Formulary Drug Reviews

Elbasvir/Grazoprevir

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Generic Name:	Elbasvir/Grazoprevir
Proprietary Name:	Zepatier (Merck & Co)
Approval Rating:	4P
Therapeutic Class:	Antiviral Agents; Hepatitis C Virus Direct-Acting Antivirals
Similar Drugs:	Ledipasvir/Sofosbuvir, Sofosbuvir/Velpatasvir
Sound- or Look-Alike Names:	Zebeta, Boceprevir, Telaprevir, Daclatasvir, Ledipasvir, Sofosbuvir, Velpatasvir

INDICATIONS

Elbasvir/grazoprevir is indicated with or without ribavirin for the treatment of adults infected with chronic hepatitis C virus (HCV) genotype 1 or 4.¹ The efficacy and safety of elbasvir/grazoprevir have also been tested in other genotypes.²⁻⁷

Table 1 compares elbasvir/grazoprevir with 2 sofosbuvir-combination regimens.^{1,8-11}

CLINICAL PHARMACOLOGY

Elbasvir and grazoprevir are direct-acting antiviral agents against HCV; elbasvir is a potent inhibitor of HCV nonstructural protein 5A (NS5A) and grazoprevir is a potent reversible inhibitor of HCV nonstructural protein 3/4A (NS3/4A) protease.^{1,4,6,12-14} Elbasvir binds to the replication complex protein NS5A, which disrupts HCV RNA replication and virion assembly.^{1,15,16} Grazoprevir binds to the serine NS3/4A protease responsible for cleaving the HCV polyprotein into the proteins that enable HCV RNA replication and virion assembly.^{1,14}

Elbasvir is effective against HCV genotypes 1 and 4 at picomolar and lower levels.¹ In vitro studies show that grazoprevir is effective against HCV genotypes 1, 2, 3, and 4 at nanomolar and lower levels.^{1,17} The efficacy of elbasvir is reduced against many resistance-associated variants (RAVs) of NS5A. Similarly, the efficacy of grazoprevir is reduced against many NS3 RAVs. Clinical trial patients with HCV genotype 1a infection and certain baseline NS5A RAVs (eg, M28, Y93, Q30, L31) showed a lower sustained virologic response 12 weeks after end of therapy (SVR12) rate with elbasvir/grazoprevir alone (70%) than with elbasvir/grazoprevir plus ribavirin (100%).

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Table 1. Comparison of elbasvir/grazoprevir, ledipasvir/sofosbuvir, and sofosbuvir/velpatasvir treatment regimens for hepatitis C infection^{a,1,8-11}

	Elbasvir/Grazoprevir (Zepatier)	Ledipasvir/Sofosbuvir (Harvoni)	Sofosbuvir/Velpatasvir ^b
Genotype	1 or 4	1, 4, 5, or 6	1, 2, 3, 4, 5, or 6 ^b
Therapy duration	12 or 16 weeks	12 or 24 weeks	8, 12, or 24 weeks ^b
Contraindications	<ul style="list-style-type: none"> • Moderate or severe hepatic impairment • Coadministration with OATP1B1/3 inhibitors, strong CYP3A inducers, or efavirenz • Ribavirin-related contraindications if coadministered 	Ribavirin-related contraindications if coadministered	Ribavirin-related contraindications if coadministered

^aCYP3A4 = cytochrome P450 3A; OATP1B1/3 = organic anion transporting polypeptides 1B1/3.

^bApproval pending at time of manuscript submission.

The decrease in elbasvir/grazoprevir efficacy due to baseline RAVs is genotype dependent and RAV specific, as efficacy was not impacted in patients infected with HCV genotypes 1b and 4; in patients infected with HCV genotype 1a, the NS3 Q80K RAV did not impact treatment response.¹ There is in vitro evidence that the combination of grazoprevir and elbasvir decreases the risk of resistance and the risk of developing new RAVs.¹⁸ However, pooled analysis of data from clinical trials showed that certain RAVs emerged and persisted posttreatment with elbasvir/grazoprevir. The long-term effects of emergent or persistent RAVs against elbasvir/grazoprevir are unknown.¹

There is no cross resistance between elbasvir/grazoprevir and NS5B inhibitors, but cross resistance may occur with NS5A inhibitors and NS3/4A protease inhibitors. There are no data regarding the cross resistance of elbasvir/grazoprevir with NS5A inhibitors.¹

Patients coinfecting with HCV and HIV have higher baseline levels of HCV RNA compared with patients only infected with HCV. High HCV RNA levels can accelerate the progression of liver disease and increase the risk of cirrhosis, end-stage liver disease, and hepatocellular carcinoma.^{6,12}

QTc intervals are not prolonged with either elbasvir or grazoprevir exposure.¹

PHARMACOKINETICS

Elbasvir exhibits a dose-proportional pharmacokinetic profile over a daily dosing range of 5 to 100 mg. The pharmacokinetic profile of elbasvir in healthy volunteers and HCV-infected patients is the same.¹ However, grazoprevir concentrations increase

by 2-fold in HCV-infected patients compared with healthy volunteers.^{1,14} Also, grazoprevir exhibits a greater than dose-proportional pharmacokinetic profile over a daily dosing range of 10 to 800 mg.¹

Based on population pharmacokinetic analysis, the mean maximum plasma concentration (C_{max}) was 121 ng/mL for elbasvir and 165 ng/mL for grazoprevir. The median time to maximum plasma concentration (T_{max}) was 3 hours for elbasvir and 2 hours for grazoprevir. The area under the curve (AUC) was 1,920 ng•h/mL for elbasvir and 1,420 ng•h/mL for grazoprevir.¹

The coadministration of ribavirin with elbasvir/grazoprevir did not clinically affect the AUC or C_{max} of elbasvir or grazoprevir when compared with administration of elbasvir/grazoprevir alone.¹

Administration of elbasvir/grazoprevir with food (high-fat meal) affects absorption; C_{max} and AUC of elbasvir decreased by 11% and 15%, respectively, whereas C_{max} and AUC of grazoprevir increased by 1.5-fold and 2.8-fold, respectively. However, these changes are not clinically meaningful; thus, elbasvir/grazoprevir may be taken with or without food.¹

The volumes of distribution for elbasvir and grazoprevir are 680 L and 1,250 L, respectively. Elbasvir distributes to all tissues, while grazoprevir mainly distributes into the liver via the active transporter OATP1B1/3. Both drugs are highly bound to plasma proteins (99.9% for elbasvir and 98.8% for grazoprevir).¹

Elbasvir and grazoprevir are P-glycoprotein (P-gp) substrates, but intestinal P-gp transporters minimally affect the absorption of either drug. Both

elbasvir and grazoprevir are metabolized by CYP3A enzymes, but metabolites of either drug are not found in plasma. The main route of elimination is through feces (more than 90% of elbasvir and grazoprevir is excreted in feces and less than 1% through urine).¹

Steady-state levels for elbasvir/grazoprevir are reached within about 6 days, with a half-life of 24 hours for elbasvir and 31 hours for grazoprevir.^{1,14}

Population pharmacokinetic analyses indicate that the AUC of elbasvir and grazoprevir will be increased by 16% and 45%, respectively, in patients 65 years or older compared with patients younger than 65 years of age; increased by 50% and 30%, respectively, in female patients compared with male patients; and increased by 15% and 50%, respectively, in Asian patients compared with White patients.¹ Population pharmacokinetic analyses indicate that the pharmacokinetics of elbasvir and grazoprevir are not clinically altered by weight or renal impairment. For patients with hepatic impairment, elbasvir pharmacokinetics remain unchanged but grazoprevir pharmacokinetics are altered (increased by 1.7-fold with mild, 5-fold with moderate, and 1.65-fold with severe hepatic impairment).¹

COMPARATIVE EFFICACY

Indication: Hepatitis C Virus Infection

Guidelines

Guideline: HCV guidance: recommendations for testing, managing, and treating hepatitis C

Reference: AASLD/IDSA/IAS-USA, 2016¹⁹

Comments: The recommended therapies for treating HCV infections (genotypes 1, 4, and 6) are listed below according to prior treatment exposure, cirrhosis status, and HCV genotype.

Treatment-naïve:

Genotype 1a

Without cirrhosis: Elbasvir/grazoprevir; ledipasvir/sofosbuvir; paritaprevir/ritonavir/ombitasvir and dasabuvir (PrOD) with ribavirin; simeprevir plus sofosbuvir; or daclatasvir plus sofosbuvir. An alternative regimen is elbasvir/grazoprevir with ribavirin.

Compensated cirrhosis: Elbasvir/grazoprevir; or ledipasvir/sofosbuvir. Alternative regimens are PrOD with ribavirin; simeprevir plus sofosbuvir with or without ribavirin; daclatasvir plus sofosbuvir with or without ribavirin; or elbasvir/grazoprevir with ribavirin.

Genotype 1b

Without cirrhosis: Elbasvir/grazoprevir; ledipasvir/sofosbuvir; PrOD; simeprevir plus sofosbuvir; or daclatasvir plus sofosbuvir.

Compensated cirrhosis: Elbasvir/grazoprevir; ledipasvir/sofosbuvir; or PrOD. Alternative regimens are simeprevir plus sofosbuvir with or without ribavirin; or daclatasvir plus sofosbuvir with or without ribavirin.

Genotype 4

With or without cirrhosis: Paritaprevir/ritonavir/ombitasvir with ribavirin; elbasvir/grazoprevir; or ledipasvir/sofosbuvir. An alternative regimen is sofosbuvir with ribavirin plus peginterferon.

Genotype 6

With or without cirrhosis: Ledipasvir/sofosbuvir. An alternative regimen is sofosbuvir with ribavirin plus peginterferon.

Treatment-experienced:

Failed peginterferon plus ribavirin

Genotype 1a

Without cirrhosis: Elbasvir/grazoprevir; ledipasvir/sofosbuvir; PrOD with ribavirin; simeprevir plus sofosbuvir; or daclatasvir plus sofosbuvir. An alternative regimen is elbasvir/grazoprevir with ribavirin.

Compensated cirrhosis: Elbasvir/grazoprevir; ledipasvir/sofosbuvir; or ledipasvir/sofosbuvir with ribavirin. Alternative regimens include PrOD with ribavirin; elbasvir/grazoprevir with ribavirin; daclatasvir plus sofosbuvir with or without ribavirin; and simeprevir plus sofosbuvir with or without ribavirin.

