Annals of Internal Medicine ORIGINAL RESEARCH

Grazoprevir–Elbasvir Combination Therapy for Treatment-Naive Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis C Virus Genotype 1, 4, or 6 Infection

A Randomized Trial

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Background: Novel interferon- and ribavirin-free regimens are needed to treat hepatitis C virus (HCV) infection.

Objective: To evaluate the safety and efficacy of grazoprevir (NS3/4A protease inhibitor) and elbasvir (NS5A inhibitor) in treatment-naive patients.

Design: Randomized, blinded, placebo-controlled trial. (ClinicalTrials.gov: NCT02105467)

Setting: 60 centers in the United States, Europe, Australia, Scandinavia, and Asia.

Patients: Cirrhotic and noncirrhotic treatment-naive adults with genotype 1, 4, or 6 infection.

Intervention: Oral, once-daily, fixed-dose grazoprevir 100 mg/elbasvir 50 mg for 12 weeks, stratified by fibrosis and genotype. Patients were randomly assigned 3:1 to immediate or deferred therapy.

Measurements: Proportion of patients in the immediate-treatment group achieving unquantifiable HCV RNA 12 weeks after treatment (SVR12); adverse events in both groups.

Results: Among 421 participants, 194 (46%) were women, 157 (37%) were nonwhite, 382 (91%) had genotype 1 infection, and 92 (22%) had cirrhosis. Of 316 patients receiving immediate treatment, 299 of 316 (95% [95% CI, 92% to 97%]) achieved SVR12, including 144 of 157 (92% [CI, 86% to 96%]) with genotype 1a, 129 of 131 (99% [CI, 95% to 100%]) with genotype 1b, 18 of 18 (100% [CI, 82% to 100%]) with genotype 4, 8 of 10 (80% [CI, 44% to 98%]) with genotype 6, 68 of 70 (97% [CI, 90% to 100%]) with cirrhosis, and 231 of 246 (94% [CI, 90% to 97%]) without cirrhosis. Virologic failure occurred in 13 patients (4%), including 1 case of breakthrough infection and 12 relapses, and was associated with baseline NS5A polymorphisms and emergent NS3 or NS5A variants or both. Serious adverse events occurred in 9 (2.8%) and 3 (2.9%) patients in the active and placebo groups, respectively (difference <0.05 percentage point [CI, −5.4 to 3.1 percentage points]); none were considered drug related. The most common adverse events in the active group were headache (17%), fatigue (16%), and nausea (9%).

Limitation: The study lacked an active-comparator control group and included relatively few genotype 4 and 6 infections.

Conclusion: Grazoprevir–elbasvir achieved high SVR12 rates in treatment-naive cirrhotic and noncirrhotic patients with genotype 1, 4, or 6 infection. This once-daily, all-oral, fixed-combination regimen represents a potent new therapeutic option for chronic HCV infection.

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Chronic hepatitis C virus (HCV) infection remains a growing cause of cirrhosis, hepatocellular carcinoma, hepatic decompensation, and liver transplantation (1). Effective therapy for HCV infection diminishes long-term liver-related complications and mortality (2). Convenient, oral, direct-acting antiviral regimens are being investigated for chronic HCV infection (3).

Grazoprevir is an NS3/4A protease inhibitor that has high potency in vitro against HCV genotype (GT) 1, GT2, GT4, GT5, and GT6 but is less active against GT3 (4). Grazoprevir retains substantial activity against resistance-associated variants (RAVs) commonly detected after failed therapy with first-generation protease inhibitors (4, 5). Elbasvir is an NS5A inhibitor active against GT1, GT2a, GT3, GT4, GT5, and GT6, even in the presence of RAVs associated with failure of other NS5A inhibitors, such as daclatasvir and ledipasvir (6, 7). Grazoprevir–elbasvir has been evaluated in an extensive phase 2 clinical development program (5, 8–10). The C-WORTHY study indicated that grazoprevir–elbasvir with or without ribavirin for 12 weeks provided efficacious and well-tolerated therapy for monoinfected and HIV–co-infected patients, treatment-naive and treatment-experienced patients, and noncirrhotic and cirrhotic patients (9, 10).

The objective of the phase 3 C-EDGE Treatment-Naive trial was to evaluate the efficacy and safety profile of a once-daily, fixed-dose, oral, 12-week regimen of grazoprevir–elbasvir without interferon or ribavirin in treatment-naive monoinfected patients with and without cirrhosis and with GT1, GT4, or GT6 infection.

Methods

Study Design

The C-EDGE Treatment-Naive study was an international, randomized, blinded, placebo-controlled, parallel-group trial of a fixed-dose combination of grazoprevir 100 mg/elbasvir 50 mg for treatment-naive cirrhotic and noncirrhotic patients with chronic HCV GT1, GT4, or GT6 infections. A historical SVR12 rate was used as the comparator for efficacy. A deferred-treatment group was included as a concurrent placebo

EDITORS' NOTES

Context

Various oral interferon- and ribavirin-free regimens are becoming available to treat chronic hepatitis C virus (HCV) infection. A grazoprevir–elbasvir combination regimen has shown promise in phase 2 trials.

Contribution

This phase 3 trial found a once-daily grazoprevir–elbasvir regimen to be effective and well-tolerated in patients with HCV genotype 1, 4, or 6 infection. Outcomes were similar in patients with and without cirrhosis.

Caution

The study did not include an active comparator, so how this regimen compares with others is unknown.

Implication

Grazoprevir–elbasvir represents a new therapeutic option for chronic HCV infection.

group to assess safety; after the follow-up period, placebo recipients received open-label grazoprevir–elbasvir so that all participants would receive therapy during the study.

Recruitment of Study Participants

Patients were recruited from general medical clinics at 60 trial centers: 4 in Australia, 4 in the Czech Republic, 5 in France, 5 in Germany, 5 in Israel, 3 in Puerto Rico, 3 in South Korea, 4 in Sweden, 3 in Taiwan, and 24 in the United States. Patients who fulfilled inclusion criteria were asked to participate in the trial. Selected clinical sites were experienced in the management and care of HCV-infected patients, with a history of successful study conduct and the capability for rapid enrollment. Sites were chosen to allow a wide geographic distribution and to ensure that requirements for minority representation, enrollment of patients with cirrhosis, and genotype distribution were met.

Eligibility Criteria

Adults (aged >18 years) with HCV RNA levels greater than 10^4 IU/mL were eligible. Hepatic fibrosis was staged by biopsy or noninvasive assessment (**Appendix 1**, available at www.annals.org) (11). Exclusion criteria were decompensated liver disease, hepatocellular carcinoma, HIV or hepatitis B virus co-infection, uncontrolled diabetes mellitus (hemoglobin A_{1c} level >10%), elevated prothrombin time unrelated to anticoagulation, creatinine clearance less than 50 mL/min, hemoglobin level less than 95 g/L, thrombocytopenia (platelet count <50 × 10^9 cells/L), aminotransferase levels more than 10 times the upper limit of normal, or hypoalbuminemia (albumin level <30 g/L). Enrollment was constrained to meet the following targets: 20% of the participants having cirrhosis and 15% having GT4 or GT6 infection. All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Independent ethics committees reviewed and approved the protocol and applicable amendments for each institution.

Randomization and Masking

After stratification by presence or absence of cirrhosis and GT1, GT4, or GT6, patients were randomly assigned in a 3:1 ratio to receive immediate or deferred therapy with grazoprevir–elbasvir through a central interactive voice-response system according to a computer-generated random allocation schedule. Patients took 1 fixed-dose combination tablet of grazoprevir–elbasvir (immediate-treatment group) or matching placebo (deferred-treatment group) once daily at approximately the same time, without regard to food, for 12 weeks. Patients, clinical site, and sponsor personnel were blinded to treatment assignment (except for a separate unblinded medical team that monitored virologic failures and serious adverse events). Four weeks after completion of therapy, treatment allocation was unblinded, and patients in the deferred-treatment group then received open-label grazoprevir–elbasvir for 12 weeks. All patients were to be followed for 24 weeks after cessation of active study therapy (**Figure 1**).

Outcome Measures

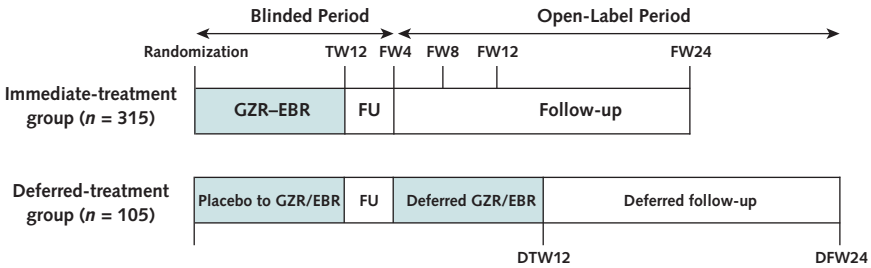
This report describes the efficacy among patients enrolled in the immediate-treatment group through 12 weeks after treatment and the safety findings among patients enrolled in both groups through 14 days after the end of therapy in the initial treatment period. Efficacy and safety results for both groups through follow-up week 24 are still being collected and will be presented in a future report. The primary efficacy outcome variable was the proportion of patients in the immediate-treatment group achieving unquantifiable HCV RNA 12 weeks after the end of study treatment (SVR12). Virologic failures encompassed breakthrough viremia (confirmed HCV RNA level at or above the lower limit of quantification [LLOQ] during treatment after previously being below the LLOQ) and relapse (confirmed HCV RNA level at or above the LLOQ subsequent to cessation of study therapy after becoming undetectable at the end of treatment).

Viral and Resistance Assays

Plasma HCV RNA levels were measured by the COBAS AmpliPrep/COBAS TaqMan HCV test, version 2.0 (Roche Molecular Diagnostics, Branchburg, NJ), with an LLOQ of 15 IU/mL. Specimens for viral load measurements were collected at screening; baseline; treatment weeks 4, 8, and 12; and follow-up weeks 4, 12, and 24.

Circulating viral quasi-species at baseline or at the time of virologic failure underwent population sequencing with a detection limit for variants of approximately 25% prevalence (12). The complete NS3 and NS5A genes were amplified from samples with RNA levels of 1000 IU/mL or greater by using reverse transcription polymerase chain reaction (5, 12, 13). Resultant amino acid sequences were compared with wild-

Figure 1. Diagram of study design.



DFW = deferred follow-up week; DTW = deferred-treatment week; FU = follow-up; FW = follow-up week; GZR-EBR = grazoprevir–elbasvir; TW = treatment week.

type GT1a (H77; accession number NC004102), GT1b (Con1; AJ238799), GT4a (ED43; GU814265), or GT6a (EUHK2; Y12083) reference sequences.

