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A SPECIAL MEETING REVIEW EDITION

Highlights in Hepatitis C Virus From the 2018 AASLD Liver Meeting

A Review of Selected Presentations From the 2018 AASLD Liver Meeting • November 9-13, 2018 • San Francisco, CA

Special Reporting on:

- Preliminary Efficacy and Safety of 8-Week Glecaprevir/Pibrentasvir in Patients With HCV Genotype 1-6 Infection and Compensated Cirrhosis: The EXPEDITION-8 Study
- Real-World Effectiveness of Sofosbuvir/Velpatasvir/Voxilaprevir in 573 Treatment-Experienced Patients With Hepatitis C
- High Efficacy of Glecaprevir/Pibrentasvir in Patients With Chronic HCV GT1 Infection Who Failed Prior Treatment With NS5A-Inhibitor Plus Sofosbuvir Regimens
- Hepatitis C Virus Reinfection and Injecting Risk Behavior Following Elbasvir/Grazoprevir Treatment in Participants on Opiate Agonist Therapy: C-EDGE CO-STAR Part B
- Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Pediatric Patients With Genotypes 1-6 Chronic HCV Infection: Part 1 of the DORA Study
- Sustained Virologic Response Reduces the Incidence of Extrahepatic Manifestations in Chronic Hepatitis C Infection
- Quality of Life in Patients With Psychiatric Disorders: Pooled Analysis From Glecaprevir/Pibrentasvir Registrational Studies
- High SVR in People Who Inject Drugs With HCV Despite Imperfect Medication Adherence: Data From the ANCHOR Study

PLUS Meeting Abstract Summaries

With Expert Commentary by:
Fred Poordad, MD
Professor of Medicine
Chief, Hepatology
University Transplant Center
The University of Texas Health, San Antonio
San Antonio, Texas

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MAVYRET: FOR CHRONIC HCV

TREAT ALL GENOTYPES IN AS FEW AS 8 WEEKS

THE ONLY 8-WEEK† PANGENOTYPIC REGIMEN FOR GT 1-6 TREATMENT-NAÏVE, NON-CIRRHOTIC PATIENTS[2]

*IQVIA data includes NPA week ending 1/19/18-8/10/18, WSP and LRx week ending 1/19/18-8/3/18.[1]
†Liver or kidney transplant recipients are not eligible for an 8-week regimen.[2]
GT = Genotype; HCV = Hepatitis C virus.

INDICATION[2]

MAVYRET™ (glecaprevir and pibrentasvir) tablets are indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). MAVYRET is also indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor (PI), but not both.

IMPORTANT SAFETY INFORMATION[2]

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV: Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with MAVYRET. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct-acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

CONTRAINDICATIONS

MAVYRET is contraindicated:

- In patients with severe hepatic impairment (Child-Pugh C)
- With the following drugs: atazanavir or rifampin

WARNINGS AND PRECAUTIONS

Risk of Reduced Therapeutic Effect Due to Concomitant Use of MAVYRET with Carbamazepine, Efavirenz-containing Regimens, or St. John's Wort

- Carbamazepine, efavirenz, and St. John's Wort may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect of MAVYRET. The use of these agents with MAVYRET is not recommended.

ADVERSE REACTIONS

Most common adverse reactions observed with MAVYRET:

- >10% of subjects: headache and fatigue
- ≥5% of subjects: headache, fatigue, and nausea

MAVYRET DEMONSTRATED HIGH CURE‡ RATES IN 8 WEEKS[2]

98%

CURE‡ RATE (SVR12)

across 3 studies in GT 1-6 treatment-naïve and GT 1, 2, 4-6 PRS-experienced,§ non-cirrhotic patients who received 8 weeks of treatment (n=745/763).[2]

SVR12 range: 93-100% (ITT); 96-100% (mITT).[2]

- **NO** baseline viral load restrictions[2]
- **NO** dose adjustment for renal impairment[2]
- **NO** baseline resistance testing required[2]
- **NO** ribavirin[2]

0.3% on-treatment virologic failure (n=2/763)[2]
1% relapse (n=7/751)[2]