Genotype 1b

Without cirrhosis: Elbasvir/grazoprevir; ledipasvir/sofosbuvir; PrOD; simeprevir plus sofosbuvir; or daclatasvir plus sofosbuvir.

Compensated cirrhosis: Elbasvir/grazoprevir; ledipasvir/sofosbuvir with ribavirin; ledipasvir/sofosbuvir; or PrOD. Alternative regimens are daclatasvir plus sofosbuvir with or without ribavirin; or simeprevir plus sofosbuvir with or without ribavirin.

Genotype 4

Without cirrhosis: Paritaprevir/ritonavir/ombitasvir with ribavirin; elbasvir/grazoprevir; or ledipasvir/sofosbuvir. An alternative regimen is sofosbuvir plus ribavirin with or without peginterferon.

Compensated cirrhosis: Paritaprevir/ritonavir/ombitasvir with ribavirin; elbasvir/grazoprevir; or ledipasvir/sofosbuvir with or without ribavirin. An alternative regimen is sofosbuvir plus ribavirin with or without peginterferon.

Genotype 6

With or without cirrhosis: Ledipasvir/sofosbuvir. An alternative regimen is sofosbuvir with ribavirin plus peginterferon.

Failed sofosbuvir plus ribavirin with or without peginterferon

Genotype 1

With or without cirrhosis: Ledipasvir/sofosbuvir with ribavirin.

Failed telaprevir, boceprevir, or simeprevir plus peginterferon and ribavirin

Genotype 1

Without cirrhosis: Ledipasvir/sofosbuvir; daclatasvir plus sofosbuvir; or elbasvir/grazoprevir with ribavirin.

With compensated cirrhosis: Ledipasvir/sofosbuvir with or without ribavirin; daclatasvir plus sofosbuvir with or without ribavirin; or elbasvir/grazoprevir with ribavirin.

Renal impairment:

Genotype 1a: Elbasvir/grazoprevir. An alternative regimen is PrOD with ribavirin.

Genotype 1b: Elbasvir/grazoprevir; or PrOD.

Genotype 4: Elbasvir/grazoprevir.

Genotype 6: Peginterferon with ribavirin.

Studies

Drug: Elbasvir/Grazoprevir vs Placebo

Reference: Zeuzem S, et al, 2015 (C-EDGE Treatment-Naive trial)^{1,4,20}

Study Design: Randomized, double-blind, placebo-controlled, parallel-group, multicenter, international study

Study Funding: Merck

Patients: 421 patients 18 years or older with hepatitis C. All treatment-naive patients had HCV genotype 1, 4, or 6 and HCV RNA levels greater than 10,000 units/mL. Up to 20% of patients could have cirrhosis and up to 15% could have either HCV genotype 4 or 6. At baseline, average age was 52.6 years (median, 54 years; range, 20 to 78 years); 54% were male; 63% were White, 18% were Black, and 16% were Asian; 91% had HCV genotype 1 (50% genotype 1a and 41% genotype

1b), 6% had HCV genotype 4, and 3% had HCV genotype 6; 65% had interleukin 28B (IL28B) non-CC genotype, 34% had IL28B CC genotype, and 0.7% had unknown IL28B genotype; 68% had HCV RNA levels greater than 800,000 units/mL and 32% had HCV RNA levels 800,000 units/mL or less; and 66% had Metavir F0 to F2 stage fibrosis, 12% had F3 stage fibrosis, and 22% had F4 stage fibrosis. Other average baseline characteristics included body mass index (BMI) 26.37 kg/m², HCV RNA level 6.4 log₁₀ units/mL, hemoglobin level 142 g/L, albumin level 4.3 g/L, ALT level 77 units/L, AST level 65 units/L, bilirubin level 0.5 mg/dL, and platelet count 191 × 10⁹ cells/L. Patients were excluded if they had decompensated liver disease, hepatocellular carcinoma, concomitant HIV or hepatitis B virus infection, uncontrolled diabetes mellitus (ie, hemoglobin A_{1c} greater than 10%), increased prothrombin time not due to anticoagulation therapy, creatinine clearance (CrCl) less than 50 mL/min, hemoglobin level less than 95 g/L, thrombocytopenia (ie, platelet count less than 50 × 10⁹ cells/L), aminotransferase levels higher than 10 times the upper limit of normal (ULN), or hypoalbuminemia (ie, albumin level less than 3 g/dL).

Intervention: Patients were randomized 3:1 with concealed allocation to elbasvir/grazoprevir (*n* = 316) or placebo (*n* = 105) for 12 weeks. The single, fixed-dose combination tablet of elbasvir 50 mg/grazoprevir 100 mg was taken orally once daily with or without food. Patients were stratified based on presence of cirrhosis and HCV genotype. Patients in the placebo group were scheduled to receive open-label treatment with the combination tablet of elbasvir and grazoprevir 4 weeks after end of study (deferred therapy). After the last dose of active treatment, patients were followed for an additional 24 weeks.

Results

Primary Endpoint(s)

- Percentage of patients treated with elbasvir/grazoprevir who achieved sustained virologic response 12 weeks after end of therapy (SVR12), defined as HCV RNA levels below the lower limit of quantification (LLQ) of 15 units/mL, was 95% (95% confidence interval [CI], 92%-97%). SVR12 was achieved by 92% (95% CI, 86%-96%) of genotype 1a patients, 98% (95% CI, 95%-100%) of genotype 1b patients, 100%

(95% CI, 82%-100%) of genotype 4 patients, and 80% (95% CI, 44%-98%) of genotype 6 patients. SVR12 was achieved by 97% (95% CI, 90%-100%) of patients with cirrhosis and 94% (95% CI, 90%-97%) of patients without cirrhosis.

- Of the 316 patients treated with elbasvir/grazoprevir, 13 did not achieve SVR12 due to breakthrough (1 patient) or relapse (12 patients), but 4 of these patients were considered non-virologic failures (2 deaths, 1 discontinuation due to palpitations and anxiety, and 1 withdrawal). Excluding these 4 non-virologic failures produced similar SVR12 findings (SVR12 was achieved by 94% of patients with genotype 1a and 99% of patients with genotype 1b). At time of failure, the patients with virologic relapse had RAVs of NS3/4A and/or NS5A.
- Subgroup analyses showed SVR12 results were not impacted by age, gender, race, ethnicity, or IL28B genotype, but the baseline HCV RNA level may influence the ability to achieve SVR12; 100% of patients with a baseline HCV RNA level of 800,000 units/mL or less achieved SVR12 compared with 92% of those with a baseline HCV RNA level greater than 800,000 units/mL.
- Common adverse events reported from both treatment arms included headache (17%), fatigue (15%), and nausea (9%). Treatment-emergent adverse events were observed in 36.1% of elbasvir/grazoprevir patients and 39% of placebo patients (percentage point difference of -2.9; 95% CI, -13.7 to 7.5; not significant [NS]). Serious adverse events (none of which were considered to be related to study drug) were observed in 2.8% with elbasvir/grazoprevir and 2.9% with placebo (percentage point difference of less than 0.05; 95% CI, -5.4 to 3.1; NS).
- Percentages of patients discontinuing study drugs due to adverse events were similar between the 2 arms: 0.9% (3 patients) in the elbasvir/grazoprevir group (elevated aminotransferase level or palpitations and anxiety) and 0.9% (1 patient) in the placebo group (rash).

Secondary Endpoint(s)

- Percentage of patients treated with elbasvir/grazoprevir who achieved sustained virologic response 4 weeks after end of therapy (SVR4) was 97% (95% CI, 95%-99%).

Endpoint(s)

- Depending on the genotype, the presence of baseline NS3 and/or NS5A RAVs affected SVR12 rates. Genotype 1a and 1b patients with baseline NS3 RAVs and genotype 1b patients with baseline NS5A achieved higher rates of SVR12 (94%-97%) compared with genotype 1a patients with baseline NS5A RAVs (58%). Of the sixteen genotype 1 patients with both baseline NS3 and NS5A RAVs, 12 patients (75%) achieved SVR12.

Comments: Elbasvir/grazoprevir was investigated in treatment-naïve patients with HCV genotypes 1a, 1b, 4, and 6 (including some patients with cirrhosis). No statistical comparison was done between the active and placebo groups during the randomized phase because this phase was used only for a safety comparison between the treatment groups. All analyses were conducted for the intention-to-treat (ITT) population (missing data were regarded as failures, unless both preceding and anteceding data were successes). After elbasvir/grazoprevir therapy, the overall SVR12 rate, as well as the SVR12 rates corresponding to each genotype subpopulation, was higher than the historical rate of 73%, based on 2 trials investigating simeprevir with peginterferon plus ribavirin in treatment-naïve patients. This study was conducted in the United States, Australia, Czech Republic, France, Germany, Israel, Korea, Sweden, and Taiwan.

Drug: Elbasvir/Grazoprevir with or without Ribavirin

Reference: Kwo PY, et al, 2015 (C-EDGE Treatment-Experienced trial)^{1,5,21,22}

Study Design: Randomized, open-label, parallel-group, multicenter, international study

Study Funding: Merck

Patients: 420 patients 18 years or older with hepatitis C. All patients had HCV genotype 1, 4, or 6 that was previously treated with peginterferon plus ribavirin. At baseline, 65% were male; 18% were Black and 9% were Hispanic; 35% were cirrhotic; 5% were coinfecting with HIV; and 35% had relapsed, 22% had a partial response, and 43% had a null response after peginterferon plus ribavirin therapy. Average baseline HCV RNA level was 6.3 log₁₀ units/mL. Patients were excluded if they had decompensated liver disease, hepatocellular carcinoma, Child-Pugh class B or C cirrhosis, concomitant hepatitis B virus infection, previous exposure to direct anti-acting antiviral therapy, or history of

malignancy within 5 years of study, or if they were receiving a concomitant antiretroviral regimen that included ritonavir, efavirenz, or etravirine.