To assess the effect of baseline NS3 variants, specific amino acid loci prone to selection by early-generation NS3/4A protease inhibitors (positions 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, and 175) were studied in replicon cell lines encoding mutations in a GT1a backbone (5, 14). These substitutions were categorized according to whether they conferred a greater than 5-fold reduced susceptibility to grazoprevir. Likewise, to assess the effect of baseline NS5A variants, amino acid loci selected by NS5A inhibitors (positions 28, 30, 31, 58, and 93) were categorized according to whether they conferred a greater than 5-fold reduced susceptibility to elbasvir in the replicon assay.

Statistical Analysis

The C-EDGE Treatment-Naive study was designed to randomly assign approximately 400 patients, with 300 patients in the immediate-treatment group and 100 patients in the deferred-treatment group (which served as the placebo control group for the first 12 weeks). After a 4-week follow-up period, placebo recipients were unblinded at study week 16 and received open-label grazoprevir–elbasvir. The primary efficacy hypothesis exclusively applied to patients in the immediate-treatment group. Assuming a response rate of 85% or greater, the study had more than 99% power to demonstrate an SVR12 rate superior to the reference rate of 73% at an overall 1-sided α value of 0.025. The historical reference rate of 73% was derived from phase 3 trials of simeprevir/peginterferon + ribavirin in treatment-naive monoinfected patients, after adjustment for the expected proportion of cirrhotic patients and the anticipated improved tolerability with an interferon-free regimen (**Appendix 1**) (15, 16).

The primary efficacy and safety analyses were performed on the full data set, which included all patients receiving at least 1 dose of the study treatment. The primary efficacy end point was prespecified as the proportion of patients with an HCV RNA level below the LLOQ 12 weeks after the end of treatment (SVR12) (17). Missing outcome data were imputed as failures unless the values immediately before and after the missing result were both successes, in which case the absent value was imputed as a success. The 95% CIs were computed by the conservative Clopper–Pearson method, which provides an exact CI based on the binomial distribution (18). A *P* value was calculated to support the primary hypothesis based on a 1-sided exact test. Because only a single primary efficacy hypothesis was stipulated by protocol, no multiplicity adjustments were needed. Secondary efficacy analyses were intended as supportive, hypothesis-generating estimations.

Serious adverse events occurring at any time during the study, and other adverse events up until 14 days after cessation of treatment, were to be reported. Investigators assessed the relationship of each adverse event to study therapy; adverse events were counted as drug related if judged as at least possibly related to the study drug. Frequencies of adverse events with corresponding 95% CIs were calculated for the grazoprevir–elbasvir and placebo groups during the treatment period through the first 14 days of posttherapy follow-up (see **Appendix 1** for power calculations for differences in adverse-event frequencies between groups).

Role of the Funding Source

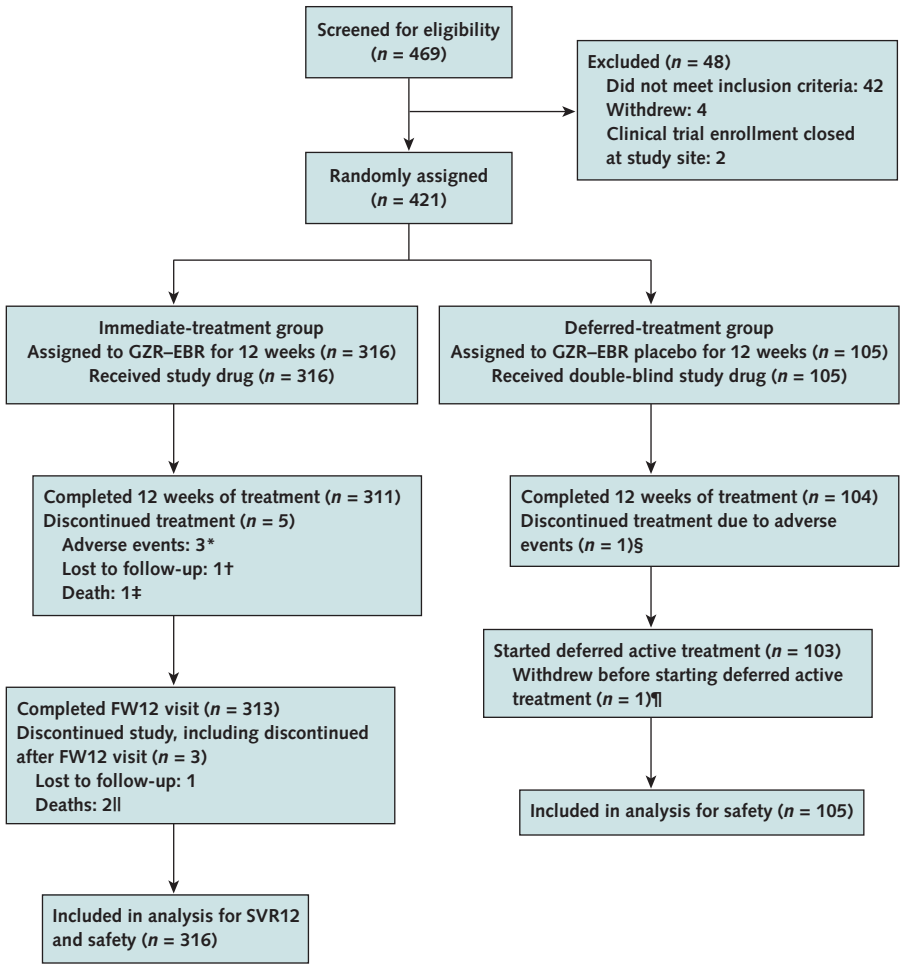
Merck is developing grazoprevir–elbasvir for treatment of HCV infection. The company contributed to the trial design, study execution and management, data collection, statistical analyses, and drafting of this report. The sponsor reviewed a penultimate version of the paper. All coauthors had access to the study data, approved the final report, and assume full responsibility for the veracity of the data and analyses. The lead/corresponding author had full access to all data and had final responsibility for the decision to submit the manuscript for publication.

RESULTS

Patient Accounting and Baseline Characteristics

Study enrollment began on 25 June 2014, and data collection for the primary efficacy end point concluded 4 March 2015. The study involved 60 centers in 9 countries on 4 continents. A total of 421 (90%) of 469 screened patients was enrolled and randomly as-

Figure 2. Study flow diagram.



FW12 = follow-up week 12; GZR–EBR = grazoprevir–elbasvir; SVR12 = sustained virologic response at 12 weeks after the end of treatment.
* Three patients in the immediate-treatment group discontinued use of the study drug because of adverse events. One patient discontinued use because of palpitations and anxiety on treatment day 4. Two patients had elevated liver aminotransferase levels: 1 at treatment week 8 and 1 at treatment week 10; they discontinued use of the study drug per protocol. Both remained in the study for follow-up and achieved SVR12.
† One patient in the immediate-treatment group was lost to follow-up after treatment week 6.
‡ One patient had virologic breakthrough at treatment week 8.
§ One patient in the deferred-treatment group discontinued use of the study drug on treatment day 10 because of a rash that developed on treatment day 2.
‖ Two patients in the immediate-treatment group died: 1 of an incarcerated hiatal hernia between treatment weeks 2 and 4 and 1 found dead after treatment but before follow-up week 4 (death presumed to be due to an arrhythmia from autopsy-documented coronary disease).
¶ One patient in the deferred-treatment group withdrew from the study after completing 12 weeks of placebo treatment but before receiving active study drug in the deferred active-treatment period.

signed; 316 and 105 patients received grazoprevir–elbasvir or placebo, respectively, during the initial treatment period (Figure 2). Overall, the median age was 54 years (range, 20 to 78 years); 46% of patients were women, 37% were nonwhite, and 91% had GT1 infections (50% of which were GT1a). Most patients enrolled from Australia, Sweden, and the United States had GT1a infections, whereas most patients from the Czech Republic and Taiwan and all patients from Israel and the Republic of Korea had GT1b infections (Appendix Table 1, available at www.annals.org). Most of the GT4-infected patients were enrolled from France and the United States, whereas most of the GT6-infected patients were enrolled from Taiwan and the United States. Baseline HCV RNA levels were greater than 800 000 IU/mL in 68% of patients. Of the 92 (22%) patients with cirrhosis, the diagnosis was biopsy proven in 26 (28%). The median platelet count and albumin level among cirrhotic patients were 124×10^9 cells/L (range, 49 to 298) and 41 g/L (range, 30 to 52), respectively (Table 1).

Efficacy Analysis

Viremia was rapidly suppressed with therapy (Appendix Table 2, available at www.annals.org). Of the 316 patients in the immediate-treatment group, 299 (95% [CI, 92% to 97%]) achieved SVR12. SVR12 rates were 92% (144 of 157 [CI, 86% to 96%]) in patients with

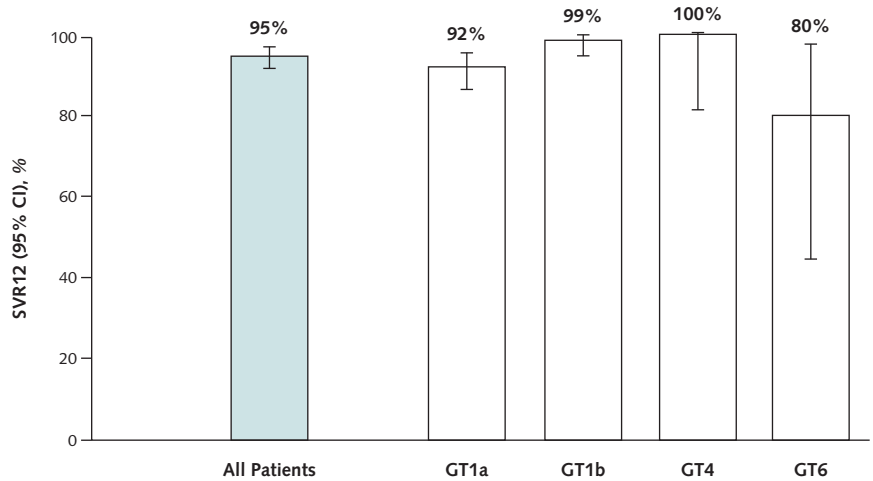
Table 1. Baseline Characteristics of Randomly Assigned Patients

