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ORIGINAL ARTICLE

Efficacy and safety of elbasvir/grazoprevir in treatment-naive Chinese adults with hepatitis C virus infection: A randomized trial

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Abstract

Background and Aim: In China, clinical experience with direct-acting antiviral treatments for hepatitis C virus (HCV) infection is still emerging. C-CORAL is a phase 3, multinational, placebo-controlled, double-blind trial of elbasvir/grazoprevir (EBR/GZR) in participants with HCV infection from the Asia-Pacific region and Russia. Here, we report the data from participants enrolled in China.

Methods: Treatment-naive participants with chronic HCV genotype (GT) 1, GT4, or GT6 infection were randomly assigned to receive 50 mg EBR/100 mg GZR for 12 weeks (immediate-treatment group, ITG) or placebo followed by deferred treatment with EBR/GZR (deferred-treatment group, DTG). The primary efficacy end-point was sustained virologic response at 12 weeks after completing treatment (SVR12), and the primary safety end-point was a comparison of safety between participants receiving EBR/GZR and placebo (NCT02251990; Protocol PN-5172-067).

Results: A total of 152 participants in China were randomly assigned (ITG, n = 115; DTG, n = 37). SVR12 was achieved in 96.7% (146/151) participants overall and in 97.3% (142/146) of those with GT1b infection. Four participants relapsed (GT1b, n = 3; GT6a, n = 1). Drug-related AEs were reported in 25 (21.7%) and 9 (24.3%) participants receiving EBR/GZR and placebo, respectively; no drug-related serious adverse events (AEs) occurred. Two (1.7%) participants receiving EBR/GZR had late hepatic transaminase elevations. Patient-reported outcomes indicate improved quality of life at follow-up week 4 in participants receiving EBR/GZR compared to placebo.

Conclusion: EBR/GZR administered for 12 weeks represents a highly effective and safe treatment option for Chinese individuals with HCV GT1 infection.

Ming Xiang Zhang, Yan Huang, Mao Rong Wang, Shan Ming Wu, Ying Ren Zhao, and Zhan Sheng Jia declare that they have no competing interests.
Author contribution: All authors made substantial contributions to the conception and design of the study, the acquisition of data, or the analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Introduction

In China, nearly 9 million people have hepatitis C virus (HCV) infection, amounting to 0.8% of the total population.[1] In fact, there are more adults with HCV infection in China than in any other country worldwide, predominantly with HCV genotype (GT) 1b (57%), GT2 (15%), or GT3 (9%) infection.[1,2] While the use of direct-acting antiviral (DAA) regimens has dramatically improved the treatment of people with HCV infection, clinical experience with these therapies in China is still emerging, and to date, sofosbuvir, simeprevir, and the combinations of daclatasvir/asunaprevir and ombitasvir/dasabuvir plus paritaprevir/ritonavir have been approved in China.

Elbasvir (EBR) plus grazoprevir (GZR) is a once-daily fixed-dose combination treatment that is approved in many Western countries for the treatment of HCV GT1 and GT4 infection and in Japan for HCV GT1 infection.[3–5] EBR and GZR are potent antiviral agents in vitro[6–10] and were shown to be safe and effective in phase 2/3 clinical studies.[11–20] The safety profile of EBR/GZR was similar in participants with and without cirrhosis and was also similar to that seen in participants who received placebo treatment.[13,14,20] Notably, sustained virologic response (SVR) at 12 weeks after completing treatment (SVR12) was high in participants with HCV GT1b infection.[21]

The aim of the C-CORAL study was to assess the safety and efficacy of a 12-week regimen of EBR/GZR in participants with HCV infection from countries in the Asia-Pacific region and Russia. This publication describes the data from participants enrolled in mainland China.

Methods

The C-CORAL study was a placebo-controlled, randomized, double-blind, phase 3 study conducted at 49 centers in mainland Russia (15), China (13), Taiwan (7), South Korea (6), Vietnam (3), Thailand (3) and Australia (2) (Appendix 1). Data from participants enrolled outside China have been reported separately.[22] This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines (ClinicalTrials.gov Identifier: NCT02251990). The protocol was reviewed and approved by institutional review boards or ethics committees at each institution and is available online as a supplementary file (Protocol PN-5172-067). All participants provided informed consent prior to any study-related procedures. The study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Participants. Participants aged ≥18 years with chronic HCV GT1, GT4, or GT6 infection and baseline HCV RNA ≥10 000 IU/mL were enrolled at 13 study sites in China. Treatment-naive persons with and without cirrhosis were eligible, with cirrhosis defined based on liver biopsy (METAVIR F4 within 24 months of enrollment), FibroScan® (a reading of >12.5 kPa within 12 months of enrollment), or a combination of FibroTest® (>0.75) and aspartate aminotransferase (AST):platelet ratio index (>2). Participants with evidence of human immunodeficiency virus (HIV) coinfection, chronic hepatitis B infection, or evidence of decompensated liver disease were excluded.