Intervention: Patients were randomized 1:1:1:1 to elbasvir/grazoprevir plus ribavirin ($n = 104$) or elbasvir/grazoprevir alone ($n = 105$) for 12 weeks, or elbasvir/grazoprevir plus ribavirin ($n = 106$) or elbasvir/grazoprevir alone ($n = 105$) for 16 weeks. The single, fixed-dose combination tablet of elbasvir 50 mg and grazoprevir 100 mg was taken orally once daily and ribavirin was taken orally twice daily with food. Weight-based dosing was used for ribavirin (800 to 1,400 mg). Randomization was stratified based on the presence of cirrhosis and previous response to peginterferon and ribavirin therapy.

Results

Primary Endpoint(s)

- Percentage of patients who achieved SVR12, defined as HCV RNA levels below the LLQ of 15 units/mL, after 12 weeks of therapy was 94% with elbasvir/grazoprevir plus ribavirin and 94% with elbasvir/grazoprevir alone. Percentage of those achieving SVR12 after 16 weeks of therapy was 99% with elbasvir/grazoprevir plus ribavirin and 92% with elbasvir/grazoprevir alone. SVR12 was achieved by 90% of genotype 1a patients and 100% of genotype 1b patients after 12 weeks of therapy and by 95% of genotype 1a patients and 100% of genotype 1b patients after 16 weeks of therapy. SVR12 was achieved by 94% of patients with cirrhosis and without cirrhosis after 12 weeks of therapy and by 100% of patients with cirrhosis and 95% of patients without cirrhosis after 16 weeks of therapy.
- Common adverse events occurring in at least 10% of patients included fatigue (23%), headache (20%), and nausea (11%).
- One patient discontinued study drugs on day 14 due to reasons not reported, and another patient discontinued study drugs on day 7 due to alcoholism. One death occurred during the study, but it was attributed to lymphoma.

Comments: Elbasvir/grazoprevir was investigated with or without ribavirin in treatment-experienced patients with HCV genotypes 1, 4, and 6 (including some patients with cirrhosis) for 12 weeks and 16 weeks. No confidence intervals were provided in the abstract or press release; whether the SVR12 rates were similar with elbasvir/grazoprevir alone or in combination with ribavirin in patients treated

for 12 weeks or 16 weeks cannot be concluded from these available data. However, SVR12 rates were 92% to 99%, which illustrate the efficacy of elbasvir/grazoprevir with or without ribavirin in the treatment of this patient population.

Limitations: Results for this phase 3 study are from an abstract, press release, and the prescribing information.

Drug: Elbasvir/Grazoprevir

Reference: Rockstroh JK, et al, 2015 (C-EDGE Co-Infection trial)^{1,6,21,23,24,25}

Study Design: Open-label, single-arm, multicenter, international study

Study Funding: Merck

Patients: 218 patients coinfecting with HCV and HIV with or without cirrhosis. All patients had HCV genotype 1, 4, or 6; were HCV treatment naive; and were on a stable antiretroviral therapy with CD4 levels greater than 200 cells/mm³ and HIV viral load less than 20 copies/mL, or naive to HIV therapy with CD4 levels greater than 500 cells/mm³ and HIV viral load less than 50,000 copies/mL. At baseline, average age was 48.7 years; 83.9% were male; 76.6% were White, 17.4% were Black, and 3% were Asian; 65.6% had HCV genotype 1a, 19.3% had HCV genotype 1b, 1.8% had HCV genotype 1 of unknown subtype, 12.8% had HCV genotype 4, and 0.5% had HCV genotype 6; 16.1% had cirrhosis; 65% had IL28B non-CC genotype and 35% had IL28B CC genotype; and 22% were receiving abacavir-based therapy, 75% were receiving tenofovir-based therapy, 52% were receiving raltegravir, 27% were receiving dolutegravir, and 17% were receiving rilpivirine. Other average baseline characteristics included BMI 25.31 kg/m², HCV RNA level 6.03 log₁₀ units/mL, and CD3 or CD4 count 613 cells/mm³. Patients were excluded if they had decompensated liver disease, Child-Pugh class B or C cirrhosis, coinfection with hepatitis B, evidence of hepatocellular carcinoma, or history of malignancy.

Intervention: Patients received a single, fixed-dose combination tablet of elbasvir 50 mg and grazoprevir 100 mg orally once daily with or without food for 12 weeks.

Results

Primary Endpoint(s)

- Percentage of patients treated with elbasvir/grazoprevir who achieved SVR12, defined as

HCV RNA levels below the LLQ of 15 units/mL, after 12 weeks of therapy was 96.3% (95% CI, 92.9% to 98.4%). A sensitivity analysis based on a per-protocol (PP) analysis population ($n = 217$) produced a similar result; SVR12 was achieved by 97% (95% CI, 93.5%-98.7%). SVR12 was 94.4% (95% CI, 84.5%-99.4%) for genotype 1a patients, 95.5% (95% CI, 84.5%-99.4%) for genotype 1b patients, 96.4% (95% CI, 81.7%-99.9%) for genotype 4 patients, and 100% for the 2 genotype 6 patients included in this study. SVR12 was achieved by 100% of patients with cirrhosis and 94% of patients without cirrhosis.

- Of the 218 patients treated with elbasvir/grazoprevir, 8 did not achieve SVR12 due to relapse (7 patients) or non-virologic cause (1 patient). Of the 7 patients considered to have relapsed, 2 were infected with a different HCV genotype than the HCV genotype present at baseline; both patients were newly infected with HCV genotype 3 (baseline infections of HCV genotype 1a for one patient and 1b for the other).
- Subgroup analyses showed SVR12 results were not impacted by age, gender, race, IL28B genotype, cirrhosis status, baseline HCV RNA level, or concomitant antiretroviral therapy.
- Percentage of patients experiencing at least 1 adverse event up to 24 days after therapy was 74% (95% CI, 67.5%-79.6%). Common adverse events included fatigue (13%), headache (12%), and nausea (9%). Serious adverse events occurred in 2 patients (1%), but these events were not considered to be related to elbasvir/grazoprevir exposure. Elevated liver enzymes were rarely observed; grade 3 and 4 ALT elevations occurred in 1% of patients and grade 4 AST elevations occurred in less than 1% of patients.
- No patient discontinued study drug or died during the study.
- SVR12 rates were high for all genotypes despite the presence of RAVs. SVR12 rates ranged from 96% to 100% for genotype 1a and 1b patients with baseline NS3 RAVs, while the SVR12 rate was 87% for genotype 1 patients with baseline NS5A RAVs.

Comments: Elbasvir/grazoprevir was investigated in treatment-naïve patients with HCV genotypes 1, 4, and 6 (including some patients with cirrhosis). All analyses were conducted for the ITT population (missing data were regarded as failures). After

elbasvir/grazoprevir therapy, the overall SVR12 rate, as well as the SVR12 rates corresponding to each genotype subpopulation, was higher than the historical rate of 70%, based on a trial investigating sofosbuvir plus ribavirin in patients coinfecting with HIV. This study was conducted in the United States, Australia, and Europe.

Drug: Elbasvir plus Grazoprevir

Reference: Jacobson et al, 2015 (C-SALT Part A trial)^{7,26}

Study Design: Open-label, parallel-group study

Study Funding: Merck

Patients: 40 patients 18 years or older with hepatitis C with or without compensated cirrhosis. All patients had an HCV genotype of 1, 4, or 6. At baseline, 67% were male, 97% were White, and all patients had genotype 1 infection. Other average baseline characteristics included a Model for End-Stage Liver Disease (MELD) score of 9.79, albumin level 3.4 g/dL, and platelet count 83×10^3 cells/mL. Patients were excluded if they were pregnant or had concomitant HIV or hepatitis B virus infection, prior exposure to HCV therapy, history of malignancy within 5 years of study, hepatocellular carcinoma, history of drug or alcohol abuse within 12 months of study, history of gastric surgery or malabsorption disorders, history of organ transplants (except cornea and hair), or history of hepatitis not due to HCV. Coadministration of investigational medications or corticosteroids was not allowed.

Intervention: Patients with Child-Pugh class B cirrhosis ($n = 30$) received oral elbasvir 50 mg plus grazoprevir 50 mg once daily for 12 weeks. Patients without cirrhosis ($n = 10$) received oral elbasvir 50 mg plus grazoprevir 100 mg once daily for 12 weeks.

Results

Primary Endpoint(s)

- Percentage of patients treated with elbasvir/grazoprevir who achieved SVR12, defined as HCV RNA levels below the LLQ of 15 units/mL, after 12 weeks of therapy was 90% (95% CI, 73.5-97.9) for patients with cirrhosis and 100% (95% CI, 69.2-100) for patients without cirrhosis.

Comments: This study was proposed as a 3 part study: Part A was the phase 2 portion of the C-SALT study (completed); Part B was intended to study elbasvir 50 mg plus grazoprevir 100 mg in Child-Pugh

class B patients; and Part C was intended to study elbasvir 50 mg plus grazoprevir 50 mg or 100 mg. Parts B and C were not conducted after the manufacturer decided to focus on the fixed-dosed combination tablet of elbasvir 50 mg and grazoprevir 100 mg.

Limitations: Statistical analysis was not provided for this small phase 2 study.

Indication: Hepatitis C Virus Infection Genotype 1

Studies

Drug: Elbasvir plus Grazoprevir vs Placebo

Reference: Roth D, et al, 2015 (C-SURFER trial)^{1,27,28,29,30,31}

Study Design: Randomized, multicenter study

Study Funding: Merck

Patients: 237 patients (including an additional 11 patients reserved for open-label pharmacokinetic analyses) with hepatitis C. All patients had stage 4 or 5 chronic kidney disease and an HCV genotype of 1. Of the 237 patients, 235 received 1 dose of study drug (sensitivity analysis population) and 229 were included in the primary analysis (mITT) population (6 patients were excluded for non-virologic reasons). At baseline, average age was 56 years; 73.2% were male; 46.4% were White, 46% were Black, and 6% were Asian; 80.4% were treatment naive; 6% had cirrhosis; 51.9% had HCV genotype 1a, 47.2% had HCV genotype 1b, and 1.7% had an unspecified subtype of HCV genotype 1; 18.7% had stage 4 chronic kidney disease, 81.3% had stage 5 chronic kidney disease, and 76.2% were on hemodialysis; and 34% had diabetes. Patients were excluded if they were pregnant or had decompensated liver disease, current peritoneal dialysis therapy, concomitant HIV or hepatitis B virus infection, history of malignancy within 5 years of study, history of drug or alcohol abuse, history of organ transplant (except kidney, cornea, and hair), uncontrolled hypertension, cardiovascular disorder or procedure within 3 months of study, congestive heart failure within 3 months of study, severe active peripheral vascular disease, history of hepatitis not due to HCV, or stroke, transient ischemic attack, or neurological disorder within 3 months of study.