Characteristic	Immediate-Treatment Group	Deferred-Treatment Group	Total
Patients, *n*	316	105	421
Age, *y*			
Mean (SD)	52.2 (11.1)	53.8 (11.2)	52.6 (11.2)
Median (range)	54 (20–78)	55 (22–76)	54 (20–78)
Sex, *n (%)*			
Male	171 (54)	56 (53)	227 (54)
Female	145 (46)	49 (47)	194 (46)
Country of enrollment, *n (%)*			
Australia	12 (3.8)	5 (4.8)	17 (4.0)
Czech Republic	23 (7.3)	5 (4.8)	28 (6.7)
France	24 (7.6)	11 (10.5)	35 (8.3)
Germany	29 (9.2)	5 (4.8)	34 (8.1)
Israel	17 (5.4)	5 (4.8)	22 (5.2)
South Korea	26 (8.2)	5 (4.8)	31 (7.4)
Sweden	17 (5.4)	7 (6.7)	24 (5.7)
Taiwan	21 (6.6)	4 (3.8)	25 (5.9)
United States (including Puerto Rico)	147 (46.5)	58 (55.2)	205 (48.7)
Self-identified race, *n (%)*			
Asian	54 (17)	13 (12)	67 (16)
Black	59 (19)	18 (17)	77 (18)
White	191 (60)	73 (70)	264 (63)
Other	12 (4)	1 (1)	13 (3)
Body mass index (SD), *kg/m²*	26.16 (5.00)	26.97 (5.82)	26.37 (5.22)
Baseline HCV RNA, geometric mean, log_{10} (SD), *IU/mL*	6.4 (6.5)	6.4 (6.5)	6.4 (6.5)
HCV genotype, *n (%)*			
1a	157 (50)	54 (51)	211 (50)
1b	131 (42)	40 (38)	171 (41)
4	18 (6)	8 (8)	26 (6)
6	10 (3)	3 (3)	13 (3)
IL28B* genotype, *n (%)			
CC	106 (34)	37 (35)	143 (34)
Non-CC	208 (66)	67 (64)	275 (65)
Missing	2 (0.6)	1 (1)	3 (0.7)
Screening HCV RNA, *n (%)*			
≤800 000 IU/mL	94 (30)	39 (37)	133 (32)
>800 000 IU/mL	222 (70)	66 (63)	288 (68)
Fibrosis stage, *n (%)*			
METAVIR F4 (cirrhosis)	70 (22)	22 (21)	92 (22)
METAVIR F3	36 (11)	14 (13)	50 (12)
METAVIR F0–F2	210 (67)	69 (66)	279 (66)
Laboratory values			
Mean baseline hemoglobin level (SD), *g/L*	142 (14)	142 (12)	142 (14)
Mean baseline albumin level (SD), g/L	4.3 (0.4)	4.3 (0.3)	4.3 (0.4)
Mean baseline ALT level (SD), *IU/L*	77 (62)	75 (64)	77 (62)
Mean baseline AST level (SD), *IU/L*	66 (48)	62 (50)	65 (48)
Mean baseline bilirubin level (SD)			
μmol/L	8.55 (5.13)	10.26 (6.84)	8.55 (6.84)
mg/dL	0.5 (0.3)	0.6 (0.4)	0.5 (0.4)
Mean baseline platelet count (SD), × 10^9 *cells/L*	190 (65)	194 (61)	191 (64)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HCV = hepatitis C virus.

GT1a infection, 99% (129 of 131 [CI, 95% to 100%]) in those with GT1b, 100% (18 of 18 [CI, 82% to 100%]) in those with GT4, and 80% (8 of 10 [CI, 44% to 98%]) in those with GT6 (Figure 3). SVR12 was achieved in 97% (68 of 70 [CI, 90% to 100%]) of cirrhotic patients and 94% (231 of 246 [CI, 90% to 97%]) of noncirrhotic patients. Subgroup analyses did not identify meaningful effects of age, sex, race, ethnicity, or *IL28B* genotype on treatment outcome. SVR12 was achieved in 100% of patients with baseline HCV RNA levels of 800 000 IU/mL or less, compared with 92% of patients with baseline HCV RNA levels greater than 800 000 IU/mL,

Figure 3. Rates of sustained virologic response at the primary end point (12 weeks after cessation of study therapy).



SVR12 (95% CI), *n/N*; %	299/316; 95% (92%–97%)	144/157; 92% (86%–96%)	129/131; 99% (95%–100%)	18/18; 100% (82%–100%)	8/10; 80% (44%–98%)
Lost to follow-up or discontinued early due to reasons other than virologic failure	4*	3	1	0	0
Virologic breakthrough	1	1	0	0	0
Virologic relapse	12	9	1	0	2

For intermittently missing data points, a success was imputed only if both values immediately before or after the missing value were successes. For this study, there were no intermittently missing SVR12 data, so no outcome was imputed as a success for the primary SVR12 end point based on the data analysis plan. There were 2 patients with SVR at 4 weeks after end of treatment imputed as successes, 1 patient with treatment week 4 imputed as a success, and 1 patient with both SVR4 and treatment week 12 imputed as successes by this predetermined rule. All other intermittently missing or nonintermittently missing data were imputed as failures. GT = genotype; SVR12 = sustained virologic response at 12 weeks after the end of treatment.

***** Four patients had nonvirologic failure: 2 non–drug-related deaths (strangulated hiatal hernia and presumed cardiac arrhythmia from autopsy-documented coronary disease), 1 drug-related adverse event (palpitations and anxiety on treatment day 4), and 1 dropout.

without overlapping 95% CIs (**Figure 4** and **Appendix Figure**, available at www.annals.org).

Virologic failure occurred in 13 patients (4%), including 1 breakthrough (GT1a infection at treatment week 8) and 12 relapses (9 patients with GT1a, 1 with GT1b, and 2 with GT6 infection) (**Appendix Table 3**, available at www.annals.org). The 1 breakthrough patient appeared to be fully adherent with study medication dosing. Four additional patients (1.3%) did not achieve SVR12 (3 with GT1a and 1 with GT1b infection) because of 2 non–drug-related deaths, 1 drug-related adverse event, and 1 dropout. After exclusion of these nonvirologic failures, SVR12 was achieved in 94% of patients with GT1a and 99% of those with GT1b infection.

Virologic Analysis

NS3 RAVs were detected at baseline in 86 of 151 (57%) and 25 of 129 (19%) patients with GT1a and GT1b infection, respectively. SVR12 was achieved in 83 of 86 (97%) and 58 of 65 (89%) patients with GT1a infection with or without these RAVs, respectively. The corresponding SVR12 rates among patients with GT1b infection were 24 of 25 (96%) and 104 of 104 (100%) (**Table 2**). Three patients (all with GT1b) had NS3 RAVs with greater than 5-fold shifts to grazoprevir, and all achieved SVR12 (**Appendix Table 4**, available at www.annals.org).

NS5A RAVs were identified at baseline in 19 of 154 (12%) GT1a-infected patients. SVR12 was achieved in 11 of 19 (58%) of these patients compared with 133 of 135 (99%) patients without baseline NS5A RAVs. SVR12 in patients with baseline GT1a RAVs with a 5-fold or smaller shift to elbasvir was 90% (9 of 10) versus 22% (2 of 9) in patients with baseline GT1a RAVs with a greater than 5-fold shift (**Appendix Table 5**, available at www.annals.org). An association of GT1a RAVs with virologic failure was observed only in patients with baseline viral loads greater than 800 000 IU/mL (**Appendix Table 6**, available at www.annals.org). In 18 of 130 (14%) patients with GT1b infection and baseline NS5A RAVs, SVR12 rates were 94% (17 of 18) versus 100% (112 of 112) in those without baseline NS5A RAVs. Among the 6% (16 of 280) of GT1-infected patients with both NS3 and NS5A RAVs at baseline, SVR12 was achieved in 12 of 16 (75%) (**Appendix Table 7**, available at www.annals.org).

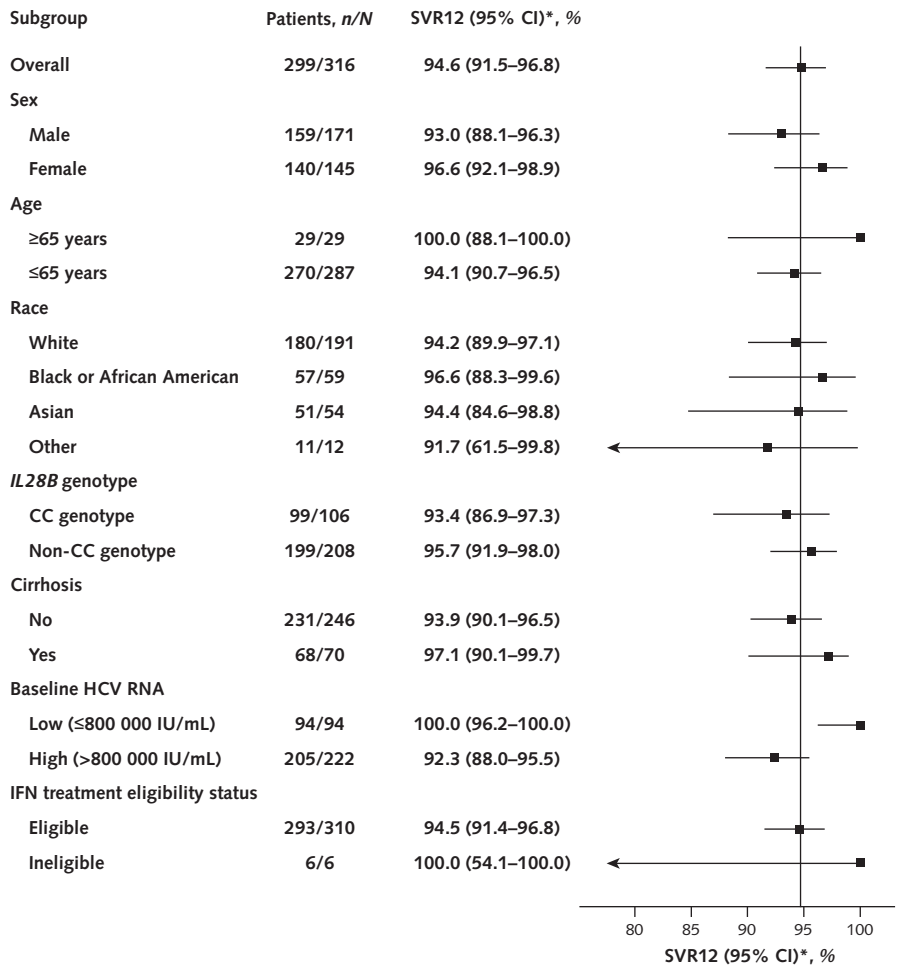
At the time of virologic failure, RAVs were detected in most patients with GT1a infection (NS3: 6 of 10; NS5A: 10 of 10; both: 6 of 10), most commonly Q80K and D168A in NS3 and M28V/A/G, Q30H/L/R, L31M, and Y93H in NS5A (**Appendix Table 3**). The 1 patient with GT1b who had virologic failure exhibited T54S and V170I substitutions in NS3 and L31F and Y93H substitutions in NS5A at the time of failure.