Study design. Participants were randomly assigned in a 3:1 ratio to receive immediate or deferred treatment with EBR/GZR. Participants in the immediate-treatment group (ITG) received once-daily 50 mg EBR/100 mg GZR for 12 weeks. Participants in the deferred-treatment group (DTG) received once-daily placebo for 12 weeks followed by a 4-week blinded follow-up period and then open-label EBR/GZR for 12 weeks.

A centrally located interactive voice response system/integrated web response system was used to perform randomization, and participant enrollment was stratified based on the presence or absence of cirrhosis and country of enrollment (China *vs* South Korea *vs* Taiwan *vs* Russia *vs* other). Participants, site personnel, and the sponsor were blinded through week 16, at which time treatment allocation was unblinded, and participants in the DTG received active therapy.

Procedures. Plasma HCV RNA levels were analyzed using the COBAS® AmpliPrep/COBAS® TaqMan® HCV test, version 2.0 (Roche Molecular Diagnostics, Branchburg, NJ, USA; lower limit of quantitation (LLoQ) = 15 IU/mL. HCV genotype was evaluated with the Abbott HCV Real Time Genotype II assay (Abbott Diagnostics, Chicago, IL, USA). HCV subtyping was determined for non-GT1b samples by a published template-independent next-generation sequencing assay.[23]

End-points. The primary efficacy end-point was SVR12, defined as the percentage of participants in the ITG with HCV RNA < LLoQ at 12 weeks after completion of treatment. Virologic failure was defined as nonresponse (HCV RNA > LLoQ

throughout treatment and at the end of treatment), rebound (>1 $\log_{10}$ increase in HCV RNA from nadir during treatment), breakthrough (HCV RNA > LLoQ after being < LLoQ during treatment), or relapse (HCV RNA > LLoQ during follow-up after having HCV RNA < LLoQ at end of treatment). SVR24 was evaluated as a secondary outcome. The primary safety outcome was a comparison of safety events between the ITG and DTG during the initial 12-week placebo-controlled period and up to 14 days after unblinding. Safety events recorded were adverse events (AEs), vital signs, and laboratory test results. Late elevations in alanine aminotransferase (ALT)/aspartate aminotransferase (AST) were defined as ALT/AST >5× the upper limit of normal (ULN) after treatment week (TW) 4 in participants with ALT/AST ≤ ULN between weeks 2 and 4. Drug resistance was evaluated in participants with virologic failure and HCV RNA >2000 IU/mL.

Health-related quality of life (HRQOL) was assessed at baseline, TW4, end of treatment, and follow-up week 4 using the Short Form-36v2 (SF-36v2®) survey,[24] the EuroQol-5D-5L (EQ-5D-5L),[25] and the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue Scale), Version 4.[26] The acute, 1-week recall version of the SF-36v2 was used to detect recent changes in health status. The SF-36v2 measures each of the following eight health domains: Role Limitations-Physical, Physical Functioning, Bodily Pain, Vitality, General Health, Social Functioning, Mental Health, and Role Limitations-Emotional, which contribute to the computation of the mental and physical component summaries (MCS and PCS, respectively). The EuroQol EQ-5D-5L is a validated, standardized 5-item health-state questionnaire (self-care, mobility, usual activities, anxiety/depression, and pain/discomfort), in which participants rate their current general state of health, from "the worst health you can imagine" to "the best health you can imagine" using a graded (0–100) visual analog scale (EQ VAS). The FACIT-Fatigue Scale is a 13-item self-report questionnaire using a 5-point Likert-type response scale to measure fatigue (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a bit; and 4 = Very Much), with a recall period of "during the past 7 days."

Statistical analysis. The planned enrollment was 453 participants from Russia and the Asia-Pacific region, with a prespecified interim analysis planned for participants enrolled in the ITG at centers outside China. The study was not powered for an assessment of efficacy in the China cohort. Overall enrollment of participants in China was not to exceed 10% of the target. A total of 250 participants were randomly assigned to the ex-China ITG, leaving a maximum of 124 Chinese participants to be enrolled.