Intervention: Patients were randomized 1:1 in blocks of 4 with concealed allocation to oral elbasvir

50 mg and grazoprevir 100 mg ($n = 111$) or placebo ($n = 113$) once daily for 12 weeks. Randomization was stratified based on diabetes status and hemodialysis status. An additional 11 patients were given oral elbasvir 50 mg and grazoprevir 100 mg as part of an open-label pharmacokinetic study. Patients in the placebo group received elbasvir plus grazoprevir 4 weeks after the end of the study (deferred therapy). After the last dose of active treatment, patients were followed for an additional 24 weeks.

Results

Primary Endpoint(s)

- Percentage of patients treated with elbasvir plus grazoprevir who achieved SVR12, defined as HCV RNA levels below the LLQ of 15 units/mL, after 12 weeks of therapy was 99.1% (95% CI, 95.3-100). The sensitivity analysis ($n = 122$) resulted in a similar SVR12 rate (94%). SVR12 was achieved by 97% of genotype 1a patients and 92% of genotype 1b patients. SVR12 was achieved by 86% of patients with cirrhosis and 95% of patients without cirrhosis; by 95% of treatment-naïve patients and 90% of treatment-experienced patients; by 93% of patients on dialysis and 97% of patients not on dialysis; and by 100% of patients with stage 4 chronic kidney disease and 93% of patients with stage 5 chronic kidney disease.
- Subgroup analyses showed SVR12 results were not impacted by age, gender, race, IL28B genotype, baseline HCV RNA level, or concomitant antiretroviral therapy.
- Percentage of patients experiencing at least 1 adverse event up to 14 days after therapy was 79.9% (179 of all 224 study patients). Common adverse events observed included headache, nausea, and fatigue. Serious adverse events occurred in 22.1% with elbasvir plus grazoprevir and 19.5% with placebo. No patient discontinued study drugs due to adverse events in the elbasvir plus grazoprevir group, but 4.4% of patients discontinued study drugs in the placebo group.

Secondary Endpoint(s)

- Percentage of patients treated with elbasvir plus grazoprevir who achieved sustained virologic response 4 weeks after end of therapy (SVR4) was 100% (95% CI, 96.9%-100%).

Comments: Elbasvir plus grazoprevir was investigated in HCV genotype 1 patients with chronic kidney disease (including some patients with cirrhosis). All analyses were conducted for the mITT population

(missing data were regarded as failures). The sensitivity analysis included the 11 patients who were part of the open-label pharmacokinetic study. Elbasvir and grazoprevir were well tolerated in patients with chronic kidney disease, as both are excreted via the liver. This study was conducted in the United States, Argentina, Australia, Canada, Estonia, France, Israel, Lithuania, the Netherlands, Korea, Spain, and Sweden.

Limitations: The SVR24 results are expected to be reported in July 2016.

Drug: Elbasvir plus Grazoprevir with Ribavirin

Reference: Forns X, et al, 2015 (C-SALVAGE trial)^{32,33,34}

Study Design: Open-label, single-arm, multicenter, international study

Study Funding: Merck

Patients: 79 patients 18 years or older with hepatitis C. All treatment-experienced patients had HCV genotype 1 and HCV RNA level greater than 10,000 units/mL. Up to 40% had cirrhosis and about 80% had previously failed HCV triple therapy (protease inhibitor plus peginterferon and ribavirin). At baseline, average age was 54.4 years (median, 55 years); 58.2% were male; 97.5% were White and 2.5% were Black; 38% had HCV genotype 1a and 62% had HCV genotype 1b; 97.5% had IL28B non-CC genotype and 2.5% had IL28B CC genotype; 46.8% had Metavir F0 to F2 stage fibrosis, 10.1% had F3 stage fibrosis, and 43% had F4 stage fibrosis; 54.4% were previously treated with telaprevir, 35.4% were previously treated with boceprevir, and 10.1% were previously treated with simeprevir; 10.1% had baseline NS5A polymorphisms; and 83.5% had a history of virologic failure and 16.5% had a history of non-virologic failure. Average baseline HCV RNA level was 6.1 log₁₀ units/mL. Patients were excluded if they were pregnant or had decompensated liver disease, hepatocellular carcinoma, concomitant HIV or hepatitis B virus infection, history of hepatitis not due to HCV, prior exposure to HCV therapy (except boceprevir, telaprevir, simeprevir, sofosbuvir, pegylated interferon, and ribavirin), history of malignancy within 5 years of study (except treated basal cell or squamous cell skin cancer, in situ cervical cancer, or carcinoma in situ), thrombocytopenia (ie, platelet count less than 50 × 10⁹ cells/L), hypoalbuminemia (ie, albumin level less than 3 g/dL), history of drug or alcohol

abuse within 12 months of study, history of gastric surgery or malabsorption disorders, or hemoglobinopathy. Coadministration of investigational medications or corticosteroids was not allowed.

Intervention: Patients received elbasvir, grazoprevir, and ribavirin for 12 weeks. Elbasvir 50 mg and grazoprevir 100 mg were taken orally once daily, and ribavirin was taken orally twice daily. Weight-based dosing was used for ribavirin (total daily dose ranging between 800 and 1,400 mg). After the last dose of therapy, patients were followed for 24 weeks.

Results

Primary Endpoint(s)

- Based on a PP analysis population ($n = 70$), the percentage of patients treated with elbasvir, grazoprevir, and ribavirin for 12 weeks who achieved SVR12, defined as HCV RNA levels below the LLQ of 15 units/mL, was 97.1% (95% CI, 90.1%-99.7%). A sensitivity analysis, based on the ITT population ($n = 79$), produced a similar result (SVR12 96.2% [95% CI, 89.3%-99.2%]).
- Of the 79 patients treated with elbasvir, grazoprevir, and ribavirin, 3 did not achieve SVR12 (all due to relapse). Of the PP analysis population, 2 of 70 patients did not achieve SVR12.
- Subgroup analyses showed SVR12 results were not impacted by age, gender, HCV subtype, cirrhosis status, baseline HCV viral load, baseline NS3 RAV, time since prior treatment, or previous protease inhibitor therapy.
- Percentage of patients experiencing at least 1 adverse event up to 14 days after therapy was 79.7% (63 of 79 patients). Common adverse events observed in at least 5% of all patients included fatigue, headache, asthenia, nausea, insomnia, anemia, diarrhea, upper abdominal pain, constipation, vomiting, and decreased hemoglobin. Treatment-emergent adverse events were reported in 57% of all patients. Serious adverse events occurred in 4 patients (bacterial pharyngitis, laryngeal squamous cell carcinoma, chronic obstructive pulmonary disease, and urinary tract infection), none of which were considered related to study drug. Grade 3 or 4 laboratory abnormalities were infrequent; 6.3% of patients had total bilirubin levels more than 2.5 times the ULN, and 5.1% of patients had triacylglycerol lipase levels more than 3 times the ULN. Only 1 patient discontinued study

drug due to adverse events (dysphagia, dehydration, and vomiting), which were deemed related to radiation therapy administered for squamous cell carcinoma.

Secondary Endpoint(s)

- Percentage of patients treated with elbasvir, grazoprevir, and ribavirin for 12 weeks who achieved SVR12 was similar regardless of previous protease inhibitor therapy: 96.4% (95% CI, 81.7%-99.9%) for patients previously receiving boceprevir; 95.3% (95% CI, 84.2%-99.4%) for telaprevir; and 100% (95% CI, 63.1%-100%) for simeprevir.

Endpoint(s)

- Based on the PP analysis population, the percentage of patients treated with elbasvir, grazoprevir, and ribavirin for 12 weeks who achieved SVR24 was 97.1%. Based on the ITT population, the percentage of patients who achieved SVR24 was 96.2% (95% CI, 89.3%-99.2%) and the percentage of patients who achieved SVR4 was 97.5% (95% CI, 91.2%-99.7%).
- Of the 34 patients with baseline NS3 RAVs, 31 (91.2%) achieved SVR12, while all 44 patients (100%) without NS3 RAVs achieved SVR12. All 6 patients (100%) with baseline NS5A RAVs achieved SVR12.

Comments: A total of 78 patients (98%) completed the study. Elbasvir plus grazoprevir was investigated with ribavirin for 2 weeks in patients with HCV genotype 1 with or without cirrhosis who previously failed HCV triple therapy (protease inhibitor plus peginterferon and ribavirin). The primary endpoint was analyzed using the PP analysis population, including all patients having minimal protocol violations and having achieved SVR12. A sensitivity analysis was conducted using the ITT population (missing data were regarded as failures, unless both preceding and anteceding data were successes), which supported the findings from the primary PP analysis. All other endpoints, including safety endpoints, were analyzed using the ITT analysis population. This study was conducted in the United States, Austria, Israel, and Spain.

Limitations: This was a phase 2 study.

Drug: Elbasvir plus Grazoprevir with or without Ribavirin

Reference: Sulkowski M, et al, 2015 (C-WORTHY trial)^{12,35}

Study Design: Randomized, open-label, parallel-group, multicenter, international study

Study Funding: Merck

Patients: 218 patients 18 years or older with hepatitis C (159 patients infected with HCV only and 59 patients coinfecting with HCV and HIV). All treatment-naïve patients had HCV genotype 1 and HCV RNA levels of 10,000 units/mL or higher. Patients with concomitant HIV infection were included if disease was well controlled while taking raltegravir in combination with 2 nucleoside/nucleotide reverse transcriptase inhibitors for a minimum of 8 weeks prior to study, HIV RNA levels were undetectable for a minimum of 24 weeks prior, and CD4 count was at least 300 cells/mL. At baseline, average age was 50 years (range, 20-73 years); 59% were male; 88% were White and 11% were non-White (of whom, 9% were Hispanic/Latino); 72% had HCV genotype 1a, 27% had HCV genotype 1b, and 1% had another subtype of HCV genotype 1; 73% had IL28B non-CC genotype, 26% had IL28B CC genotype, and 1% had unknown IL28B genotype; 77% had HCV RNA levels greater than 800,000 units/mL and 23% had HCV RNA levels 800,000 units/mL or less; and 92% had Metavir F0 to F2 stage fibrosis and 8% had F3 stage fibrosis. Other average baseline characteristics included BMI 25.5 kg/m² (86% less than 30 kg/m²), HCV RNA level 6.31 log₁₀ units/mL, hemoglobin level 14.7 g/dL, albumin level 4.43 g/L, ALT level 73.3 units/L, AST level 53.3 units/L, bilirubin level 0.481 mg/dL, and platelet count 215.1 × 10⁹ cells/L. Patients were excluded if they had decompensated liver disease, hepatocellular carcinoma, history of hepatitis not due to HCV, prior exposure to HCV therapy, and multiple other criteria.