In evaluable GT4-infected patients, NS3 RAVs, NS5A RAVs, and both NS3 and NS5A RAVs were present at baseline in 7 of 18 (39%), 9 of 18 (50%), and 2 of 18 (11%) patients, respectively (**Appendix Table 7**). All achieved SVR12. In evaluable GT6-infected patients, baseline NS3 RAVs and NS5A RAVs were present in 9 of 9 (100%) and 3 of 9 (33%) patients, respectively. SVR12 was achieved in 78% (7 of 9) of these patients, all of whom had baseline NS3 RAVs. At the time of failure, both GT6-infected patients with virologic failure had NS3 RAVs, and 1 also had an NS5A RAV (**Appendix Tables 3 to 5** and **7**).

Safety Analysis

Grazoprevir–elbasvir was generally well-tolerated (**Table 3**). The safety profile was similar in the active and placebo treatment groups (**Appendix Table 8**, available at www.annals.org) and in cirrhotic and noncirrhotic patients (**Appendix Table 9**, available at www.annals.org). Drug-related adverse events occurred in 114 (36.1%) and 41 (39.0%) patients in the active and placebo groups, respectively (difference, −2.9 percentage points [CI, −13.7 to 7.5 percentage points]). Serious adverse events during treatment and the first 14 follow-up days were reported in 9 (2.8%) and 3 (2.9%) patients in the active and placebo groups, respectively (difference <0.05 percentage points [CI, −5.4 to 3.1 percentage points]); none was considered drug related

Figure 4. Subgroup analysis.



Number of patients in the analysis who achieved sustained virologic response. Two patients were missing data for *IL28B* genotype and were not included in the forest plot. SVR12 was achieved in 1 of these 2 patients (50.0% [CI, 1.3% to 98.7%]). Patients were deemed ineligible for interferon treatment by the investigator if they had comorbid conditions (including autoimmune disorders, inflammatory bowel disease, interstitial lung disease, interstitial nephritis, sarcoidosis, significant psychiatric disease, a seizure disorder, uncontrolled thyroid disease, retinal disease, or poorly controlled diabetes) and were considered at risk for worsening during therapy with interferon. IFN = interferon; SVR12 = sustained virologic response (HCV RNA less than the lower limit of quantitation [<15 IU/mL]) at 12 weeks after the end of treatment.
* Based on the Clopper-Pearson method.

Table 2. Effect of Resistance-Associated Variants on Rates of Sustained Virologic Response at 12 Weeks After the End of Treatment in Patients With Genotype 1 Infection*

Variable	NS5A†		NS3/4A‡	
	Patients With Specified Result/Patients With Sequencing Data, *n/N (%)*§	Patients With SVR12/ Patients With Specified Result, *m/n (%* [95% CI])‖	Patients With Specified Result/Patients With Sequencing Data, *n/N (%)*§	Patients With SVR12/ Patients With Specified Result, *m/n (%* [95% CI])‖
Genotype 1a				
Baseline RAVs	19/154 (12)	11/19 (58 [34–80])	86/151 (57)	83/86 (97 [90–99])
No baseline RAVs	135/154 (88)	133/135 (99 [95–100])	65/151 (43)	58/65 (89 [79–96])
Genotype 1b				
Baseline RAVs	18/130 (14)	17/18 (94 [73–100])	25/129 (19)	24/25 (96 [80–100])
No baseline RAVs	112/130 (86)	112/112 (100 [97–100])	104/129 (81)	104/104 (100 [96–100])

RAV = resistance-associated variant; SVR12 = sustained virologic response at 12 weeks after the end of treatment.
* The table provides a summary of all patients from the full analysis set who achieved SVR12 or met criteria for virologic failure and who had sequencing data available (3 patients with genotype 1a infection and 1 with genotype 1b infection did not have NS3/4A sequencing data).
† Signature NS5A loci included amino acid positions 28, 30, 31, 58, and 93 (for genotypes 1, 4, and 6), and specifically the substitutions M28T/V/A/G, Q30E/H/R/G/K/L/D, L31M/V/F, H58D, and Y93C/H/N/S for genotype 1a and the substitutions L28T/V/A, R30E/H/G/K/L/D, L31M/V/F, P58D, and Y93C/H/N/S for genotype 1b.
‡ Signature NS3 loci included amino acid positions 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, and 175 (for genotypes 1, 4, and 6), and specifically the substitutions V36A/G/L/M/I, T54A/C/G/S, V55A/I, Y56H, Q80K/R, V107I, S122A/G/R, I132V, R155X, A156S/T/V/F/G/L, V158I, D168X, I/V170A/F/T/V, and M175L (for genotype 1).
§ *N* refers to the number of patients with baseline sequencing data; *n* refers to the number of patients with the specified baseline sequencing result.
‖ *n* refers to the number of patients with the specified baseline sequencing result; *m* refers to the number of patients with the specified baseline sequencing result achieving SVR12.

(Table 3). Two patients in the immediate-treatment group died: One GT1a-infected noncirrhotic patient died of a strangulated hiatal hernia between treatment weeks 2 and 4, and 1 GT1a-infected cirrhotic patient was found dead after treatment week 12 and before follow-up week 4 (death presumed to be due to an arrhythmia from autopsy-documented coronary disease). Neither death was considered drug related. The most common adverse events in the active-treatment group were headache (17%), fatigue (15%), and nausea (9%), with similar frequency in both groups (Table 3 and Appendix Table 10, available at www.annals.org).

Treatment was discontinued because of adverse events in 3 (0.9%) grazoprevir–elbasvir recipients (2 patients with elevated aminotransferase levels and 1 patient with palpitations and anxiety on treatment day 4) and 1 (0.9%) placebo recipient (rash on treatment day 2). One cirrhotic and 3 noncirrhotic grazoprevir–elbasvir recipients (1.3%) developed late elevations of aminotransferase level more than 5 times the upper limit of normal, without an associated increase in bilirubin (Table 3). Two of these four patients discontinued treatment because of these elevations at treatment week 8 (cirrhotic patient) and week 10 (noncirrhotic patient), as stipulated by protocol. In both patients, aminotransferase elevations resolved rapidly after cessation of study therapy and SVR12 was achieved (Appendix 1).

DISCUSSION

The C-EDGE Treatment-Naive study demonstrated the efficacy of a 12-week regimen of grazoprevir–elbasvir, with an overall virologic failure rate of 4%. This phase 3 study supports the earlier phase 2 findings with grazoprevir–elbasvir (9, 10). Although the current study had no active-control group, a historical comparator SVR rate of 73% was derived from previous studies involving simeprevir/peginterferon + ribavirin. Notably, we found similar efficacy in cirrhotic and noncirrhotic patients. Subgroup analyses showed no meaningful effects of age, sex, race, ethnicity, or *IL28B* genotype on treatment outcome but did suggest an effect of higher baseline viral load (>800 000 IU/mL), which appeared to vary by the presence of baseline NS5A RAVs.

The efficacy in GT1-infected patients was similar to the findings of the phase 2 C-WORTHY study, in which 12 weeks of grazoprevir–elbasvir without ribavirin resulted in SVR12 rates of 97% and 98% in cirrhotic and noncirrhotic patients, respectively (all of whom were treatment naive and GT1 infected) (9, 10). Efficacy was also similar to that seen with 12 weeks of the fixed-dose combination of sofosbuvir–ledipasvir, which resulted in SVR12 rates of 96% to 99% in noncirrhotic and 94% in cirrhotic treatment-naive, GT1-infected patients (19, 20).

Grazoprevir–elbasvir was highly efficacious in the small number of GT4-infected patients in this study (SVR12, 100% [18 of 18]). This high response rate is consistent with SVR12 rates seen in treatment-naive patients with GT4 infections from the combined phase 2/3 grazoprevir–elbasvir database (54 of 56 [96%]) (Rockstroh JK, Nelson M, Katlama C, Lalezari J, Mallolas J, Bloch M, et al. Efficacy and safety of grazoprevir and elbasvir in patients with hepatitis C virus and HIV co-infection [C-EDGE CO-INFECTION]: a phase 3 trial) (21) and is similar to SVR12 rates with paritaprevir–ritonavir–ombitasvir with or without ribavirin (91% to 100%) (22), sofosbuvir–ledipasvir for 12 weeks in co-infected patients (100% [8 of 8]) (23), and sofosbuvir–daclatasvir for 12 weeks (100% [3 of 3]) (24).

Few GT6-infected patients have been included in clinical trials to date. Sofosbuvir/peginterferon + ribavirin for 12 weeks resulted in an SVR12 rate of 100% (6 of

Table 3. Safety of Patients Randomly Assigned to Immediate or Deferred Therapy With Grazoprevir–Elbasvir During the Initial Treatment Period and First 14 Follow-up Days*