The full analysis set population (FAS, all randomly assigned participants who received ≥1 dose of study treatment) was used for the primary efficacy analysis. A two-sided 95% asymptotic confidence interval (CI) was calculated for SVR12 in the ITG. Evaluation of safety events was performed in all participants who received ≥1 dose of study drug.

Descriptive summary statistics are provided for change in HRQOL scores from baseline. Analyses were based on the FAS population, missing data were not imputed, and no multiplicity adjustment was applied.

Results

A total of 180 participants were screened in China, of whom 27 failed screening and 1 withdrew prior to randomization. The

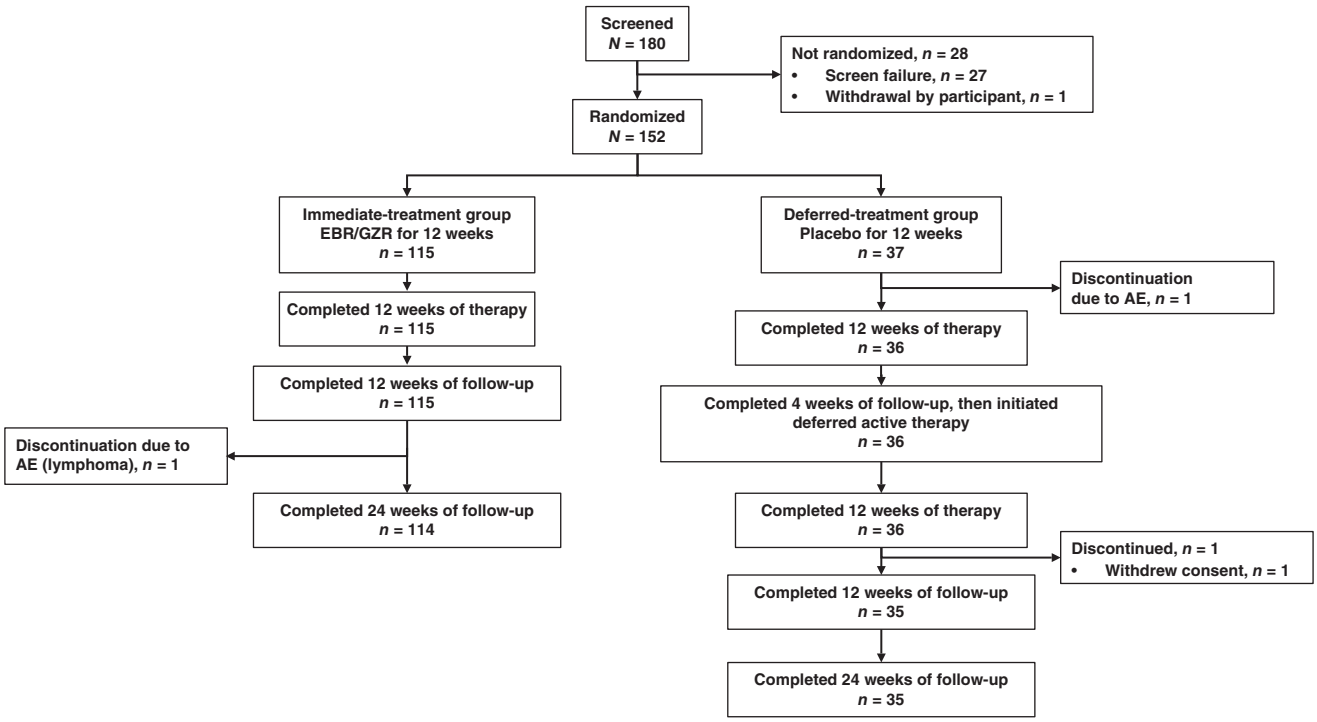


Figure 1 Participant disposition. AE, adverse event; EBR, elbasvir; GZR, grazoprevir.