Intervention: In cohort A, 65 patients infected with HCV were randomized (2:2:3 for genotype 1b and 1:1:0 for genotype 1a) with concealed allocation to receive elbasvir 20 mg, grazoprevir 100 mg, and ribavirin for 12 weeks (cohort A1; *n* = 25); elbasvir 50 mg, grazoprevir 100 mg, and ribavirin for 12 weeks (cohort A2; *n* = 27); or elbasvir 50 mg and grazoprevir 100 mg for 12 weeks (cohort A3; *n* = 13). In cohort B, 94 patients infected with HCV were randomized (2:1:2 for genotype 1a only) with concealed allocation to receive elbasvir 50 mg, grazoprevir 100 mg, and ribavirin for 8 weeks

(cohort B1; $n = 30$); elbasvir 50 mg, grazoprevir 100 mg, and ribavirin for 12 weeks (cohort B2; $n = 33$; all genotype 1b patients were assigned to B2); or elbasvir 50 mg and grazoprevir 100 mg for 12 weeks (cohort B3; $n = 31$). Also, in cohort B, 59 patients coinfecting with HCV and HIV were randomized 1:1 with concealed allocation to receive elbasvir 50 mg, grazoprevir 100 mg, and ribavirin for 12 weeks (cohort B12; $n = 29$) or elbasvir 50 mg and grazoprevir 100 mg for 12 weeks (cohort B13; $n = 30$). Randomization was stratified based on HCV genotype and HIV status. Elbasvir and grazoprevir were taken orally once daily with or without food, and ribavirin was taken orally twice daily with food. Weight-based dosing was used for ribavirin (800 to 1,400 mg). Peginterferon alfa-2b was available as rescue therapy only for cohort A patients who demonstrated virologic failure or discontinued study drugs due to reasons other than ribavirin adverse effects; there was no rescue therapy available for cohort B patients. Tables 2 and 3 summarize the regimens used in the different cohorts.

Results

Primary Endpoint(s)

- Percentage of patients infected with HCV only who achieved SVR12, defined as HCV RNA levels below the LLQ of 25 units/mL, after 12 weeks of therapy was 93% (95% CI, 85%-97%) with elbasvir, grazoprevir, and ribavirin (combined cohorts A1, A2, and B2) and 98% (95% CI, 88%-100%) with elbasvir plus grazoprevir alone (combined cohorts A3 and B3).
- Percentage of patients coinfecting with HCV and HIV who achieved SVR12 after 12 weeks of therapy was 97% (95% CI, 82%-100%) with elbasvir, grazoprevir, and ribavirin (B12) and 87% (95% CI, 69%-96%) with elbasvir plus grazoprevir alone (B13).
- Percentage of patients infected with HCV only who achieved SVR12 after 8 weeks of therapy was 80% (95% CI, 61%-92%) with elbasvir, grazoprevir, and ribavirin (B1).
- Subgroup analyses showed SVR12 results were not impacted by age, gender, race, ethnicity, HCV subtype, BMI, baseline ALT, or HIV status, but IL28B genotype may influence the ability of coinfecting patients to achieve SVR12; of patients with IL28B non-CC genotype, 95% of patients infected with HCV only achieved SVR12 compared with 88% of patients coinfecting with HCV and HIV.
- Of the 218 patients, 18 did not achieve SVR12 due to breakthrough (3 patients, 1 of whom presented with a new HCV genotype 2b infection), relapse (9 patients, 1 of whom only received elbasvir and ribavirin [no grazoprevir] for the first month of therapy), or non-virologic failure (6 patients). Post hoc analysis of SVR12 rates after excluding these 6 non-virologic failures produced similar results; with 12 weeks of therapy, SVR12 was achieved by 97% of patients with HCV only (A1, A2, A3, B2, and B3) and 95% of patients coinfecting with HIV (B12 and B13). The majority of patients with virologic failure were infected with HCV genotype 1a (10 of 12 patients). A higher failure

Table 2. Individual cohorts

Cohort A1	Cohort A2	Cohort A3
HCV only genotypes 1a, 1b Elbasvir (20 mg) + Grazoprevir + Ribavirin 12 weeks	HCV only genotypes 1a, 1b Elbasvir (50 mg) + Grazoprevir + Ribavirin 12 weeks	HCV only genotype 1b Elbasvir (50 mg) + Grazoprevir 12 weeks
Cohort B1	Cohort B2	Cohort B3
HCV only genotype 1a Elbasvir (50 mg) + Grazoprevir + Ribavirin 8 weeks	HCV only genotypes 1a, 1b Elbasvir (50 mg) + Grazoprevir + Ribavirin 12 weeks	HCV only genotype 1a Elbasvir (50 mg) + Grazoprevir 12 weeks
	Cohort B12	Cohort B13
	HCV and HIV genotypes 1a, 1b Elbasvir (50 mg) + Grazoprevir + Ribavirin 12 weeks	HCV and HIV genotypes 1a, 1b Elbasvir (50 mg) + Grazoprevir 12 weeks

Table 3. Cohort combinations

Cohorts A1, A2, B2	Cohorts A3, B3
Elbasvir + Grazoprevir + Ribavirin 12 weeks	Elbasvir + Grazoprevir 12 weeks

rate (statistical analysis not performed) was observed with only 8 weeks of therapy; 7 of 188 patients (4%) treated for 12 weeks did not achieve SVR12 and 5 of 30 patients (17%) treated for 8 weeks did not achieve SVR12. However, there were considerably fewer patients enrolled in the 8-week treatment group (B1) than in the 12-week treatment group (all other cohorts).

- Percentage of patients experiencing at least 1 adverse event up to 14 days after therapy was 75% (163 of 218 patients). Percentages for cohort combinations were 76% (65 of 86 patients) with elbasvir, grazoprevir, and ribavirin (A1, A2, and B2); 88% (38 of 43 patients) with elbasvir plus grazoprevir alone (A3 and B3); 87% (26 of 30 patients) with 8 weeks of elbasvir, grazoprevir, and ribavirin (B1); 66% (19 of 29 HIV patients) with elbasvir, grazoprevir, and ribavirin (B12); and 50% (15 of 30 HIV patients) with elbasvir plus grazoprevir alone (B13).
- Common adverse events observed in at least 10% of all patients (both patients infected with HCV only and those coinfecting with HCV and HIV) included mild to moderate fatigue, headache, nausea, and diarrhea. Serious adverse events occurred in 3 patients, 2 of which were considered related to study therapy (nausea and asthenia). More patients treated with ribavirin reported drug-related adverse events and increased bilirubin and hemoglobin levels compared with patients not treated with ribavirin. No patient discontinued study drug due to an adverse event.

Secondary Endpoint(s)

- For all cohorts, HCV RNA levels less than 25 units/mL were attained as early as treatment week 2 and maintained up to 12 weeks after end of therapy (ie, SVR12). SVR24 data were not available at time of publication.
- SVR12 rates were comparable between patients with and without NS3 RAVs; however, patients with NS5A RAVs achieved a lower rate of SVR12 (68%) compared with patients without NS5A RAVs (95%).

- No patients coinfecting with HCV and HIV developed HIV antiretroviral failure or loss of HIV suppression during the study.

Comments: This study reported data from a subset of all patients enrolled in the large C-WORTHY study (the study summarized in the following section focused on a different population). Elbasvir plus grazoprevir was effective with or without ribavirin for 8 and 12 weeks in treatment-naïve patients with HCV genotype 1 without cirrhosis (including some patients with concomitant HIV infection). SVR12 rates in noncirrhotic, treatment-naïve, genotype 1 patients treated with elbasvir plus grazoprevir were similar, whether treated with or without ribavirin for 8 or 12 weeks. For cohorts A1 and A2, administration of elbasvir (20 mg or 50 mg) was double-blinded using double-dummy placebo capsules (eg, cohort A1 patients received an elbasvir 20 mg capsule and a placebo capsule similar to the elbasvir 50 mg capsule); all other treatment arms were open-label. All analyses were conducted using the ITT population (missing data were regarded as failures, unless both preceding and anteceding data were successes). No patient reported being noncompliant with study drugs. This study was conducted in the United States, Australia, Canada, Denmark, France, Hungary, Israel, New Zealand, Puerto Rico, Spain, Sweden, and Turkey.

Limitations: This was a phase 2 study. The LLQ was 25 units/mL and the limit of detection was 15 units/mL. Some secondary endpoints (time to first achievement of undetectable levels of HCV RNA, percentage of patients achieving SVR24, and change in CD4+ T-cell counts from baseline in coinfecting patients) were not reported.