‡Cure = Sustained virologic response (SVR12); HCV RNA <LLOQ at 12 weeks after the end of treatment.[2]

§PRS-experienced = Prior treatment experience with regimens containing (peg)IFN, RBV, and/or SOF, but no prior treatment experience with an HCV NS3/4A protease inhibitor or an NS5A inhibitor.[2]

ITT = Intention to treat; LLOQ = Lower limit of quantification; mITT = ITT population modified to exclude patients who did not achieve SVR12 for reasons other than virologic failure; (peg)IFN = (Pegylated) interferon; RBV = Ribavirin; SOF = Sofosbuvir.

Study Designs

SURVEYOR-2, Parts 2 and 4[2-5]: A randomized, open-label, multicenter, 4-part, phase 2 study to evaluate the efficacy, safety, and pharmacokinetics of MAVYRET with or without RBV in 691 TN or treatment-experienced (ie, IFN or pegIFN ± RBV, or SOF + RBV ± pegIFN) GT 2-6–infected adults, without cirrhosis or with compensated cirrhosis. Part 2: GT 2, 3 NC patients were administered MAVYRET for 8 weeks and GT 3 patients without cirrhosis or with compensated cirrhosis were administered MAVYRET with or without RBV for 12 weeks. Part 4: GT 2, 4-6 NC patients were administered MAVYRET for 8 weeks. Primary endpoints: SVR12 in each treatment arm and noninferiority of SVR12 for GT 2 (Part 4) to historical control with 12 weeks of SOF + RBV.

ENDURANCE-1[2,6]: A randomized, open-label, multicenter, phase 3 study to evaluate the efficacy and safety of MAVYRET for 8 or 12 weeks in 703 TN or prior treatment–experienced (ie, IFN or pegIFN ± RBV, or SOF + RBV ± pegIFN) GT 1-infected adults without cirrhosis and with or without HIV-1 co-infection. Primary endpoints: SVR12 in the 12-week ITT-PS population (ITT population excluding patients with HIV co-infection and patients with SOF experience); SVR12 in the 8-week arm compared with the 12-week arm in the ITT-PS and per-protocol ITT-PS populations ("per-protocol" excludes patients with premature discontinuation or virologic failure prior to week 8 and missing data in the SVR12 window).

NC = Non-cirrhotic; TN = Treatment-naïve.

ENDURANCE-3[2,6]: A partially randomized, open-label, active-controlled, multicenter, phase 3 study to evaluate the efficacy and safety of MAVYRET for 8 or 12 weeks vs SOF + daclatasvir (DCV) for 12 weeks in 505 TN GT 3-infected adults without cirrhosis. Primary endpoints: Demonstrate noninferiority in the percentage of patients achieving SVR12 with 12 weeks of MAVYRET treatment to 12 weeks of treatment with SOF + DCV, and demonstrate noninferiority of 8 weeks of MAVYRET treatment to 12 weeks of MAVYRET treatment.

References: 1. Data on File, AbbVie Inc. IQVIA. National Prescription Audit (NPA), Weekly Sales Perspective (WSP), Longitudinal Prescription Claims (LRx). August 2018. (IQVIA, all rights reserved.) **2.** MAVYRET [package insert]. North Chicago, IL: AbbVie Inc.; 2018. **3.** Data on file. ABVRRTI64729. AbbVie Inc.; 2017. **4.** Kwo PY, Wyles DL, Wang S, et al. 100% SVR12 with ABT-493 + ABT-530 with or without ribavirin in treatment-naïve HCV genotype 3-infected patients with cirrhosis. Poster presented at: 51st Annual Meeting of the European Association for the Study of the Liver; April 16, 2016; Barcelona, Spain. **5.** Hassanein T, Wyles D, Wang S, et al. SURVEYOR-II, Part 4: glecaprevir/pibrentasvir demonstrates high SVR rates in patients with HCV genotype 2, 4, 5, or 6 infection without cirrhosis following an 8-week treatment duration. Poster presented at: 67th Annual Meeting of the American Association for the Study of Liver Diseases; November 11-15, 2016; Boston, MA. **6.** Zeuzem S, Foster GR, Wang S, et al. Glecaprevir-pibrentasvir for 8 or 12 weeks in HCV genotype 1 or 3 infection. *N Engl J Med.* 2018;378(4):354-369.