Table 1 Baseline demographics

Characteristic	ITG EBR/GZR 12 weeks (*n* = 115)	DTG placebo for 12 weeks (*n* = 37)	All participants (*N* = 152)
Gender, *n* (%)			
Male	55 (47.8)	17 (45.9)	72 (47.4)
Female	60 (52.2)	20 (54.1)	80 (52.6)
Age, years			
Mean (SD)	44.4 (13.6)	43.5 (14.1)	44.1 (13.7)
Median (range)	46.0 (20–77)	45.0 (22–76)	45.0 (20–77)
Race, *n* (%)			
Asian	115 (100.0)	37 (100.0)	152 (100.0)
HCV genotype, *n* (%)			
GT1b	106 (92.2)	35 (94.6)	141 (92.8)
GT1-other	5 (4.3)	1 (2.8)	6 (4.0)
GT6*	4 (3.5)	1 (2.8)	5 (3.3)
BMI, *n* (%)			
<30 kg/m^2	109 (94.8)	35 (94.6)	144 (94.7)
≥30 kg/m^2	6 (5.2)	2 (5.4)	8 (5.3)
Baseline HCV RNA, *n* (%)			
≤800 000 IU/mL	32 (27.8)	9 (24.3)	41 (27.0)
>800 000 IU/mL	83 (72.2)	28 (75.7)	111 (73.0)
≤2 000 000 IU/mL	59 (51.3)	16 (43.2)	75 (49.3)
>2 000 000 IU/mL	56 (48.7)	21 (56.8)	77 (50.7)
≤10 000 000 IU/mL	111 (96.5)	36 (97.3)	147 (96.7)
>10 000 000 IU/mL	4 (3.5)	1 (2.7)	5 (3.3)
IL28B genotype (rs12979860)			
CC	89 (77.4)	29 (78.4)	118 (77.6)
Non-CC	26 (22.6)	7 (18.9)	33 (21.7)
Missing	0 (0)	1 (2.7)	1 (0.6)
METAVIR stage, *n* (%)			
F0–F2	85 (73.9)	27 (73.0)	112 (73.7)
F3	10 (8.7)	4 (10.8)	14 (9.2)
F4	20 (17.4)	6 (16.2)	26 (17.1)
Cirrhosis†, *n* (%)			
Yes	20 (17.4)	6 (16.2)	26 (17.1)
By biopsy	3 (2.6)	0 (0)	3 (2.0)
By FibroScan	17 (14.8)	6 (16.2)	23 (15.1)
No	95 (82.6)	31 (83.8)	126 (82.9)
By biopsy	24 (20.9)	9 (24.3)	33 (21.7)
By FibroTest	1 (0.9)	0 (0)	1 (0.7)
By FibroScan	70 (60.9)	22 (59.5)	92 (60.5)
Hemoglobin, mean (SD), g/dL	14.3 (1.5)	14.3 (1.7)	14.3 (1.5)
Albumin, mean (SD), g/dL	4.78 (0.33)	4.84 (0.34)	4.80 (0.33)
Bilirubin, mean (SD), g/dL	0.75 (0.38)	0.76 (0.27)	0.75 (0.36)

*All five HCV GT6 samples were subtyped as HCV GT6a by template-independent next-generation sequencing assay.

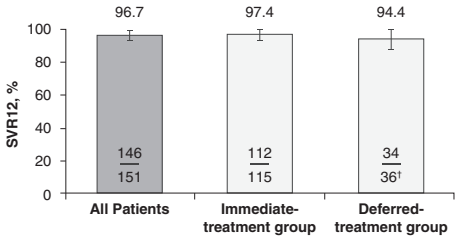
†A total of 27 participants in the ITG had liver fibrosis stage based on liver biopsy. The majority of participants in the ITG (*n* = 87) had fibrosis stage assigned based on transient elastography: FibroScan scores <8.0 kPa were interpreted as F0–F2 fibrosis, scores of 8.0–12.5 kPa were considered METAVIR F3 fibrosis, and scores >12.5 kPa were interpreted as METAVIR F4.

Data are *n* (%) unless otherwise indicated.

BMI, body mass index; DTG, deferred-treatment group; EBR, elbasvir; GT, genotype; GZR, grazoprevir; HCV, hepatitis C virus; ITG, immediate-treatment group; IU, international units; SD, standard deviation.

remaining 152 participants were randomly assigned (ITG, *n* = 115; DTG, *n* = 37) (Fig. 1). The first participant started treatment on 18 March 2016, and the last participant in the ITG completed 12 weeks of follow-up on 27 September 2016. All participants in the ITG completed 12 weeks of treatment and 12 weeks of follow-up. One participant in the ITG discontinued between follow-up week (FW) 12 and FW24 owing to an AE of lymphoma. Of the 37 participants randomly assigned to the DTG, one discontinued during placebo treatment because of an AE, and a second participant withdrew consent after completing 12 weeks of active deferred therapy (Fig. 1).

Most participants had GT1b infection (96.7%, 147/152) and had F0–F2 fibrosis (73.7%, 112/152) (Table 1). Approximately half of all enrolled participants had baseline HCV RNA



Non-SVR12, *n*	5	3	2
Relapse	4	3	1
Lost to follow-up	1	0	1‡

Figure 2 Sustained virologic response at 12 weeks after completion of treatment. EBR, elbasvir; GZR, grazoprevir; SVR12, sustained virologic response at 12 weeks after completion of treatment. †One participant in the deferred-treatment group discontinued from the study owing to an adverse event during the initial placebo treatment phase and did not enter the deferred EBR/GZR active treatment phase. ‡One participant in the deferred-treatment group completed treatment during the active treatment phase and was lost to follow-up.

