or NS5A RASs had no impact on SVR12 (**Figure 5**)

### Figure 5. Prevalence and impact on SVR12 of NS3 and NS5A RASs




Next-generation sequencing: detection limit for variants of 15% prevalence.

- Based on next-generation sequencing with a detection limit of 1%, 9 participants had Y93 RASs present at baseline (**Table 4**)
  - Four participants had Y93 present in ≥11% of the circulating viral population

### Table 4: Presence of Y93 RASs at baseline (next-generation sequencing 1%)

| Participant | Treatment history | Treatment | Y93H in viral population (%) | Other NS5A RASs (% in total viral population) | Treatment outcome |
|---|---|---|---|---|---|
| 1 | TN | EBR/GZR + SOF + RBV for 8 weeks | 1 | A30V (2) | SVR12 |
| 2 | TN | EBR/GZR + SOF + RBV for 8 weeks | 44 | P58S (99); S62A (3) S62T (62) | Relapse |
| 3 | TN | EBR/GZR + SOF for 12 weeks | 87 | A30L (7); A30S (5) A30V (2); S62T (90) S621T (62) | SVR12 |
| 4 | TN | EBR/GZR + SOF for 12 weeks | 11 | A30M (14) | SVR12 |
| 5 | TE | EBR/GZR + SOF for 12 weeks | 2 | S62T (99) | SVR12 |
| 6 | TE | EBR/GZR + SOF + RBV for 12 weeks | 1 | A30V (1) | 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 + RBV for 12 weeks | 2 | P58T (1) | SVR12 |
| 9 | TE | EBR/GZR + SOF for 16 weeks | 7 | P58H (1); P58T (1) | SVR12 |

TE, treatment-experienced; TN, treatment-naive.

### Adverse events

- AEs are shown in **Table 5**

### Table 5. Adverse events

| | EBR/GZR + SOF + RBV 8 weeks (n = 23) | EBR/GZR + SOF 12 weeks (n = 41) | EBR/GZR + SOF + RBV 12 weeks (n = 18) | EBR/GZR + SOF 16 weeks (n = 18) |
|---|---|---|---|---|
| Drug-related AEs, n (%) | | | | |
| Fatigue | 3 (13.0) | 9 (22.0) | 9 (50.0) | 5 (27.8) |
| Nausea | 4 (17.4) | 4 (9.8) | 6 (33.3) | 3 (16.7) |
| Skin rash/pruritus | 2 (8.7) | 3 (7.3) | 8 (44.4) | 2 (11.1) |
| Serious AE (SAE), n (%)† | 0 | 1 (2.4) | 3 (16.7) | 1 (5.6) |
| Discontinued study medication due to AE, n (%)‡ | 0 | 0 | 0 | 1 (5.6) |
| Hemoglobin <10 g/dL, n (%)¶ | 0 | 1 (2.4) | 2 (11.1) | 0 |
| Total bilirubin >5× baseline, n (%) | 0 | 0 | 0 | 0 |
| ALT/AST >5× ULN, n (%) | 0 | 0 | 0 | 0 |

AST, aspartate aminotransferase; ULN, upper limit of normal.
†SAEs of lung infection, creatinine increased, chest pain, opiate overdose, and cellulitis were reported.
‡One participant had a drug-related SAE of vomiting on day 4 and then subsequently discontinued treatment at day 7 due to drug-related cellulitis.
¶Lowest hemoglobin level was 8.9 g/dL.

## Conclusions

- High efficacy of EBR/GZR was demonstrated in treatment-naive and -experienced cirrhotic HCV GT3-infected participants
  - In the mFAS analysis, SVR12 was 100% among participants receiving EBR/GZR + SOF for 12 weeks
  - There were no virologic failures among participants receiving EBR/GZR + SOF ± RBV for 12 or 16 weeks
- Treatment duration longer than 12 weeks is not needed
- High efficacy regardless of presence of baseline NS5A RASs or participant characteristics
- Generally safe and well tolerated

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## Acknowledgments

- We extend our gratitude to the participants, their families, investigators, and site personnel who participated in this study
- Medical writing assistance was provided by Tim Ibbotson, PhD, of ApotheCom (Yardley, PA, USA) and funded by Merck & Co., Inc., Kenilworth, NJ, USA.