Please see adjacent page for a brief summary of the full Prescribing Information.

MAVYRET™
glecaprevir/pibrentasvir
100 mg/40 mg tablets

MAVYRET™ (glecaprevir and pibrentasvir) tablets, for oral use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with MAVYRET. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct-acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

MAVYRET is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). MAVYRET is also indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor (PI), but not both.

CONTRAINDICATIONS

MAVYRET is contraindicated in patients with severe hepatic impairment (Child-Pugh C) *[see Use in Specific Populations]*.

MAVYRET is contraindicated with atazanavir or rifampin *[see Drug Interactions]*.

WARNINGS AND PRECAUTIONS

Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV

Hepatitis B virus (HBV) reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct-acting antivirals, and who were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure and death. Cases have been reported in patients who are HBsAg positive and also in patients with serologic evidence of resolved HBV infection (i.e., HBsAg negative and anti-HBc positive). HBV reactivation has also been reported in patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV direct-acting antivirals may be increased in these patients.

HBV reactivation is characterized as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level. In patients with resolved HBV infection reappearance of HBsAg can occur. Reactivation of HBV replication may be accompanied by hepatitis, i.e., increase in aminotransferase levels and, in severe cases, increases in bilirubin levels, liver failure, and death can occur.

Test all patients for evidence of current or prior HBV infection by measuring HBsAg and anti- HBc before initiating HCV treatment with MAVYRET. In patients with serologic evidence of HBV infection, monitor for clinical and laboratory signs of hepatitis flare or HBV reactivation during HCV treatment with MAVYRET and during post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

Risk of Reduced Therapeutic Effect Due to Concomitant Use of MAVYRET with Carbamazepine, Efavirenz Containing Regimens, or St. John's Wort

Carbamazepine, efavirenz, and St. John's wort may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect of MAVYRET. The use of these agents with MAVYRET is not recommended.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of MAVYRET cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Overall Adverse Reactions in HCV-Infected Adults without Cirrhosis or with Compensated Cirrhosis (Child-Pugh A)

The adverse reactions data for MAVYRET in subjects without cirrhosis or with compensated cirrhosis (Child-Pugh A) were derived from nine Phase 2 and 3 trials which evaluated approximately 2,300 subjects infected with genotype 1, 2, 3, 4, 5, or 6 HCV who received MAVYRET for 8, 12 or 16 weeks.

The overall proportion of subjects who permanently discontinued treatment due to adverse reactions was 0.1% for subjects who received MAVYRET for 8, 12 or 16 weeks.

The most common adverse reactions, all grades, observed in greater than or equal to 5% of subjects receiving 8, 12, or 16 weeks of treatment with MAVYRET were headache (13%), fatigue (11%), and nausea (8%). In subjects receiving MAVYRET who experienced adverse reactions, 80% had an adverse reaction of mild severity (Grade 1). One subject experienced a serious adverse reaction.

Adverse reactions (type and severity) were similar for subjects receiving MAVYRET for 8, 12 or 16 weeks. The type and severity of adverse reactions in subjects with compensated cirrhosis (Child-Pugh A) were similar to those seen in subjects without cirrhosis.

Adverse Reactions in HCV-Infected Adults treated with MAVYRET in Controlled Trials

ENDURANCE-2

Among 302 treatment-naïve or PRS treatment-experienced, HCV genotype 2-infected adults enrolled in ENDURANCE-2, adverse reactions (all intensity) occurring in at least 5% of subjects treated with MAVYRET for 12 weeks are presented in Table 1. In subjects treated with MAVYRET for 12 weeks, 32% reported an adverse reaction, of which 98% had adverse reactions of mild or moderate severity. No subjects treated with MAVYRET or placebo in ENDURANCE-2 permanently discontinued treatment due to an adverse drug reaction.