>2 000 000 IU/mL (50.7%, 77/152). Overall, 23 of 26 participants with cirrhosis had their fibrosis stage diagnosed by FibroScan®.

Efficacy

In the FAS population, the SVR12 rate was 96.7% (146/151), with similar rates achieved in the ITG (97.4%, 112/115) and DTG (94.4%, 34/36) (Fig. 2). SVR12 was achieved by 97.1% (136/140) and 80% (4/5) of participants with HCV GT1b and GT6a infection, respectively. Six participants did not achieve SVR12, including one participant in the DTG who discontinued during placebo treatment because of AEs of chest discomfort, headache, and oral hypoesthesia. This participant did not receive a dose of EBR/GZR and was excluded from the FAS population for efficacy analyses. Five participants in the FAS population failed to achieve SVR12. One participant from the DTG withdrew consent after completing 12 weeks of active therapy, and four participants relapsed (ITG, n = 3 [GT1b, n = 2; GT6, n = 1]; DTG, n = 1 [GT1b, n = 1]). All relapses occurred prior to FW12, and no virologic failures occurred between FW12 and FW24. SVR12 rates were high in most subgroups evaluated, including 88.5% (23/26) in participants with cirrhosis, 94.7% (72/76) in participants with baseline viral load >2 000 000 IU/mL, and 85.7% (5/6) in participants aged ≥65 years (Fig. 3).

Of 140 participants with HCV GT1b infection in the FAS, one withdrew, and the remaining 139 were eligible for inclusion in the resistance analysis. Of 139 participants, 35 (25.2%) had at least one baseline NS5A resistance-associated substitution (RAS) at amino acid position 28, 30, 31, or 93, of whom 32 achieved SVR12 (91.4%). All 104 participants with HCV GT1b infection and no baseline NS5A RASs at positions 28, 30, 31, or 93 achieved SVR12. Three participants with HCV GT1b infection relapsed. All had a baseline NS5A RAS at position 93 and were selected for either 28 M, 31 I, or 31 M at failure. The participant with HCV GT6 who relapsed had no identified baseline NS5A RAS and no treatment-emergent NS5A RAS at failure.

The only difference between virologic outcomes at FW12 and FW24 (i.e. SVR12 and SVR24) was a single participant in the ITG who discontinued between FW12 and FW24 with an AE of lymphoma. Thus, SVR24 was achieved by 96.0% of participants (145/151).

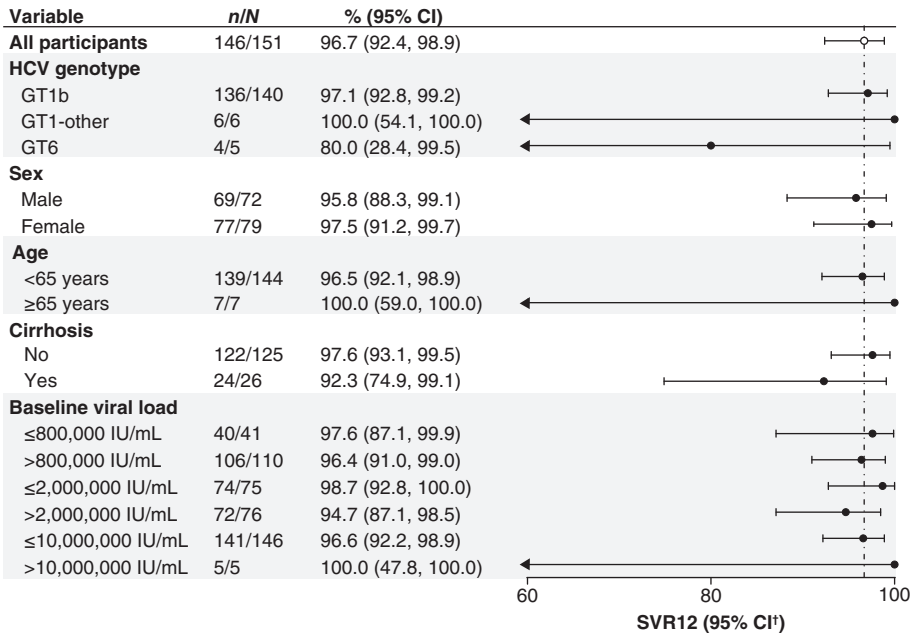


Figure 3 SVR12 subgroup analyses. CI, confidence interval; GT, genotype; HCV, hepatitis C virus; IU, international unit; SVR12, sustained virologic response at 12 weeks after completion of treatment. †Asymptotic CI for proportion.