Variable	Immediate-Treatment Group (*N* = 316), *n* (%)	Deferred-Treatment Group (*N* = 105), *n* (%)	Total (*N* = 421), *n* (%)
Serious adverse events†			
≥1 serious adverse event	9 (3)	3 (3)	12 (3)
Ventricular arrhythmia	1 (0.3)‡§	–	1 (0.2)
Ménière disease	1 (0.3)‡	–	1 (0.2)
Renal colic	1 (0.3)‡	–	1 (0.2)
Multiple fractures	1 (0.3)‡	–	1 (0.2)
Skin ulcer	1 (0.3)‡	–	1 (0.2)
Strangulated hiatal hernia	1 (0.3)‡§	–	1 (0.2)
Upper abdominal pain	1 (0.3)‡	–	1 (0.2)
Muscular weakness	1 (0.3)‡	–	
Accidental overdose	1 (0.3)‡‖	–	1 (0.2)
Retinal hemorrhage	–	1 (1)‡	1 (0.2)
Myocardial infarction	–	1 (1)‡	1 (0.2)
Osteoarthritis	–	1 (1)‡	1 (0.2)
Discontinuations due to adverse events	3 (0.9)¶	1 (1)**	4 (1)
Deaths	2 (0.6)§	0 (0)	2 (0.5)
Adverse events occurring in ≥10% of patients††			
≥1 adverse event	213 (67)	72 (69)	285 (68)
Headache	52 (17)	19 (18)	71 (17)
Fatigue	49 (16)	18 (17)	67 (16)
ALT‡‡			
1.1–2.5 times baseline	9 (3)	58 (55)	67 (16)
>2.5–5.0 times baseline	2 (0.6)	2 (2)	4 (1)
>5.0 times baseline	3 (0.9)	0 (0)	3 (0.7)
AST‡‡			
1.1–2.5 times baseline	9 (4)	49 (47)	58 (14)
>2.5–5.0 times baseline	4 (1)	2 (2)	6 (1)
>5.0 times baseline	1 (0.3)	0 (0)	1 (0.2)
Late elevation of ALT or AST§§‖‖¶¶			
>2.0–5.0 times ULN	3 (1)	4 (4)	7 (2)
>5.0 times ULN	4 (1)	0 (0)	4 (1)
Elevation of total bilirubin			
>2.5–5.0 times baseline	3 (0.9)	0 (0)	3 (0.7)
>5.0 times baseline	1 (0.3)	0 (0)	1 (0.2)
>10.0 times baseline	0 (0)	0 (0)	0 (0)
Hemoglobin			
Grade 1 (100–109 g/L)	6 (2)	4 (4)	10 (2)
Grade 2 (90–99 g/L)	3 (0.9)	0 (0)	3 (0.7)
Grade 3 (79–89 g/L)	0 (0)	0 (0)	0 (0)
Grade 4 (<70 g/L)	0 (0)	0 (0)	0 (0)
Creatinine			
Grade 1 (1.1–1.3 times ULN)	2 (0.6)	1 (1)	3 (0.7)
Grade 2 (1.4–1.8 times ULN)	0 (0)	0 (0)	0 (0)
Grade 3 (1.9–3.4 times ULN)	0 (0)	0 (0)	0 (0)
Grade 4 (≥3.5 times ULN)	0 (0)	0 (0)	0 (0)

Continued on following page

6) in GT6-infected patients (25), and sofosbuvir–ledipasvir for 12 weeks was associated with an SVR12 rate of 96% (24 of 25; 1 patient with relapse discontinued therapy at week 8) (26). In the C-EDGE Treatment-Naive study, the SVR12 rate was 80% (8 of 10), similar to the overall SVR12 of 80% (12 of 15) in treatment-naive patients from the combined phase 2/3 grazoprevir–elbasvir program (Rockstroh JK, Nelson M, Katlama C, Lalezari J, Mallolas J, Bloch M, et al. Efficacy and safety of grazoprevir and elbasvir in patients with hepatitis C virus and HIV co-infection [C-EDGE CO-INFECTION]: a phase 3 trial [21]). Conclusions regarding the efficacy of grazoprevir–elbasvir for GT6 infections are constrained by the small sample size. On the basis of available data, grazoprevir–elbasvir appears to possess clinically meaningful activity against GT6, although SVR12 rates have been consistently lower than those seen with GT1 and GT4.

Table 3–Continued

Variable	Immediate-Treatment Group (*N* = 316), *n (%)*	Deferred-Treatment Group (*N* = 105), *n (%)*	Total (*N* = 421), *n (%)*
Neutrophils¶¶			
Grade 1 (1.00–1.3 × 10^9 cells/L)	12 (4)	4 (4)	16 (4)
Grade 2 (0.75–0.999 × 10^9 cells/L)	3 (1)	0 (0)	3 (1)
Grade 3 (0.50–0.749 × 10^9 cells/L)	0 (0)	1 (1)	1 (0.2)
Grade 4 (<0.50 × 10^9 cells/L)	1 (0.3)	0 (0)	1 (0.2)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.
* All adverse events, serious adverse events, and laboratory findings were recorded from the initiation of study treatment through the first 14 days of follow-up. The relatedness (probable or possible) of the adverse event to the regimen was determined by the investigator; patients could have had more than 1 adverse event.
† Four patients in the immediate-treatment group had serious adverse events (none were considered drug-related) after the first 14 days of follow-up, which included tooth abscess (2 months, 7 days since last dose), chest pain (1 month, 27 days since last dose), asthenia/hypotension/acute pancreatitis (3 months, 1 day to 3 months, 17 days since last dose), and pancreatic mass (4 months, 1 day since last dose).
‡ Not reported to be treatment related.
§ Neither death was considered to be related to the study treatment. These 2 deaths are also listed under serious adverse events (strangulated hiatal hernia and ventricular arrhythmia).
‖ Accidental overdose of clonidine.
¶ Two patients had elevated liver aminotransferase levels and 1 had palpitations and anxiety in the immediate-treatment group on treatment day 4.
** One patient had rash in the deferred-treatment group on treatment day 2.
†† Common adverse events occurring in at least 10% of the total group during the treatment period and the first 14 days of follow-up; shown in decreasing frequency based on the total.
‡‡ No ALT or AST elevations were associated with elevations in total bilirubin.
§§ Late ALT or AST elevations were defined as elevations in ALT or AST occurring after treatment week 4 among patients who had ALT or AST levels within normal limits between week 2 and week 4, inclusive.
‖‖ No late ALT or AST elevations were associated with elevations in total bilirubin.
¶¶ *N* = 314 in the immediate-treatment group; *N* = 104 in the deferred-treatment group (2 early discontinuations in immediate-treatment group [adverse event, *n* = 1; death, *n* = 1], and 1 early discontinuation in deferred-treatment group [adverse event, *n* = 1]); and *N* = 314 in the immediate-treatment group because 2 patients were missing the requisite laboratory data.

As with other interferon- and ribavirin-free regimens, virologic failure in the C-EDGE Treatment-Naive study was predominantly due to relapse (12 of 13 virologic failures), with only 1 patient developing breakthrough viremia while receiving therapy. Among patients with GT1 and GT6 infections, failure was associated with baseline GT1a NS5A RAVs and emergence of NS3 or NS5A RAVs. Although the overall prevalence of baseline NS3-RAVs was approximately 40%, no association between baseline NS3 RAVs and virologic failure was evident. SVR12 was not affected by mutations with more than 5-fold shifts to grazoprevir in vitro, consistent with the results from C-WORTHY, in which baseline mutations to grazoprevir did not affect efficacy (9, 10). In contrast, baseline NS3 RAVs may affect outcome for other protease inhibitor–based regimens, as exemplified by the negative effect of the common baseline Q80K polymorphism on the efficacy of simeprevir/peginterferon + ribavirin (SVR12, 84% without Q80K and 58% with Q80K) (27). In the phase 3 trials of ombitasvir–paritaprevir–dasabuvir with or without ribavirin, baseline samples from 47 patients with GT1a in whom treatment failed were compared with those from 94 demographically matched patients. At baseline, Q80K was detected in approximately 38% of patients and was noted to be about 2-fold more common in patients with virologic failures than responders (28). Specific virologic failure rates for patients with or without baseline Q80K were not reported, but the overall phase 3 SVR12 rates for treatment-naive noncirrhotic patients after 12 weeks of treatment with ombitasvir–paritaprevir–dasabuvir +ribavirin were 98.0% to 99.5% in GT1b-infected patients and 95.3% to 97.0% in GT1a-infected patients; without ribavirin, the corresponding SVR12 rates were 99.0% for GT1b-infected and 90.2% for GT1a-infected patients (29, 30).

Baseline NS5A RAVs were detected in 13% of patients with GT1 infection. The data suggest an association between virologic failure and baseline NS5A RAVs, which was most apparent in the few GT1a-infected patients with baseline RAVs demonstrating a greater than 5-fold shift to elbasvir. Although the numbers of patients with baseline NS5A RAVs were small, the relationship between baseline GT1a RAVs and virologic failure was most pronounced in patients with high baseline viral load. A similar effect of baseline NS5A RAVs on efficacy has also been noted with other NS5A inhibitor regimens. In treatment-naive patients receiving sofosbuvir–ledipasvir, the response rate with and without NS5A RAVs varied by study. In ION-3, in which treatment-naive patients received sofosbuvir/ledipasvir with or without ribavirin for 8 weeks or sofosbuvir/ledipasvir for 12 weeks, NS5A RAVs were detected at baseline by deep sequencing in 18% of patients, of whom 90% achieved SVR12 (20). Specific virologic failure rates in patients with and without baseline RAVs by genotype were not reported, but 47% (9 of 19) of GT1a-infected patients and 25% (1 of 4) of GT1b-infected patients with virologic failure had baseline NS5A RAVs (20). In treatment-naive patients in ION-1 and ION-3 combined, 94% of patients with baseline NS5A RAVs versus 95% without RAVs achieved SVR12 after 8 weeks of treatment, whereas 99% with and without RAVs achieved SVR12 after 12 weeks of treatment (31). In treatment-experienced patients receiving 12 weeks of sofosbuvir–ledipasvir, 78% with NS5A RAVs versus 98% without RAVs achieved SVR12 (31). In pivotal trials of ombitasvir–paritaprevir–

dasabuvir with or without ribavirin, baseline NS5A RAVs were approximately twice as common in patients with virologic failure as in responders (28). Separate virologic failure rates in patients with or without baseline NS5A RAVs against ombitasvir were not explicitly reported.

Coincident with virologic failure, GT1 NS3 or NS5A RAVs were detected by population sequencing in most GT1a-infected patients, most commonly NS3_Q80K and D168A and NS5A_M28V/A/G, Q30H/L/R, L31M, and Y93H. These findings may have implications for salvage therapy in the small percentage of patients who experience virologic failure while receiving grazoprevir–elbasvir.

The prognostic utility of pretreatment resistance testing requires continued scrutiny as the use of different classes of directly acting antiviral agents for chronic HCV infection becomes increasingly widespread (3–5, 7, 32). In this study, only 5.7% of patients with genotype 1a had baseline RAVs with greater than 5-fold decreased susceptibility to elbasvir, making up 2.8% of the total population. The cost-effectiveness of screening all patients for the small number who harbor highly resistant variants at baseline should be considered when practice guidelines are formulated.

The deferred-treatment group in this study allowed a concurrent placebo control group to evaluate safety. Grazoprevir–elbasvir was generally well-tolerated, with a similar safety profile in cirrhotic and noncirrhotic patients and in the active and placebo treatment groups. Serious adverse events were infrequent, with a similar incidence in the active and placebo groups. No serious adverse event was judged to be drug related by site investigators. Discontinuations for adverse events were likewise uncommon. The most common adverse events were headache, fatigue, and nausea, occurring with similar frequencies in noncirrhotic and cirrhotic patients and in the active and placebo groups.

Late elevations in aminotransferase levels greater than 5 times the upper limit of normal occurred in 4 patients (1.3%) in the immediate-treatment group; none was associated with hyperbilirubinemia. These abnormalities were reversible and had no major clinical consequences. The hepatic safety profile of grazoprevir–elbasvir in this study was similar to the findings of the phase 2 C-WORTHY study, in which fewer than 1% of patients experienced a late elevation in alanine aminotransferase level greater than 5 times the upper limit of normal (9, 10).