Reference: Lawitz E, et al, 2015 (C-WORTHY trial)^{13,35}

Study Design: Randomized, open-label, parallel-group, multicenter, international study

Study Funding: Merck

Patients: 253 patients 18 years or older with hepatitis C (170 patients with Child-Pugh A cirrhosis). All patients had a body weight of 50 to 125 kg, HCV genotype 1, and HCV RNA levels 10,000 units/mL or higher. Treatment-naïve patients (cohort 1) and null responders (cohort 2) to peginterferon plus ribavirin were included. At baseline, average age was 56.3 years (range, 18 to 82 years); 58% were

male; 92% were White and 8% were non-White (of whom, 5% were Hispanic/Latino); 64% had HCV genotype 1a, 34% had HCV genotype 1b, and less than 1% had another subtype of HCV genotype 1; 81% had IL28B non-CC genotype, 16% had IL28B CC genotype, and 3% had unknown IL28B genotype; 91% had HCV RNA levels greater than 800,000 units/mL and 9% had HCV RNA levels 800,000 units/mL or less; and 25% had Metavir F0 to F2 stage fibrosis, 8% F3 stage fibrosis, and the majority (67%) F4 stage fibrosis. Other average baseline characteristics included BMI 26.65 kg/m² (80% less than 30 kg/m²), HCV RNA level 6.61 log₁₀ units/mL, hemoglobin level 14.69 g/dL, albumin level 4.23 g/L, ALT level 97.8 units/L, AST level 81.5 units/L, bilirubin level 0.645 mg/dL, and platelet count 168.3 × 10⁹ cells/L. Patients were excluded using criteria similar to those reported by Sulkowski M et al (C-WORTHY trial).^{12,35}

Intervention: Cohort 1 consisted of treatment-naïve patients with cirrhosis: 60 patients were randomized 1:1 to receive elbasvir, grazoprevir, and ribavirin for 12 weeks (cohort B4; *n* = 29) or elbasvir and grazoprevir for 12 weeks (cohort B5; *n* = 31); 63 patients were randomized 1:1 to receive elbasvir, grazoprevir, and ribavirin for 18 weeks (cohort B6; *n* = 32) or elbasvir and grazoprevir for 18 weeks (cohort B7; *n* = 31). Cohort 2 consisted of null responders with or without cirrhosis: 65 patients were randomized 1:1 to receive elbasvir, grazoprevir, and ribavirin for 12 weeks (cohort B8; *n* = 32) or elbasvir and grazoprevir for 12 weeks (cohort B9; *n* = 33); 65 patients were randomized 1:1 to receive elbasvir, grazoprevir, and ribavirin for 18 weeks (cohort B10; *n* = 33) or

elbasvir and grazoprevir for 18 weeks (cohort B11; *n* = 32). Elbasvir 50 mg and grazoprevir 100 mg were taken orally once daily with or without food, and ribavirin was taken orally twice daily with food. Weight-based dosing was used for ribavirin (800-1,400 mg). All randomization occurred with concealed allocation after stratifying for HCV genotype and cirrhosis status. No rescue therapy was provided. Table 4 summarizes the regimens used in the different cohorts.

Results

Primary Endpoint(s)

- Percentage of treatment-naïve patients with cirrhosis who achieved SVR12, defined as HCV RNA levels below the LLQ of 25 units/mL, after 12 weeks of therapy was 90% (95% CI, 74% to 98%) with elbasvir, grazoprevir, and ribavirin (B4) and 97% (95% CI, 82%-100%) with elbasvir plus grazoprevir alone (B5). Percentage of those achieving SVR12 after 18 weeks of therapy was 97% (95% CI, 84%-100%) with elbasvir, grazoprevir, and ribavirin (B6) and 94% (95% CI, 79%-99%) with elbasvir plus grazoprevir alone (B7).
- Percentage of null responders with or without cirrhosis who achieved SVR12 after 12 weeks of therapy was 94% (95% CI, 79%-99%) with elbasvir, grazoprevir, and ribavirin (B8) and 91% (95% CI, 76%-98%) with elbasvir plus grazoprevir alone (B9). Percentage of those achieving SVR12 after 18 weeks of therapy was 100% (95% CI, 89%-100%) with elbasvir, grazoprevir, and ribavirin (B10) and 97% (95% CI, 84%-100%) with elbasvir plus grazoprevir alone (B11).
- Subgroup analyses showed SVR12 results were not impacted by age, gender, race, ethnicity,

Table 4. Individual cohorts

12 weeks		18 weeks	
With ribavirin	No ribavirin	With ribavirin	No ribavirin
Cohort B4	Cohort B5	Cohort B6	Cohort B7
Treatment-naïve, cirrhosis Elbasvir + Grazoprevir + Ribavirin 12 weeks	Treatment-naïve, cirrhosis Elbasvir + Grazoprevir 12 weeks	Treatment-naïve, cirrhosis Elbasvir + Grazoprevir + Ribavirin 18 weeks	Treatment-naïve, cirrhosis Elbasvir + Grazoprevir 18 weeks
Cohort B8	Cohort B9	Cohort B10	Cohort B11
Null responder, with or without cirrhosis Elbasvir + Grazoprevir + Ribavirin 12 weeks	Null responder, with or without cirrhosis Elbasvir + Grazoprevir 12 weeks	Null responder, with or without cirrhosis Elbasvir + Grazoprevir + Ribavirin 18 weeks	Null responder, with or without cirrhosis Elbasvir + Grazoprevir 18 weeks

HCV subtype, BMI, baseline ALT, HCV viral load, cirrhosis status, prior treatment status, treatment duration, or IL28B genotype.

- Of the 253 patients, 10 did not achieve SVR12 due to breakthrough (2 patients), relapse (8 patients), or non-virologic failure (3 patients). Treatment-naïve patients with cirrhosis had a virological failure rate of 5% (6 of 123 patients), while null responders with or without cirrhosis had a virological failure rate of 3% (4 of 130 patients). At time of failure, the majority of patients (8 of 10 patients) had NS3/4A and/or NS5A RAVs.
- Percentage of patients experiencing at least 1 adverse event up to 14 days after therapy was 79% (201 of 253 patients). For treatment-naïve patients with cirrhosis, percentages were 77% (24 of 31 patients) with elbasvir, grazoprevir, and ribavirin for 12 weeks (B4); 59% (17 of 29 patients) with elbasvir plus grazoprevir alone for 12 weeks (B5); 88% (28 of 32 patients) with elbasvir, grazoprevir, and ribavirin for 18 weeks (B6); and 81% (25 of 31 patients) with elbasvir plus grazoprevir alone for 18 weeks (B7). For null responders with or without cirrhosis, percentages were 78% (25 of 32 patients) with elbasvir, grazoprevir, and ribavirin for 12 weeks (B8); 76% (25 of 33 patients) with elbasvir plus grazoprevir alone for 12 weeks (B9); 94% (31 of 33 patients) with elbasvir, grazoprevir, and ribavirin for 18 weeks (B10); and 81% (26 of 32 patients) with elbasvir plus grazoprevir alone for 18 weeks (B11).
- Common adverse events observed in at least 10% of all patients (both treatment-naïve patients with cirrhosis and null responders with or without cirrhosis) included mild to moderate fatigue, headache, and asthenia. Serious adverse events occurred in 7 patients, 1 (abdominal pain) of which was considered to be related to study therapy. Incidences of drug-related adverse events, increased bilirubin and hemoglobin levels, and discontinuation due to adverse events were higher in patients treated with ribavirin compared with patients not administered ribavirin. Two patients discontinued study drug due to adverse events, none of which were due to grade 4 increases in ALT; 1 patient in cohort B6 discontinued due to uterine bleeding and 1 patient in cohort B8 discontinued due to atrial fibrillation. Up to 12 weeks after study therapy, no patient had liver decompensation.

Secondary Endpoint(s)

- For all cohorts, percentages of patients achieving HCV RNA levels less than 25 units/mL were low at treatment week 2 (58%-79%). However, at treatment week 4, HCV RNA levels less than 25 units/mL were attained by 90% to 100% of all patients, regardless of cohort, and maintained at least 12 weeks after end of therapy (ie, SVR12). SVR24 data were not available at time of publication.
- SVR12 rates were comparable between patients with NS3 RAVs and those without (92% and 96%, respectively); however, patients with NS5A RAVs achieved a lower rate of SVR12 (82%) compared with patients without NS5A RAVs (97%).

Endpoint(s)

- Of the 25 patients with low baseline platelet levels (less than 90×10^9 cells/L), 18 achieved SVR12. Of the 5 patients with low baseline platelet levels and low baseline albumin levels (less than 3.5 g/dL), 4 achieved SVR12.

Comments: This study reported data of another subset of all patients enrolled in the large C-WORTHY study; the previously summarized study focused on a different population. Elbasvir plus grazoprevir was effective with or without ribavirin for 12 and 18 weeks in treatment-naïve patients with cirrhosis and in null responders with or without cirrhosis. SVR12 rates were not significantly different between treatment-naïve patients with cirrhosis and null responders with or without cirrhosis, and SVR12 rates were similar whether treated with or without ribavirin for 12 or 18 weeks. Null responders were defined as having a less than $2 \log_{10}$ reduction in HCV RNA after 12 weeks of peginterferon and ribavirin therapy or having a less than $1 \log_{10}$ reduction in HCV RNA after 4 weeks of peginterferon and ribavirin therapy. All analyses were conducted using the ITT population (missing data were regarded as failures, unless both preceding and anteceding data were successes). One patient without cirrhosis was randomized to an 18-week treatment arm (cohort B6 or B7) and was analyzed as 1 of the cirrhotic patients. One null responder treated with elbasvir, grazoprevir, and ribavirin for 12 weeks (cohort B8) died during the study. This study was conducted in the United States, Australia, Canada, Denmark, France, Hungary, Israel, New Zealand, Spain, Sweden, and Turkey.

Limitations: The LLQ was 25 units/mL and the limit of detection was 15 units/mL in this phase 2 study. Certain secondary endpoints (time to first achievement of undetectable levels of HCV RNA, percentage achieving SVR24, or percentage achieving undetectable HCV RNA at week 12 for those treated for 18 weeks) were not reported.

Indication: Hepatitis C Virus Infection Genotype 2, 4, 5, or 6

Studies

Drug: Grazoprevir plus Ribavirin with or without Elbasvir, or Elbasvir plus Grazoprevir with or without Ribavirin

Reference: Brown A, et al, 2015 (C-SCAPE trial)^{2,36}

Study Design: Randomized, open-label, multicenter study

Study Funding: Merck

Patients: 100 patients 18 years or older with hepatitis C. All treatment-naïve, noncirrhotic patients had an HCV genotype of 2, 4, 5, or 6. At baseline, 57% were male; 85% were White; and 60% had HCV genotype 2, 20% had HCV genotype 4, 8% had HCV genotype 5, and 12% had HCV genotype 6. Average baseline HCV RNA level was 6.9 log₁₀ units/mL. Of the 100 patients, 98 were included in the primary analysis (mITT) population. Patients were excluded if they were pregnant or had prior exposure to HCV therapy, concomitant HIV or hepatitis B virus infection, hepatocellular carcinoma, history of drug or alcohol abuse, history of malignancy within 5 years of study, or uncontrolled diabetes.