Table 2 Summary of adverse events

	ITG EBR/GZR for 12 weeks (*n* = 115)	DTG Placebo for 12 weeks (*n* = 37)	DTG EBR/GZR for 12 weeks (*n* = 36)
Any AE, *n* (%)	59 (51.3)	18 (48.6)	14 (38.9)
Upper respiratory tract infection	9 (7.8)	4 (10.8)	6 (16.7)
Dizziness	8 (7.0)	1 (2.7)	1 (2.8)
Fatigue	8 (7.0)	1 (2.7)	0 (0)
Diarrhea	6 (5.2)	4 (10.8)	0 (0)
AST increased	2 (1.7)	4 (10·8)	1 (2.8)
Chest discomfort	0 (0)	4 (10.8)	0 (0)
Drug-related AE, *n* (%)	25 (21.7)	9 (24.3)	3 (8.3)
SAE, *n* (%)	3 (2.6)	1 (2.7)	0 (0)
Discontinued due to AE, *n* (%)	0 (0)	1 (2.7)	0 (0)
Death, *n* (%)	0 (0)	0 (0)	0 (0)
Tier 1 AE, *n* (%)			
First instance of ALT or AST >500 IU/L	0 (0)	0 (0)	0 (0)
First instance of ALT or AST >3× baseline and >100 IU/L	2 (1.7)	2 (5.4)	0 (0)
First instance of alkaline phosphatase >3× ULN	0 (0)	0 (0)	0 (0)
ALT, *n* (%)			
1.1–2.5× baseline	4 (3.5)	19 (51.4)	0 (0)
>2.5–5.0× baseline	0 (0)	1 (2.7)	0 (0)
>5.0× baseline	1 (0.9)	1 (2.7)	0 (0)
AST, *n* (%)			
1.1–2.5× baseline	5 (4.3)	14 (37.8)	1 (2.8)
>2.5–5.0× baseline	1 (0.9)	2 (5.4)	0 (0)
>5.0× baseline	2 (1.7)	0 (0)	0 (0)
Bilirubin, *n* (%)			
>2.5–5.0× baseline	4 (3.5)	0 (0)	0 (0)
>5.0–10.0× baseline	0 (0)	0 (0)	0 (0)
>10.0× baseline	0 (0)	0 (0)	0 (0)

Data are *n* (%) unless otherwise indicated.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DTG, deferred-treatment group; EBR, elbasvir; GT, genotype; GZR, grazoprevir; HCV, hepatitis C virus; ITG, immediate-treatment group; ULN, upper limit of normal.

Safety

EBR/GZR was generally well tolerated, with a safety profile similar to that of placebo (Table 2). The incidence of AEs was similar in participants receiving EBR/GZR and those receiving placebo (DTG-placebo; 51.3% *vs* 48.6%, respectively). The most common AEs in participants receiving EBR/GZR and placebo, respectively, were upper respiratory tract infection (7.8% *vs* 10.8%), diarrhea (5.2% *vs* 10.8%), fatigue (7.0% *vs* 2.7%), and dizziness (7.0% *vs* 2.7%). Drug-related AEs were reported in 25 (21.7%) participants receiving EBR/GZR in the ITG and 9 (24.3%) of those receiving placebo in the DTG; the most common were diarrhea (3.5% *vs* 8.1%) and fatigue (5.2% *vs* 2.7%). Serious AEs (SAEs) were reported by three participants (2.6%) in the ITG (Evans syndrome, lymphoma, and enteritis) and one participant (2.7%) receiving placebo in the DTG (foot fracture). All were considered unrelated to study drug. No deaths or drug-related SAEs occurred in either treatment arm. One participant in the DTG receiving placebo discontinued treatment owing to AEs of chest discomfort, headache, and oral hypoesthesia, which were considered drug-related and not serious.

Four hepatic laboratory events of clinical interest (ECIs) were reported, two each in the ITG (1.7%, 2/115) and the placebo phase of the DTG (5.4%, 2/37). Both hepatic ECIs in the ITG were late ALT/AST elevations (>5× ULN after TW4, after having a normal ALT between TW2 and TW4), and in both participants, ALT/AST levels returned to within normal limits during treatment or soon after treatment was completed. Narratives for these participants are provided in Appendix 2. Neither of these participants had concomitant increased bilirubin levels or discontinued study medication because of the protocol-specified stopping rule for hepatic laboratory abnormalities. No other hepatic laboratory abnormalities or symptoms of hepatic impairment were reported. Overall, transaminase elevations that were attributed to EBR/GZR were infrequent and reversible and were unlikely to be accompanied by other laboratory abnormalities or clinical symptoms.