The C-EDGE Treatment-Naive study confirmed that an oral fixed-dose combination of an NS3/4A protease inhibitor (grazoprevir) and an NS5A inhibitor (elbasvir) provides a highly efficacious and well-tolerated regimen for chronic HCV-GT1, GT4, or GT6 infection in treatment-naive, compensated cirrhotic and noncirrhotic patients. This once-daily, single-tablet, 2-drug combination constitutes a potent new therapeutic option for chronic HCV infection.

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Appendix 1: Supplementary Information

Background and Summary

Chronic infection with hepatitis C virus (HCV) presents an expanding challenge worldwide. Without therapy, almost half of persistently infected patients will progress to cirrhosis, placing them at risk for hepatocellular carcinoma and hepatic decompensation requiring liver transplantation. As a consequence of contamination of blood supplies in the 1960s through 1992 and the aging of the HCV-infected population, the number of patients with HCV-related complications continues to increase dramatically. Effective HCV therapy with virologic cure can reduce long-term HCV complications and mortality.

Interferon- and ribavirin-free regimens can achieve sustained virologic response (SVR) rates >90% in treatment-naive populations in randomized controlled clinical trials. However, efficacy across HCV genotypes (GT), in certain historically difficult-to-treat patient subgroups, and in the presence of NS3 and/or NS5A variants differs by regimen.

C-EDGE Treatment-Naive demonstrated that an all-oral, once-daily, fixed-dose combination of a protease inhibitor (grazoprevir) plus an NS5A inhibitor (elbasvir) can be a highly efficacious and well-tolerated regimen for chronic HCV GT1, -4, or -6 infection in treatment-naive patients both with and without cirrhosis. Virologic failure was uncommon and was predominantly due to virologic relapse following completion of therapy. The presence of NS3 resistance-associated variants (RAVs) at baseline did not affect outcome, although NS5A RAVs at baseline were associated with lower rates of SVR at 12 weeks after the end of treatment in GT1a infections. Grazoprevir–elbasvir was associated with few serious adverse events and rare discontinuations, including in patients with compensated cirrhosis. Overall, grazoprevir–elbasvir provides a novel therapeutic option for treatment-naive HCV-infected patients with GT1a, -1b, -4, or -6.

Derivation of Historical SVR12 Reference Rate

The historical reference rate of 73% was derived from the phase 3 trials of simeprevir/PR in treatment-naive monoinfected patients after adjustment for the expected proportion of cirrhotic patients and the anticipated improved tolerability with an interferon-free regimen (15, 16). In QUEST 1 and 2, SVR12 was achieved by 60% of patients with compensated cirrhosis and 82% of noncirrhotic patients. Assuming that 20% of C-EDGE Treatment-Naive patients had cirrhosis, a SVR of 78% was computed. A 5% decrease was then applied because of the expected improved tolerability.

Power Assumptions and Calculations for Safety Analyses

For power assumptions and calculations for safety analyses, see Appendix Tables 11 and 12.

Staging of Liver Injury

Hepatic fibrosis was staged by biopsy or noninvasive assessment. Cirrhosis was defined as a liver biopsy showing METAVIR stage F4 at any time prior to entry; transient elastography (Fibroscan) performed within 12 months of entry yielding a result >12.5 kPa; or biochemical markers of liver fibrosis (FibroTest or FibroSure) yielding a score of >0.75 along with an aspartate aminotransferase–platelet ratio index (APRI) >2. Patients were considered noncirrhotic if a liver biopsy performed within the previous 24 months did not reveal cirrhosis; a Fibroscan performed during the previous 12 months had a result of ≤12.5 kPa; or a FibroSure or FibroTest score was ≤0.48 with an APRI of ≤1 in the preceding 12 months.

Narratives of Patients With Late Aminotransferase Elevations 5 Times the Upper Limit of Normal (ULN)

In an earlier study of grazoprevir given with pegylated interferon plus ribavirin (8), some patients receiv-

ing doses of grazoprevir higher than the 100-mg dose used in the current study experienced late elevations in aminotransferases; therefore, liver safety signals were carefully monitored in this study. Four patients (1.3%) in the immediate-treatment group had late aminotransferase elevations > 5 times ULN. None of these cases were associated with elevated serum bilirubin. All cases were manageable and reversible and had no major clinical consequences.

Late ALT or AST elevations are defined as elevations in ALT or AST occurring after treatment week 4 among patients who had ALT or AST within normal limits between week 2 and week 4. The 4 cases with late elevations of aminotransferases observed in the current study are summarized below.

Elevation of ALT at Treatment Week 6

This 62-year-old noncirrhotic white woman with HCV GT1b was randomly assigned to the immediate-treatment group. While on study medication, her aminotransferases normalized from a baseline ALT/AST of 46/47 U/L to a nadir of 18/22 U/L at treatment week 2. At treatment week 6 she was noted to have an ALT increase to 376 U/L (11.4 times ULN) and an AST increase of 198 U/L (5.5 times ULN) associated with an eosinophil differential of 5.3% (ULN of 7.0%). She was asymptomatic, without nausea, vomiting, or upper right quadrant pain. She had not taken any new medications, consumed alcohol, or taken any over-the-counter or herbal remedies. The patient's ALT/AST and eosinophils decreased to within normal limits on continued therapy and she completed the full course of study drug and achieved SVR12.

Elevation of ALT at Treatment Week 8

This 52-year-old cirrhotic Asian woman with HCV GT1b infection was randomly assigned to the immediate-treatment group. While on study medication, her aminotransferases normalized from a baseline ALT/AST of 80/70 U/L to a nadir of 22/26 U/L at treatment week 2. At treatment week 8 she was noted to have an ALT of 199 U/L (6.0 times ULN) and an AST of 167 U/L (4.6 times ULN), with an increase in eosinophils to 8.8% (ULN 7.0). The patient had been seen in a local clinic and diagnosed with an upper respiratory infection. New concomitant medications included a theophylline derivative, loxoprofen (a nonsteroidal anti-inflammatory drug), an antacid, a mucolytic, and cough syrup. She had not consumed any alcohol and did not take any herbal remedies or other new prescription or over-the-counter medications except for those detailed above. She did not have any new or worsening nausea, vomiting, or upper right quadrant pain/tenderness. At treatment week 10 her ALT was 668 U/L, AST was 459 U/L, and eosinophils were 4.9%. The aminotransferases elevations met the protocol-specified criterion for study drug discontinuation. Her ALT/AST and eosinophils decreased to within normal limits after the discontinuation of study drug. The patient had completed 70 days of study drug therapy and subsequently achieved SVR12.

Elevation of ALT at Treatment Week 10

This 67-year-old noncirrhotic African American woman with HCV GT1b infection was randomly assigned to the immediate-treatment group. While on study medication, her aminotransferases normalized from a baseline ALT/AST of 94/99 U/L to a nadir of 18/26 U/L at treatment week 8. At treatment week 10 she was noted to have an ALT of 399 U/L (12 times ULN) and an AST of 338 U/L (9.4 times ULN) associated with an eosinophil differential of 5.1% (ULN 7.0%). She was asymptomatic and her physical examination was normal. She had not taken any new medications or taken any over-the-counter or herbal remedies; she had one glass of wine 4 days previously. Repeat lab test 5 days later demonstrated an ALT/AST of 474/352, which decreased the following day despite continued treatment to 439/310, respectively. Study drug was discontinued per the protocol stopping rules. Her ALT/AST resolved to within normal limits off treatment. The patient completed 78 days of therapy and subsequently achieved SVR12.

Elevation of ALT at Treatment Week 12

This 61-year-old noncirrhotic woman of Asian descent with HCV GT6 infection was randomly assigned to the immediate-treatment group. While on study medication, her aminotransferases normalized from a baseline ALT of 59 U/L and AST of 67 U/L to within normal limits. At treatment week 12 her ALT/AST increased to 170/133 U/L; eosinophils, prothrombin international normalized ratio, alkaline phosphatase and total bilirubin values remained within normal limits during treatment. The patient did not report new or worsening nausea, vomiting, jaundice, arthralgia, or upper right quadrant pain/tenderness. She denied taking any new medications, including herbal supplements and over the counter medications, and did not drink alcohol. An abdominal ultrasound showed no liver abnormalities. At follow-up week 4, laboratory testing showed the patient's ALT/AST levels had decreased to 63/65 U/L. However, HCV RNA testing showed virologic relapse with a viral RNA of 73,104 IU/mL.

Appendix 2: C-EDGE P060 Principal Investigators

The C-EDGE P060 principal investigators by country are as follows: *Australia:* Joshua Davis, Amanda Ni-

coll, Katherine Stuart, Lindsay Mollison; *Czech Republic:* Vaclav Hejda, Jan Sperl, Petr Husa, Petr Urbanek; *France:* Victor De Ledinghen, Dominique Larrey, Veronique Loustaud-Ratti, Patrick Marcellin, Vincent Di Martino; *Germany:* Michael Manns, Claus Niederau, Renate Heyne, Hartwig Klinker, Stefan Zeuzem; *Israel:* Eli Zuckerman, Oren Shibolet, Ziv Ben Ari, Yoav Lurie, Michal Cohen; *Puerto Rico:* Javier Morales-Ramirez, Maribel Rodriguez-Torres, Esther Torres; *South Korea:* Jeong Heo, Seung Woon Paik, Youn-Jae Lee; *Sweden:* Ola Weiland, Anders Lannergard, Rune Wejstal, Leo Flamholc; *Taiwan:* Jia-Horng Kao, Cheng-Yuan Peng, Wan-Long Chuang; *United States:* Luis Balart, Paul Chittick, Christopher Christensen, Edwin DeJesus, Hany Elbeshbeshy, Robert Emslie, Reem Ghalib, Eric Lawitz, William Lee, James Levin, Velimir Luketic, Jonathan McCone, Barry Migicovsky, Timothy Morgan, Roberto Firpi-Morell, Steven O'Marro, Paul Pockros, Natarajan Ravendhran, Rajender K. Reddy, Christopher Bowlus, Michael Saag, Kenneth Sherman, Harvey Tatum, John Vierling.