Intervention: In part A, patients with HCV genotype 2 were randomized to receive elbasvir, grazoprevir, and ribavirin (*n* = 30) or grazoprevir plus ribavirin (*n* = 30) for 12 weeks. In part B, patients with HCV genotype 4, 5, or 6 were randomized to receive elbasvir, grazoprevir, and ribavirin (*n* = 10, 4, and 5 for genotypes 4, 5, and 6, respectively) or elbasvir plus grazoprevir (*n* = 10, 4, and 5 for genotypes 4, 5, and 6, respectively) for 12 weeks. Elbasvir 50 mg and grazoprevir 100 mg were taken orally once daily, and ribavirin was taken orally twice daily. Weight-based dosing was used for ribavirin (800-1,400 mg).

Results

Primary Endpoint(s)

- Percentage of patients with HCV genotype 2 who achieved SVR12, defined as HCV RNA

levels below 25 units/mL, was 80% with elbasvir, grazoprevir, and ribavirin and 67% with grazoprevir plus ribavirin.

- Percentage of patients with HCV genotype 4 who achieved SVR12 was 100% with elbasvir, grazoprevir, and ribavirin and 90% with elbasvir plus grazoprevir.
- Percentage of patients with HCV genotype 5 who achieved SVR12 was 100% with elbasvir, grazoprevir, and ribavirin and 25% with elbasvir plus grazoprevir.
- Percentage of patients with HCV genotype 6 who achieved SVR12 was 80% with elbasvir, grazoprevir, and ribavirin and with elbasvir plus grazoprevir.
- Common adverse events included fatigue (26%), headache (21%), and asthenia (16%).
- One patient discontinued study drugs on day 8 due to an asymptomatic increase in ALT (greater than 10 times the ULN), which was deemed possibly related to study drugs and/or the concurrent use of etifoxine.

Comments: All patients included in this study were treatment naïve and noncirrhotic. Grazoprevir plus ribavirin with or without elbasvir was investigated in patients with HCV genotype 2 and elbasvir plus grazoprevir with or without ribavirin was investigated in patients with HCV genotype 4, 5, or 6. A greater percentage of genotype 2 patients achieved SVR12 with elbasvir, grazoprevir, and ribavirin than without elbasvir. While 100% of genotype 4 patients achieved SVR12 with elbasvir, grazoprevir, and ribavirin, 90% achieved SVR12 without ribavirin. Genotype 5 patients did not respond well without ribavirin, and genotype 6 patients responded equally well to elbasvir plus grazoprevir with or without ribavirin.

Limitations: Few patients comprised each genotype subpopulation in this phase 2 study. The LLQ was 25 units/mL. Results for this study are only available in a meeting abstract.

Indication: Hepatitis C Virus Infection Genotype 1 or 3

Studies

Drug: Elbasvir/Grazoprevir with Sofosbuvir

Reference: Poordad F, et al, 2015 (C-SWIFT trial)^{3,37,38}

Study Design: Randomized, open-label, parallel-group, single-center study

Study Funding: Merck

Patients: 143 patients 18 years or older with hepatitis C. All treatment-naïve patients had an HCV genotype of 1 or 3 with or without cirrhosis. At baseline, 66% were male; 98% were White and 45% were Hispanic; and 71.3% had HCV genotype 1 and 28.7% had genotype 3. The average baseline HCV RNA level was 6.65 log₁₀ units/mL. Patients were excluded if they had decompensated liver disease, concomitant HIV or hepatitis B virus infection, history of malignancy within 5 years of study, hepatocellular carcinoma, or history of drug or alcohol abuse. Coadministration of corticosteroids was not allowed.

Intervention: HCV genotype 1 patients without cirrhosis were randomized to receive oral elbasvir/grazoprevir and sofosbuvir for 4 weeks (*n* = 31) or for 6 weeks (*n* = 30). HCV genotype 1 patients with cirrhosis were randomized to receive oral elbasvir/grazoprevir and sofosbuvir for 6 weeks (*n* = 20) or for 8 weeks (*n* = 21). HCV genotype 3 patients without cirrhosis were randomized to receive oral elbasvir/grazoprevir and sofosbuvir for 8 weeks (*n* = 15) or for 12 weeks (*n* = 14). HCV genotype 3 patients with cirrhosis were assigned to receive oral elbasvir/grazoprevir and sofosbuvir for 12 weeks (*n* = 12). The single, fixed-dose combination tablet of elbasvir 50 mg/grazoprevir 100 mg was taken with sofosbuvir 400 mg orally once daily.

Results**Primary Endpoint(s)**

- Percentage of patients who achieved SVR12, defined as HCV RNA levels below the LLQ of 15 units/mL, will be reported.
- No patient discontinued study drugs due to adverse events, and there were no reports of serious adverse events related to exposure to study drugs.

Secondary Endpoint(s)

- Percentage of HCV genotype 1 patients without cirrhosis who achieved SVR8 was 39% after 4 weeks of therapy and 87% after 6 weeks of therapy. Percentage of HCV genotype 1 patients with cirrhosis who achieved SVR8 was 80% after 6 weeks of therapy and 89% after 8 weeks of therapy.
- Percentage of HCV genotype 3 patients without cirrhosis who achieved SVR4 was 100% after both 8 and 12 weeks of therapy. Percentage of HCV genotype 3 patients with cirrhosis who achieved SVR4 was 90% after 12 weeks of therapy.

Comments: Combination therapy with elbasvir/grazoprevir and sofosbuvir was investigated at various treatment intervals in treatment-naïve patients with HCV genotypes 1 and 3 with and without cirrhosis. Interim data were presented in a presentation abstract (up to 8 weeks after end of treatment for HCV genotype 1 patients and up to 4 weeks after end of treatment for HCV genotype 3 patients). Based on these preliminary data presented, adding sofosbuvir to the fixed-dose combination of elbasvir and grazoprevir appears to be promising for the patient population studied.

Limitations: Results for this phase 2 study are only available as a meeting abstract. SVR12 results have not yet been reported.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS**Contraindications**

Patients with moderate or severe hepatic impairment are expected to have significantly increased levels of elbasvir/grazoprevir and abnormal elevations in ALT; elbasvir/grazoprevir is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh class B or C).¹

The concomitant use of OATP1B1/3 inhibitors (eg, atazanavir, darunavir, lopinavir, saquinavir, tipranavir, cyclosporine) is contraindicated due to the increased risk of ALT elevations secondary to increased grazoprevir levels.¹

The concomitant use of strong CYP3A inducers (eg, phenytoin, carbamazepine, rifampin, St. John's wort, efavirenz) is contraindicated due to potential loss of efficacy secondary to decreased grazoprevir/elbasvir levels.¹

Refer to the ribavirin prescribing information for information regarding contraindications associated with ribavirin.¹

Warnings and Precautions

Transient, asymptomatic ALT elevations of more than 5 times the ULN occurred in 1% of patients exposed to elbasvir/grazoprevir in clinical trials. ALT elevations were observed at a greater frequency (2%) in females, Asians, and older adults (65 years or older).^{1,2,4,6,7,12,13,32}

The warnings and precautions associated with ribavirin (eg, avoiding pregnancy) should be taken into account for patients who require concomitant therapy of elbasvir/grazoprevir with ribavirin. Refer to the ribavirin prescribing information for more information.¹

Drug interactions with elbasvir/grazoprevir may result in increased risk of adverse events or in decreased efficacy of elbasvir/grazoprevir and/or increased resistance (see Contraindications and Drug Interactions).¹

The efficacy and safety of elbasvir/grazoprevir have not been studied in pregnant patients. Animal data indicate that the individual components of elbasvir/grazoprevir are not teratogenic; no adverse effects on pregnancy or embryofetal development were observed in rats and rabbits exposed to elbasvir or grazoprevir. However, if elbasvir/grazoprevir is used in combination with ribavirin, ribavirin is contraindicated in pregnant women and in men whose female partners are pregnant.^{1,39}

The degree to which elbasvir/grazoprevir is excreted in human milk and its effects on milk production and the infant is unknown. It is recommended that patients consider both the benefits of breast-feeding and the clinical need for elbasvir/grazoprevir therapy. If elbasvir/grazoprevir is used in combination with ribavirin, a decision should be made to discontinue breast-feeding or ribavirin therapy.^{1,39}

If elbasvir/grazoprevir is used in combination with ribavirin, the ribavirin prescribing information should be consulted for information regarding use in pregnancy (contraindicated) and during lactation. Similarly, the requirements detailed in the ribavirin prescribing information regarding pregnancy testing, contraception, and infertility should be consulted if elbasvir/grazoprevir is administered in combination with ribavirin.^{1,39}

The efficacy and safety of elbasvir/grazoprevir have not been studied in pediatric patients (younger than 18 years).¹

Elbasvir/grazoprevir dose adjustments based on age, gender, or race are not recommended despite the higher elbasvir/grazoprevir plasma levels and higher rates of late ALT elevations observed in patients 65 years or older, in females, and in Asians.¹

No dosage adjustments are recommended for patients with any degree of renal impairment or mild hepatic impairment. However, elbasvir/grazoprevir is contraindicated in patients with moderate hepatic impairment due to the lack of clinical safety and efficacy data and in severe hepatic impairment due to a 12-fold increase in grazoprevir levels, respectively. The efficacy and safety of elbasvir/grazoprevir have not been studied in patients awaiting liver transplant or in liver transplant recipients.¹ Refer to the ribavirin prescribing information for information regarding

ribavirin dosage adjustments for patients with renal impairment (CrCl 50 mL/min or lower).¹

ADVERSE REACTIONS

The most common adverse events observed in clinical trials included fatigue, headache, nausea, insomnia, diarrhea, and asthenia.^{1,2,4,5,6,12,13,27,32}

Common adverse events observed at a rate of at least 2% in clinical trial patients exposed to elbasvir/grazoprevir plus ribavirin included anemia, headache, fatigue, dyspnea, rash/pruritus, irritability, insomnia, abdominal pain, depression, arthralgia, and diarrhea. If ribavirin therapy is required, refer to the ribavirin prescribing information for information on ribavirin-specific adverse events.¹