The safety profile of EBR/GZR for 12 weeks was also similar in participants in the DTG when receiving deferred EBR/GZR for 12 weeks. AEs were reported in 14 (38.9%) participants, and three participants reported a total of four drug-related AEs (ALT increased, AST increased, conjugated bilirubin increased, and blood bilirubin increased). None of these drug-

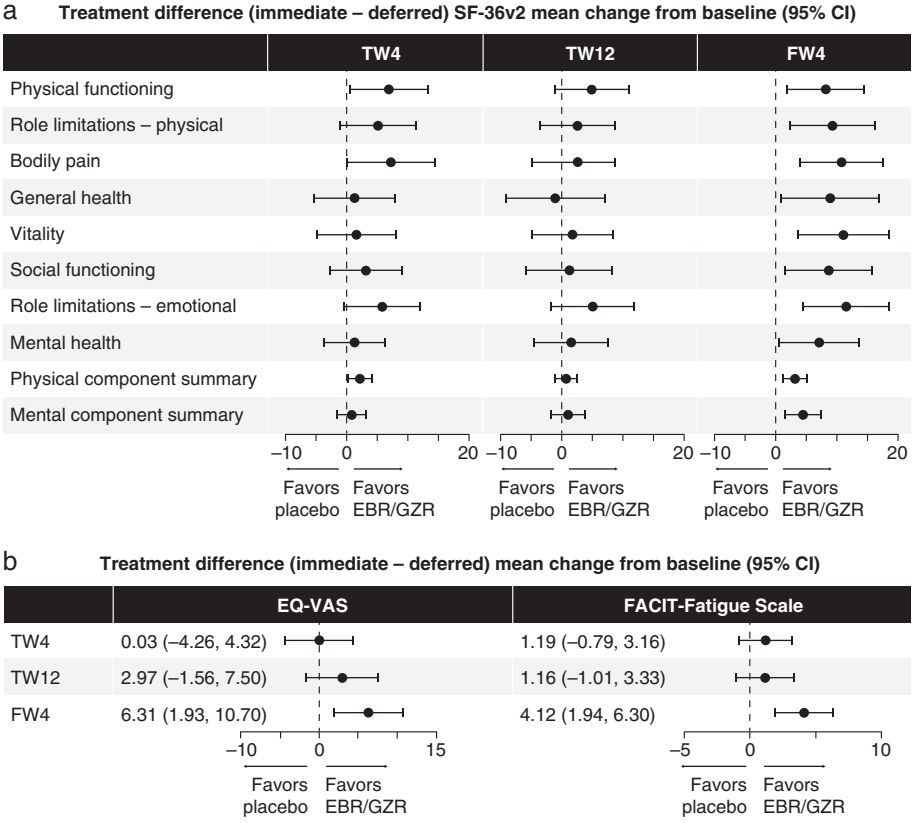


Figure 4 Differences in health-related quality of life between immediate (EBR/GZR) and deferred (placebo) treatment groups at treatment week 4, treatment week 12, and follow-up week 4 (prior to unblinding). Data represent treatment difference (immediate – deferred) mean change from baseline ± 95% CI in the (a) SF-36v2 and (b) EQ-VAS and FACIT-fatigue scale scores. CI, confidence interval; EBR, elbasvir; EQ-VAS, EuroQol-Visual Analog Scales; FACIT-Fatigue Scale, Functional Assessment of Chronic Illness Therapy-Fatigue Scale; GZR, grazoprevir; SF-36v2, short-form 36 survey version 2; TW4, treatment week 4; TW12, treatment week 12; FW4, follow-up week 4.

related AEs met the criteria to be considered hepatic ECIs. No participant receiving deferred active therapy discontinued treatment, and no SAEs or deaths occurred.