Appendix Table 1. Genotype Distribution and Number of Virologic Failures by Country of Enrollment

Genotype/Sub-genotype	Country of Enrollment									
	Australia	**Czech Republic**	**France**	**Germany**	**Israel**	**Republic of Korea**	**Sweden**	**Taiwan**	**USA (including Puerto Rico)**	**Total**
1a	12 8 Active 4 Placebo [1 VF]	6 5 Active 1 Placebo	13 10 Active 3 Placebo [1 VF]	14 12 Active 2 Placebo	0	0	19 15 Active 4 Placebo [1 VF]	2 2 Active 0 Placebo	145 105 Active 40 Placebo [7 VF]	211 157 Active 54 Placebo [10 VF]
1b	3 2 Active 1 Placebo	22 18 Active 4 Placebo	10 7 Active 3 Placebo	15 12 Active 3 Placebo	22 17 Active 5 Placebo	31 26 Active 5 Placebo	5 2 Active 3 Placebo	17 14 Active 3 Placebo	46 33 Active 13 Placebo [1 VF]	171 131 Active 40 Placebo [1 VF]
4	2 2 Active 0 Placebo	0	11 6 Active 5 Placebo	4 4 Active 0 Placebo	0	0	0	0	9 6 Active 3 Placebo	26 18 Active 8 Placebo
6	0	0	1 1 Active 0 Placebo [1 VF]	1 1 Active 0 Placebo	0	0	0	6 5 Active 1 Placebo	5 3 Active 2 Placebo [1 VF]	13 10 Active 3 Placebo [2 VF]
Total	17 12 Active 5 Placebo [1 VF]	28 23 Active 5 Placebo	35 24 Active 11 Placebo [2 VF]	34 29 Active 5 Placebo	22 17 Active 5 Placebo	31 26 Active 5 Placebo	24 17 Active 7 Placebo [1 VF]	25 21 Active 4 Placebo	205 147 Active 58 Placebo [9 VF]	421 316 Active 105 Placebo [13 VF]

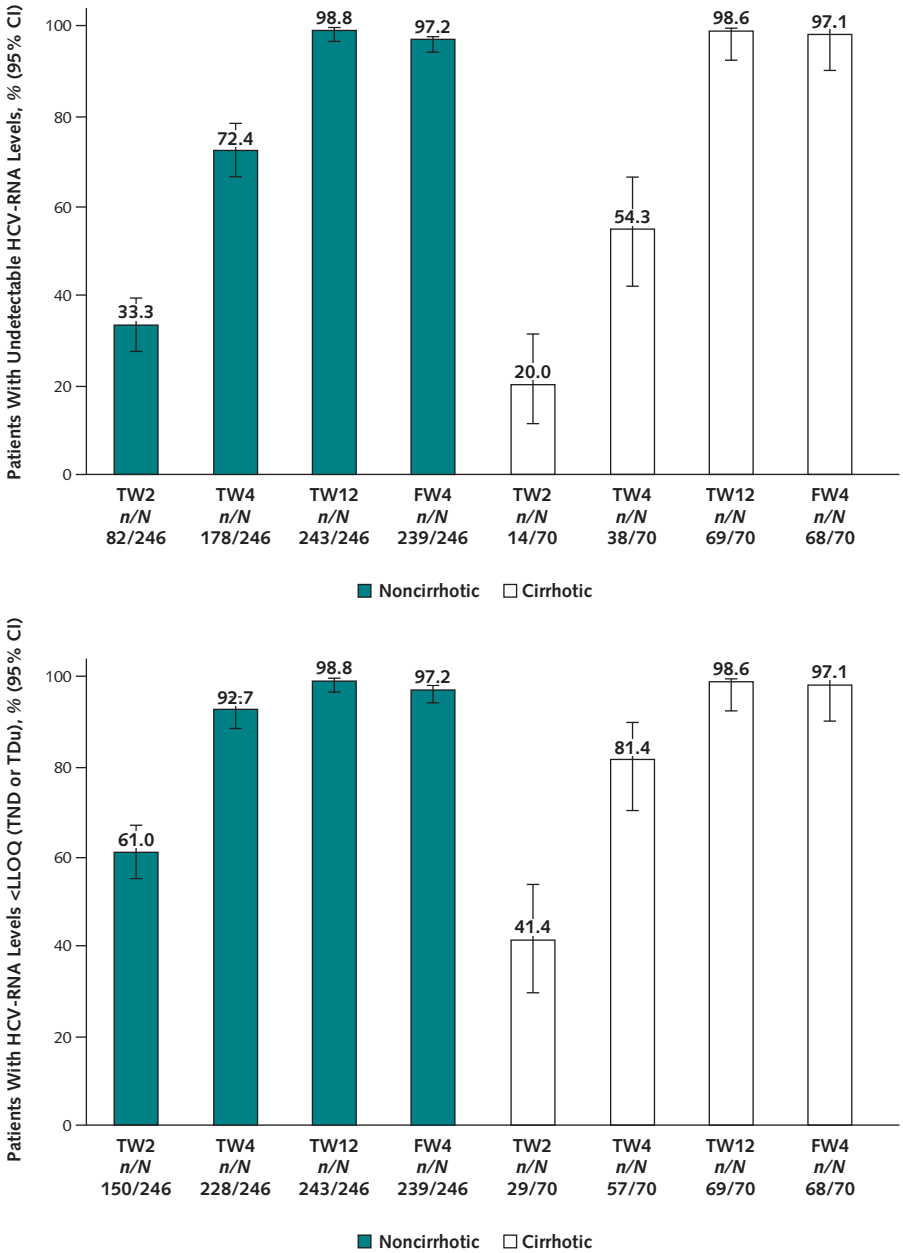
Active and Placebo identify the arm to which the patient was randomized.
VF, virologic failures refer exclusively to patients randomized to the immediate active arm and are shown in brackets under the country where they occurred.

Appendix Table 2. Analysis of the Proportion of Subjects With HCV RNA Level Below the Lower Limit of Quantification at Time Points During the Initial Treatment and Follow-up Period (Full Analysis Set)

Treatment	Time Point	N	Patients with HCV RNA <LLOQ	
			n (%)	95% CI†
Immediate treatment arm: GZR–EBR for 12 weeks	TW2	316	179 (56.6)	(51.0, 62.2)
	TW4	316	285 (90.2)	(86.4, 93.2)
	TW12	316	312 (98.7)	(96.8, 99.7)
	FW4	316	307 (97.2)	(94.7, 98.7)
	FW12	316	299 (94.6)	(91.5, 96.8)

CI=confidence interval; EBR=elbasvir; FW=follow-up week; GZR=grazoprevir; HCV=hepatitis C virus; LLOQ=lower limit of quantification; N=number of subjects included in the analysis; *n* (%)=number of subjects who achieved the corresponding HCV RNA end point and the percentage calculated as (n/N)*100; TW=treatment week; FW=follow-up week post-treatment; also see **Appendix Figure 1**.
Missing outcomes were assumed to be failures unless the flanking values were each successes. There were 2 subjects with SVR4 imputed as successes, 1 subject with TW4 imputed as a success, and 1 subject with both SVR4 and TW12 imputed as successes according to this predetermined rule. All other missing data were imputed as failures.
† Based on Clopper-Pearson method.
The Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 assay LLoQ is 15 IU/mL.

Appendix Figure. Treatment response during the blinded period at treatment weeks (TWs) 2, 4, and 12 and follow-up week (FW) 4 visits by cirrhotic status for full analysis set population.



Top. Proportion of patients with undetectable HCV RNA levels. **Bottom.** Analysis of the proportion of patients with HCV RNA levels less than the LLOQ. LLOQ = lower limit of quantification; TND = target not detected; TDu = target detected unquantifiable.

Appendix Table 3. Baseline and Emergent Resistance Variants in Grazoprevir–Elbasvir Recipients Experiencing Virologic Failure

Category of Virologic Failure	HCV Sub-Genotype	Cirrhosis	HCV RNA Level at Baseline (IU/mL)	Day of Virologic Failure Diagnosis	Variants			
					At Baseline		At Failure	
					NS3	NS5A	NS3	NS5A
Breakthrough	1a	Yes	1238923	Rx D71	Q80K, S122G	L31L/M	V36M, (Q80K, S122G), D168A	Q30R, (L31M)
Relapse	1a	No	5127102	F/U D28	WT	L31M	(WT)	Q30R, (L31M)
Relapse	1a	No	2134448	F/U D71	WT	Q30H/Q	D168A	(Q30H), Y93H
Relapse	1a	No	948279	F/U D70	Q80K	M28V, Q30L, Y93H	(Q80K), D168A	(M28V/A, Q30L), L31V, (Y93H)
Relapse	1a	No	3908965	F/U D84	WT	M28M/V, H58H/D	D168A	Q30R, (H58D)
Relapse	1a	No	5282871	F/U D62	WT	L31M	WT	Q30R, (L31M)
Relapse	1a	No	1846427	F/U D54	WT	WT	WT	Q30R, L31M
Relapse	1a	No	1939436	F/U D61	WT	WT	Y56H, D168V	Y93N
Relapse	1b	No	4475338	F/U D89	T54S	Y93H	(T54S), V170I	L31F, (Y93H)
Relapse	1a	No	3913374	F/U D29	V55A	Q30R, L31L/M	(V55A), D168A	(Q30R, L31M)
Relapse	6	No	15689194	F/U D25	[EUHK2] V36I, L80Q, S122T, I132L, I170V	[QC99] WT	([EUHK2] (V36I, L80Q, S122T, I132L), D168Y, (I170V)	[QC99] (WT)
Relapse	1a	No	1574151	F/U D56	WT	M28V	(WT)	M28G
Relapse	6	No	15056901	F/U D25	[EUHK2] L80K, I170I/V	[EUHK2] F28L	[EUHK2] Y56Y/H, (L80K), D168E, (I170V)	[EUHK2] (F28L), L31M

D=day; F/U=follow-up; HCV=hepatitis C virus; Rx=treatment; WT=wild-type.

Appendix Table 4. Impact of Baseline NS3 RAVs on Efficacy in GT1-, GT4-, and GT6-Infected Subjects, as Measured by SVR12 Rate

Population†	SVR12*			
	Overall efficacy in evaluable patients†	NS3 RAVs not detectable	NS3 RAVs with ≤5-fold shift to GZR	NS3 RAVs with >5-fold shift to GZR
Overall GT1	269/280 (96.1%)	162/169 (95.9%)	104/108 (96.3%)	3/3 (100%)
By Subtype				
GT1a	141/151 (93.4%)	58/65 (89.2%)	83/86 (96.5%)	0/0 (0%)
With Q80K variant	59/61 (96.7%)	n/a	n/a	n/a
Without Q80K variant	82/90 (91.1%)	n/a	n/a	n/a
GT1b	128/129 (99.2%)	104/104 (100%)	21/22 (95.5%)	3/3 (100%)
Overall GT4	18/18 (100%)	11/11 (100%)	7/7 (100%)	
Overall GT6	7/9 (77.8%)	0 (0%)	7/9 (77.8%)	

GT=genotype; GZR=grazoprevir; n/a=not applicable; RAVs= resistance-associated variants; SVR12=sustained virologic response at 12 weeks after the end of treatment.
* SVR12 rate was calculated as number of subjects with SVR12/Total number of subjects in each category.
† Includes all patients in the full analysis population who have relevant sequencing data available and who either achieved SVR12 or met criteria for virologic failure.