Laboratory abnormalities observed in clinical trial patients exposed to elbasvir/grazoprevir with or without ribavirin included increased serum ALT levels, increased serum bilirubin levels, and decreased hemoglobin levels.¹

DRUG INTERACTIONS

The coadministration of elbasvir/grazoprevir with OATP1B1/3 inhibitors is contraindicated due to the potential for significantly increased levels of elbasvir/grazoprevir.¹

The coadministration of elbasvir/grazoprevir with strong CYP3A inducers or efavirenz is contraindicated due to the potential for loss of efficacy and/or development of resistance from decreased levels of elbasvir/grazoprevir. While not contraindicated, coadministration with moderate CYP3A inducers is not recommended for the same reasons.¹

CYP3A inhibitors may increase the concentrations of elbasvir and grazoprevir, resulting in a higher risk of adverse events. Coadministration with certain strong CYP3A inhibitors is not recommended (see Table 5).¹

Antiretroviral medications can alter grazoprevir levels. Coadministration of grazoprevir with efavirenz can decrease grazoprevir levels, whereas coadministration with ritonavir-boosted lopinavir, atazanavir, or darunavir can increase grazoprevir levels.^{14,40,41} Grazoprevir may modestly increase ritonavir-boosted atazanavir levels.^{14,40}

Any dosage adjustments of concomitant medications made at the time of initiation of elbasvir/grazoprevir therapy should be readjusted at the time of completion of elbasvir/grazoprevir therapy.¹

No dosage adjustments are necessary if coadministering elbasvir/grazoprevir with sofosbuvir.

Table 5. A noncomprehensive list of drugs with potentially significant interactions with elbasvir/grazoprevir¹

Class (drug)	Concentration effect	Comment
Antibiotics (eg, nafcillin) HIV medication (eg, etravirine) Endothelin antagonists (eg, bosentan) Wakefulness-promoting agents (eg, modafinil)	<ul style="list-style-type: none"> • Decrease elbasvir • Decrease grazoprevir 	Moderate CYP3A inducers (eg, nafcillin, etravirine, bosentan, modafinil) may decrease the therapeutic effect of elbasvir/grazoprevir due to decreased elbasvir/grazoprevir levels. Coadministration is not recommended.
Antifungals (eg, ketoconazole) HIV medication (eg, elvitegravir / cobicistat/ emtricitabine/ tenofovir)	<ul style="list-style-type: none"> • Increase elbasvir • Increase grazoprevir 	Strong CYP3A inhibitors (eg, systemic ketoconazole, cobicistat-containing HIV regimens) may increase the risk of hepatotoxicity due to increased elbasvir/grazoprevir levels. Coadministration is not recommended.
Immunosuppressants (eg, tacrolimus)	<ul style="list-style-type: none"> • Increase tacrolimus 	Tacrolimus concentrations increase when administered with elbasvir/grazoprevir. At time of initiating coadministration, frequently monitor tacrolimus whole blood concentrations, renal function, and tacrolimus-related adverse events.
HMG-CoA reductase inhibitors (eg, atorvastatin, rosuvastatin, fluvastatin, lovastatin, simvastatin)	<ul style="list-style-type: none"> • Increase HMG-CoA reductase inhibitors 	HMG-CoA reductase inhibitor concentrations increase when administered with elbasvir/grazoprevir. Coadministered doses should not exceed 20 mg for atorvastatin and 10 mg for rosuvastatin. The lowest necessary dose of fluvastatin, lovastatin, and simvastatin should be used when coadministered with elbasvir/grazoprevir due to the increased risk of statin-related adverse events (eg, myopathy).

The pharmacokinetic parameters of sofosbuvir or its metabolite GS-331007 were minimally affected by coadministration with elbasvir/grazoprevir.¹⁵

Pharmacokinetic parameters are not altered when grazoprevir is administered with pitavastatin, methadone, buprenorphine, or naloxone; however, grazoprevir can increase atorvastatin levels by 5.7-fold.^{14,42,43} Coadministration with midazolam does not affect grazoprevir levels, but midazolam levels can be increased by 30%. Rifampin can cause increased grazoprevir levels.^{14,44}

Coadministration of grazoprevir with elbasvir or daclatasvir does not cause meaningful changes to the pharmacokinetic parameters of either drug.^{14,45,46}

No dosage adjustments are necessary when coadministering elbasvir/grazoprevir with the following medications: acid-reducing agents (proton pump inhibitors, H₂ blockers, and antacids), buprenorphine/naloxone, digoxin, dolutegravir, methadone, mycophenolate mofetil, oral contraceptives, phosphate binders, pitavastatin, pravastatin, prednisone, raltegravir, ribavirin, rilpivirine, tenofovir disoproxil fumarate, and sofosbuvir.¹ No drug-drug interactions are expected between elbasvir/grazoprevir and the following medications: abacavir, emtricitabine, entecavir, and lamivudine.¹

RECOMMENDED MONITORING

Prior to initiating therapy, it is recommended that patients be tested for HCV genotype/subtype and for NS5A RAVs to determine the appropriate dosing regimen and duration of therapy.^{1,19} HCV viral load should also be determined prior to starting anti-HCV therapy.¹⁹ Obtain baseline values for complete blood cell count (CBC), international normalized ratio, thyrotropin (TSH) (if therapy includes interferon), calculated glomerular filtration rate (GFR), and hepatic function panel (albumin, total and direct bilirubin, ALT, AST, and alkaline phosphatase levels) within 12 weeks of anti-HCV therapy.^{1,19}

During therapy, monitor for adherence, adverse events, and laboratory values, including CBC, creatinine level, GFR, hepatic function panel (at week 8 and, if receiving 16 weeks of therapy, at week 12), and TSH (if therapy includes interferon).^{1,19} Also determine efficacy of the anti-HCV therapy by measuring the HCV viral load at treatment week 4, end of therapy, posttreatment week 12, and posttreatment week 24 or longer.¹⁹

Patients should immediately contact their health provider if they experience fatigue, weakness, lack of appetite, nausea/vomiting, jaundice, or discolored feces.¹

Monitor pregnancy status of female patients and female partners of male patients. Pregnancy is not recommended for 6 months posttreatment.¹⁹

DOSING

Elbasvir/grazoprevir is available as a fixed-dose combination product that contains elbasvir 50 mg and grazoprevir 100 mg in a single tablet. The recommended dosage is one tablet orally administered once daily with or without food. In specific patient populations, elbasvir/grazoprevir should be administered in combination with ribavirin. NS5A resistance testing is recommended for patients with HCV genotype 1a infection prior to initiation of treatment. The recommended treatment regimen is dependent on prior treatment, genotype/subtype, and presence or absence of NS5A RAVs. See **Table 6** and the ribavirin prescribing information for more information.¹

The doses used for treating hepatitis C infections in dose-ranging studies included elbasvir 20 mg and 50 mg and grazoprevir 100 mg, both administered orally once daily.^{12,13} The doses mainly used in phase 3 clinical trials were elbasvir 50 mg and grazoprevir 100 mg in a fixed-dose combination tablet taken once daily.^{4,5,6,7,27}

No dosage adjustment is necessary for patients with any degree of renal impairment, including patients requiring hemodialysis, or for patients with mild hepatic impairment.^{1,27,28} However, elbasvir/grazoprevir is contraindicated in patients with moderate

or severe hepatic impairment. Refer to the ribavirin prescribing information for ribavirin dosage adjustments for patients with CrCl 50 mL/min or lower.¹

PRODUCT AVAILABILITY

Elbasvir/grazoprevir was approved under the priority review program on January 28, 2016.^{47,48} The fixed-dose combination of elbasvir 50 mg/grazoprevir 100 mg is available as tablets in cartons containing 2 child-resistant dose packs of 14 blisters, totaling 28 tablets per carton. Each tablet is beige, oval, film coated, and debossed with “770,” and contains elbasvir, grazoprevir, colloidal silicon dioxide, copovidone, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, sodium chloride, sodium lauryl sulfate, and vitamin E polyethylene glycol succinate. The coating material consists of carnauba wax, ferrous ferric oxide, hypromellose, iron oxide red, iron oxide yellow, lactose monohydrate, titanium dioxide, and triacetin.¹

The tablets should be stored at 20°C to 25°C (68°F–77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F). Keep blister packs in the original container to protect tablets from moisture.¹

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for elbasvir/grazoprevir.^{1,48}

Table 6. Recommended regimens and durations of elbasvir/grazoprevir therapy depending on patient population¹

Genotype/Subtype	Prior therapy	Regimen	Duration
Genotype 1a – without NS5A RAVs	Treatment naïve	Elbasvir/grazoprevir	12 weeks
	Peginterferon alfa/ribavirin experienced		
Genotype 1a – with NS5A RAVs	Treatment naïve	Elbasvir/grazoprevir plus ribavirin	16 weeks
	Peginterferon alfa/ribavirin experienced		
Genotype 1b	Treatment naïve	Elbasvir/grazoprevir	12 weeks
	Peginterferon alfa/ribavirin experienced		
Genotype 1a or 1b	Peginterferon alfa/ribavirin/protease inhibitor experienced	Elbasvir/grazoprevir	12 weeks
	Treatment naïve		
Genotype 4	Treatment naïve	Elbasvir/grazoprevir plus ribavirin	16 weeks
	Peginterferon alfa/ribavirinexperienced		

Note: RAVs = resistance-associated variants.

CONCLUSION

Elbasvir/grazoprevir fixed-dose combination tablet is a new drug combination approved for the treatment of HCV infections of genotypes 1 or 4 in adults. Elbasvir and grazoprevir are direct-acting antivirals; elbasvir is an inhibitor of HCV NS5A protein, and grazoprevir is an inhibitor of HCV NS3/4A protease. Inhibition of these proteins results in the disruption of HCV RNA replication and virion assembly. In general, daily elbasvir/grazoprevir therapy with or without ribavirin results in high SVR12 rates in treatment-naïve, treatment-experienced, and renally impaired patients infected with HCV genotypes 1 or 4. Elbasvir/grazoprevir therapy appears to be well tolerated, with fatigue, headache, nausea, insomnia, diarrhea, and asthenia being the most common adverse reactions.

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