Health-related quality of life

At baseline, SF36v2 scores were similar in participants receiving EBR/GZR and those receiving placebo (Supplementary Fig. 1A). Baseline scores were numerically higher (indicating better quality of life) in the DTG-placebo compared with the ITG in all domains, except the General Health domain. The difference in mean change from baseline between ITG and DTG-placebo (immediate – deferred) at TWs 4 and 12 suggested no consistent improvement in any domain, with 95% CIs for mean differences including zero for all domains (Fig. 4a). At FW4, differences in mean change from baseline suggested improvements in patients treated with EBR/GZR compared with placebo. Participants receiving EBR/GZR showed mean improvements of between 7.1% and 11.0% at FW4 compared with change from baseline in placebo recipients for all eight individual domains and with 95% CIs that did not include zero. PCS and MCS scores also showed improvements in HRQOL in EBR/GZR recipients of 3–4% relative to placebo recipients and again with 95% CIs that did not include zero.

Baseline scores on the EQ-VAS and FACIT-Fatigue scale were similar in the ITG and DTG-placebo (Supplementary Fig. 1B). A similar profile of response was also seen with the EQ-VAS and FACIT-Fatigue scale, with the difference in mean change from baseline (ITG – DTG) at TW4 and TW12 showing no difference between treatment groups but with both scales also showing notable improvements in quality of life in participants receiving EBR/GZR compared with placebo at FW4. At FW4, treatment difference (ITG – DTG) mean change from baseline was 6.31% (95% CI, 1.93%, 10.70%) for the EQ-VAS and 4.12% (95% CI, 1.94%, 6.30%) for the FACIT-Fatigue scale, indicating benefits associated with EBR/GZR therapy in terms of general health and fatigue.

Discussion

EBR/GZR is a safe and effective treatment option for people with HCV GT1 or GT4 infection in many countries worldwide. The results from the present study confirm that EBR/GZR also represents an effective treatment option for treatment-naive Chinese patients with HCV GT1 infection. In this study, the SVR12 rate was 96.7% overall and 97.3% in those with GT1b

infection. Baseline characteristics, such as presence of cirrhosis and high baseline viral load, had no impact on SVR12. The safety profile of EBR/GZR in the present study was also generally comparable to the safety profile in studies in Western regions that included a deferred-treatment arm.[13,19,20] Finally, patient-reported outcomes data indicate improved HRQOL in patients receiving EBR/GZR compared with placebo at 4 weeks after completion of therapy. Given the very high rates of SVR among participants in the ITG receiving EBR/GZR (compared with no participants in the DTG receiving placebo), these improvements in HRQOL are likely a reflection of clearance of HCV.

In the United States and Europe, testing for resistance variants at baseline is not required in people with HCV GT1b infection starting treatment with EBR/GZR.[3–5] This practice is supported by data from an integrated analysis of participants with GT1b infection who were enrolled in the phase 2/3 clinical studies of EBR/GZR.[21] In this analysis of 1070 participants with GT1b infection (of whom 462 [43.2%] were Asian), the overall SVR12 rate was 97.2% (1040/1070), with rates of 99.6% (820/823) in those with no baseline NS5A RASs at amino acid position 28, 30, 31, or 93 and 94.7% (215/227) in those with baseline NS5A RASs. Similarly, in the analysis of participants from the C-CORAL study enrolled in countries outside China, SVR rates were high in participants with GT1b infection with and without baseline NS5A RASs (97.4% [38/39] *vs* 100% [146/146]).[22] The high rates of SVR12 (97.3%) reported in Chinese participants with HCV GT1b infection in the present study are consistent with rates in previous analyses in individuals with HCV GT1b infection.

The present study did not enroll people with previous treatment experience, and the numbers of participants with HCV genotypes other than GT1b were low. In Western countries, the efficacy and safety of EBR/GZR has been established comprehensively only in people with HCV GT1 or GT4 infection. Most participants in the present study also had mild liver disease, and only 17% had well-compensated Child-Pugh A cirrhosis. Few participants underwent biopsy, and in most, cirrhosis was identified using transient elastography. Although transient elastography scores are known to correlate well with cirrhosis, it is worth noting that there is also substantial overlap of liver stiffness values between adjacent fibrosis stages, particularly in individuals with milder fibrosis.[27] People with decompensated liver disease were not enrolled in this study. Studies in Western participants indicate high rates of SVR12 in those with compensated cirrhosis, possibly owing to the higher-than-normal plasma levels of GZR seen in people with cirrhosis.[28]

In conclusion, results from the C-CORAL study support the use of EBR/GZR for the treatment of HCV GT1 infection in treatment-naive individuals in China. Based on these results, the safety and efficacy profile of EBR/GZR appears consistent with that previously reported in Western populations[13] and Japanese people[29] with HCV GT1 or GT4 infection. These data also indicate that achieving SVR following treatment with EBR/GZR is associated with improved HRQOL.

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Data sharing statement

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA's data sharing policy, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Appendix S1. Supporting information.