Table 1. Adverse Reactions Reported in ≥5% of Treatment-Naïve and PRS-Experienced Adults without Cirrhosis Receiving MAVYRET for 12 Weeks in ENDURANCE-2

Adverse Reaction	MAVYRET 12 Weeks (N = 202) %	Placebo 12 Weeks (N = 100) %
Headache	9	6
Nausea	6	2
Diarrhea	5	2

ENDURANCE-3

Among 505 treatment-naïve, HCV genotype 3-infected adults without cirrhosis enrolled in ENDURANCE-3, adverse reactions (all intensity) occurring in at least 5% of subjects treated with MAVYRET for 8 or 12 weeks are presented in Table 2. In subjects treated with MAVYRET, 45% reported an adverse reaction, of which 99% had adverse reactions of mild or moderate severity. The proportion of subjects who permanently discontinued treatment due to adverse reactions was 0%, < 1% and 1% for the MAVYRET 8 week arm, MAVYRET 12 week arm and DCV + SOF arm, respectively.

Table 2. Adverse Reactions Reported in ≥5% of Treatment-Naïve Adults without Cirrhosis Receiving MAVYRET for 8 Weeks or 12 Weeks in ENDURANCE-3

Adverse Reaction	MAVYRET* 8 Weeks (N = 157) %	MAVYRET 12 Weeks (N = 233) %	DCV[1] + SOF[2] 12 Weeks (N = 115) %
Headache	16	17	15
Fatigue	11	14	12
Nausea	9	12	12
Diarrhea	7	3	3

[1] DCV=daclatasvir

[2] SOF=sofosbuvir

* The 8 week arm was a non-randomized treatment arm.

Adverse Reactions in HCV-Infected Adults with Severe Renal Impairment Including Subjects on Dialysis

The safety of MAVYRET in subjects with chronic kidney disease (Stage 4 or Stage 5 including subjects on dialysis) with genotypes 1, 2, 3, 4, 5 or 6 chronic HCV infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) was assessed in 104 subjects (EXPEDITION-4) who received MAVYRET for 12 weeks. The most common adverse reactions observed in greater than or equal to 5% of subjects receiving 12 weeks of treatment with MAVYRET were pruritus (17%), fatigue (12%), nausea (9%), asthenia (7%), and headache (6%). In subjects treated with MAVYRET who reported an adverse reaction, 90% had adverse reactions of mild or moderate severity (Grade 1 or 2). The proportion of subjects who permanently discontinued treatment due to adverse reactions was 2%.

Adverse Reactions in HCV/HIV-1 Co-infected Subjects

The safety of MAVYRET in subjects with HIV-1 co-infection with genotypes 1, 2, 3, 4 or 6 chronic HCV infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) was assessed in 153 subjects (EXPEDITION-2) who received MAVYRET for 8 or 12 weeks. Thirty-three subjects with HIV-1 coinfection also received 8 or 12 weeks of therapy in ENDURANCE-1.

The overall safety profile in HCV/HIV-1 co-infected subjects (ENDURANCE-1 and EXPEDITION-2) was similar to that observed in HCV mono-infected subjects. Adverse reactions observed in greater than or equal to 5% of subjects receiving MAVYRET in EXPEDITION-2 for 8 or 12 weeks were fatigue (10%), nausea (8%), and headache (5%).

Adverse Reactions in Subjects with Liver or Kidney Transplant

The safety of MAVYRET was assessed in 100 post-liver or -kidney transplant recipients with genotypes 1, 2, 3, 4, or 6 chronic HCV infection without cirrhosis (MAGELLAN-2). The overall safety profile in transplant recipients was similar to that observed in subjects in the Phase 2 and 3 studies, without a history of transplantation. Adverse reactions observed in greater than or equal to 5% of subjects receiving MAVYRET for 12 weeks were headache (17%), fatigue (16%), nausea (8%) and pruritus (7%). In subjects treated with MAVYRET who reported an adverse reaction, 81% had adverse reactions of mild severity. Two percent of subjects experienced a serious adverse reaction, and no subjects permanently discontinued treatment due to adverse reactions.