Appendix Table 5. Impact of Baseline NS5A RAVs on Efficacy in Noncirrhotic and Cirrhotic GT1-, GT4-, and GT6-Infected Subjects, as Measured by SVR12

Population†	SVR12*			
	Overall efficacy in evaluable patients†	**NS5A RAVs not detectable**	**NS5A RAVs with ≤5-fold shift to EBR**	**NS5A RAVs with >5-fold shift to EBR**
Overall GT1	273/284 (96.1%)	245/247 (99.2%)	10/11 (90.9%)	18/26 (69.2%)
By GT1 Subtypes				
GT1a	144/154 (93.5%)	133/135 (98.5%)	9/10 (90.0%)	2/9 (22.2%)
GT1b	129/130 (99.2%)	112/112 (100%)	1/1 (100%)	16/17 (94.1%)
Overall GT4	18/18 (100%)	9/9 (100%)		9/9 (100%)
Overall GT6	7/9 (77.8%)	5/6 (83.3%)		2/3 (66.7%)

n/a = not applicable.
* SVR_{12} = #subjects with the selected RAVs achieving SVR12/#subjects with the selected RAVs in each category.
† Includes all patients in the full analysis population who have relevant sequencing data available and who either achieved SVR12 or met criteria for virologic failure.

Appendix Table 6. Impact of Baseline HCV RNA Levels and Baseline Selected NS5A RAVs on Efficacy in Noncirrhotic and Cirrhotic GT1-, GT4-, and GT6-Infected Subjects, as Measured by SVR12 (Full Analysis Set)

Treatment	Baseline HCV RNA and selected NS5A RAV	N	HCV RNA < LLOQ	
			***n* (%)**	**95% CI†**
Immediate-treatment arm: GZR–EBR for 12 weeks	High (>800 000 IU/mL) with selected NS5A RAV	33	22 (66.7)	(48.2, 82.0)
	High (>800 000 IU/mL) without selected NS5A RAV	189	183 (96.8)	(93.2, 98.8)
	Low (≤800 000 IU/mL) with selected NS5A RAV	17	17 (100.0)	(80.5, 100.0)
	Low (≤800 000 IU/mL) without selected NS5A RAV	77	77 (100.0)	(95.3, 100.0)

CI=confidence interval; EBR=elbasvir; GZR=grazoprevir; HCV=hepatitis C virus; LLOQ=lower limit of quantification; N=number of subjects included in the analysis; n(%)=number of subjects who achieved the corresponding HCV RNA end point and the percentage calculated as (n/N)*100; RAVs=resistance-associated variants.
† Based on Clopper-Pearson method.
The Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 LLOQ is 15 IU/mL.

Appendix Table 7. Impact of Dual Baseline NS3 and NS5A RAVs on Efficacy in Noncirrhotic and Cirrhotic GT1-, GT4-, and GT6-Infected Subjects, as Measured by SVR12

Population†	SVR_{12}*		
	Overall Efficacy in patients with both NS3 and NS5A sequences available† at baseline	**Dual NS3 and NS5A RAVs not detectable (single RAVs or wild-type virus) at baseline**	**Dual NS3 and NS5A RAVs detectable at baseline**
Overall GT1	269/280 (96.1%)	257/264 (97.3%)	12/16 (75%)
By GT1 Subtypes			
GT1a	141/151 (93.4%)	133/140 (95.0%)	8/11 (72.7%)
GT1b	128/129 (99.2%)	124/124 (100%)	4/5 (80.0%)
Overall GT4	18/18 (100%)	16/16 (100%)	2/2 (100%)
Overall GT6	7/9 (77.8%)	5/6 (83.3%)	2/3 (66.7%)

* SVR_{12} = #subjects with the selected RAVs achieving SVR12/#subjects with the selected RAVs in each category.
† Includes all patients in the full analysis population who have sequencing data available and who either achieved SVR12 or met criteria for virologic failure.

Appendix Table 8. Analysis of Tier 1 and 2 Adverse Events Occurring During the Initial Treatment Period and First 14 Follow-up Days Post-treatment

	Active treatment arm	Placebo treatment arm	Difference in % (Active – Placebo Arm)	
	n (%)	*n* (%)	Estimate (95% CI)	*p*-value†
Patients in population	316	105		
Tier 1 Adverse Events				
First instance of ALT or AST >500 IU/L	1 (0.3)	0 (0.0)	0.3 (−3.2, 1.8)	0.575
First instance of ALT or AST>3x baseline and >100 IU/L	5 (1.6)	0 (0.0)	1.6 (−2.0, 3.7)	0.195
First instance of alkaline phosphatase >3x ULN	0 (0.0)	0 (0.0)	0.0 (−3.5, 1.2)	>0.999
Tier 2 Adverse Events				
With one or more adverse events	213 (67.4)	72 (68.6)	−1.0 (−10.8, 9.6)	
With drug-related‡ adverse events	114 (36.1)	41 (39.0)	−2.9 (−13.7, 7.5)	
With serious adverse events	9 (2.8)	3 (2.9)	0.0 (−5.4, 3.1)	
With serious renal adverse events*	1 (0.3)	0 (0.0)	0.3 (−3.2, 1.8)	
With serious drug-related adverse events	0 (0.0)	0 (0.0)	0.0 (−3.5, 1.2)	
Discontinued§ due to an adverse event	3 (0.9)	1 (1.0)	−0.0 (−4.4, 2.0)	

† Based on Miettinen & Nurminen method stratified by hepatic cirrhotic status (yes, no) at baseline.
If no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
‡ Determined by the investigator to be related to the drug.
* Refers to renal/urinary serious adverse events.
§ Study medication withdrawn.
Estimated differences, confidence intervals, and p-values are provided in accordance with the statistical analysis plan.

Appendix Table 9. Summary of Adverse Events Reported in Cirrhotic and Noncirrhotic Patients During the Initial Treatment Period Through the First 14 Follow-up Days Post-therapy by Treatment Arm

Patients	Cirrhotic Patients		Noncirrhotic Patients	
	Immediate treatment arm: GZR/EBR	Deferred treatment arm: placebo	Immediate treatment arm: GZR/EBR	Deferred treatment arm: placebo
	N=70	N=22	N=246	N=83
	n (%)	*n* (%)	*n* (%)	*n* (%)
With ≥1 adverse events	38 (54.3)	15 (68.2)	175 (71.1)	57 (68.7)
With no adverse event	32 (45.7)	7 (31.8)	71 (28.9)	26 (31.3)
With drug-related† adverse events	18 (25.7)	9 (40.9)	96 (39.0)	32 (38.6)
With serious adverse events	2 (2.9)	0 (0.0)	7 (2.8)	3 (3.6)
With serious drug-related† adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Who died	1 (1.4)	0 (0.0)	1 (0.4)	0 (0.0)
Discontinued‡ due to an adverse event	1 (1.4)	1 (4.5)	2 (0.8)	0 (0.0)
Discontinued do to a drug-related† adverse event	0 (0.0)	1 (4.5)	2 (0.8)	0 (0.0)
Discontinued due to a serious adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to a serious drug-related† adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.

Appendix Table 10. Patients With Adverse Events (Incidence ≥ 5% in Either Treatment Arm During the Initial Treatment Period or First 14 Follow-up Days (All Subjects as Treated)

	Immediate treatment arm: GZR-EBR for 12 Weeks	Deferred treatment arm: GZR Placebo/EBR Placebo for 12 Weeks	Total
	n (%)	*n* (%)	*n* (%)
Subjects in population	316	105	421
With 1 or more adverse events	213 (67.4)	72 (68.6)	285 (67.7)
With no adverse events	103 (32.6)	33 (31.4)	136 (32.3)
Gastrointestinal disorders	82 (25.9)	28 (26.7)	110 (26.1)
Diarrhea	14 (4.4)	7 (6.7)	21 (5.0)
Nausea	28 (8.9)	8 (7.6)	36 (8.6)
General disorders and administration site conditions	69 (21.8)	23 (21.9)	92 (21.9)
Fatigue	49 (15.5)	18 (17.1)	67 (15.9)
Infections and infestations	58 (18.4)	19 (18.1)	77 (18.3)
Nasopharyngitis	14 (4.4)	6 (5.7)	20 (4.8)
Injury, poisoning and procedural complications	13 (4.1)	7 (6.7)	20 (4.8)
Investigations	18 (5.7)	5 (4.8)	23 (5.5)
Metabolism and nutrition disorders	21 (6.6)	6 (5.7)	27 (6.4)
Musculoskeletal and connective tissue disorders	48 (15.2)	22 (21.0)	70 (16.6)
Arthralgia	20 (6.3)	6 (5.7)	26 (6.2)
Nervous system disorders	65 (20.6)	31 (29.5)	96 (22.8)
Dizziness	9 (2.8)	7 (6.7)	16 (3.8)
Headache	52 (16.5)	19 (18.1)	71 (16.9)
Psychiatric disorders	41 (13.0)	17 (16.2)	58 (13.8)
Insomnia	4 (1.3)	6 (5.7)	10 (2.4)
Respiratory, thoracic and mediastinal disorders	26 (8.2)	8 (7.6)	34 (8.1)
Skin and subcutaneous tissue disorders	37 (11.7)	18 (17.1)	55 (13.1)
Pruritus	7 (2.2)	8 (7.6)	15 (3.6)

EBR=elbasvir; GZR=grazoprevir.
A subject is counted once for each applicable row and column. A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title after rounding.

Appendix Table 11. Power to Detect Differences in Adverse Event Rate

True event rate in the placebo arm	True event rate in the active arm	Power to detect difference at a 2-sided 0.05 α-level
Two-fold increment		
5%	10%	31%
10%	20%	64%
15%	30%	87%
20%	40%	97%
Three-fold increment		
2%	6%	32%
4%	12%	67%
6%	18%	89%
8%	24%	97%

Appendix Table 12. Power to Exclude a 50% or 100% Higher Adverse Event Rate in the Immediate Treatment Arm (Assuming Both Arms have the Same Event Rate)

True event rate in both the active and placebo arms	Power to rule out a 50% increase in the active treatment arm	Power to rule out a 100% increase in the active treatment arm
5%	22%	62%
10%	37%	89%
15%	52%	98%
20%	65%	> 99%
25%	76%	> 99%