Laboratory Abnormalities

Serum bilirubin elevations

Elevations of total bilirubin at least 2 times the upper limit of normal occurred in 3.5% of subjects treated with MAVYRET versus 0% in placebo; these elevations were observed in 1.2% of subjects across the Phase 2 and 3 trials. MAVYRET inhibits OATP1B1/3 and is a weak inhibitor of UGT1A1 and may have the potential to impact bilirubin transport and metabolism, including direct and indirect bilirubin. No subjects experienced jaundice and total bilirubin levels decreased after completing MAVYRET.

DRUG INTERACTIONS

Mechanisms for the Potential Effect of MAVYRET on Other Drugs

Glecaprevir and pibrentasvir are inhibitors of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide (OATP) 1B1/3. Coadministration with MAVYRET may increase plasma concentration of drugs that are substrates of P-gp, BCRP, OATP1B1 or OATP1B3. Glecaprevir and pibrentasvir are weak inhibitors of cytochrome P450 (CYP) 3A, CYP1A2, and uridine glucuronosyltransferase (UGT) 1A1.

Fluctuations in INR values may occur in patients receiving warfarin concomitant with HCV treatment, including treatment with MAVYRET. If MAVYRET is coadministered with warfarin, close monitoring of INR values is recommended during treatment and post-treatment follow-up.

Mechanisms for the Potential Effect of Other Drugs on MAVYRET

Glecaprevir and pibrentasvir are substrates of P-gp and/or BCRP. Glecaprevir is a substrate of OATP1B1/3. Coadministration of MAVYRET with drugs that inhibit hepatic P-gp, BCRP, or OATP1B1/3 may increase the plasma concentrations of glecaprevir and/or pibrentasvir.

Coadministration of MAVYRET with drugs that induce P-gp/CYP3A may decrease glecaprevir and pibrentasvir plasma concentrations.

Carbamazepine, phenytoin, efavirenz, and St. John's wort may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect of MAVYRET. The use of these agents with MAVYRET is not recommended *[see Warnings and Precautions]*.

Established and Other Potential Drug Interactions

Table 3 provides the effect of MAVYRET on concentrations of coadministered drugs and the effect of coadministered drugs on glecaprevir and pibrentasvir *[see Contraindications and Warnings and Precautions]*.

Table 3. Potentially Significant Drug Interactions Identified in Drug Interaction Studies

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
Antiarrhythmics:		
Digoxin	↑ digoxin	Measure serum digoxin concentrations before initiating MAVYRET. Reduce digoxin concentrations by decreasing the dose by approximately 50% or by modifying the dosing frequency and continue monitoring.
Anticoagulants:		
Dabigatran etexilate	↑ dabigatran	If MAVYRET and dabigatran etexilate are coadministered, refer to the dabigatran etexilate prescribing information for dabigatran etexilate dose modifications in combination with P-gp inhibitors in the setting of renal impairment.
Anticonvulsants:		
Carbamazepine	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced therapeutic effect of MAVYRET and is not recommended.
Antimycobacterials:		
Rifampin	↓ glecaprevir ↓ pibrentasvir	Coadministration is contraindicated because of potential loss of therapeutic effect *[see Contraindications]*.
Ethinyl Estradiol-Containing Products:		
Ethinyl estradiol-containing medications such as combined oral contraceptives	↔ glecaprevir ↔ pibrentasvir	Coadministration of MAVYRET may increase the risk of ALT elevations and is not recommended.
Herbal Products:		
St. John's wort (*hypericum perforatum*)	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced therapeutic effect of MAVYRET and is not recommended.
HIV-Antiviral Agents:		
Atazanavir	↑ glecaprevir ↑ pibrentasvir	Coadministration is contraindicated due to increased risk of ALT elevations *[see Contraindications]*.
Darunavir Lopinavir Ritonavir	↑ glecaprevir ↑ pibrentasvir	Coadministration is not recommended.
Efavirenz	↓ glecaprevir ↓ pibrentasvir	Coadministration may lead to reduced therapeutic effect of MAVYRET and is not recommended.
HMG-CoA Reductase Inhibitors:		
Atorvastatin Lovastatin Simvastatin	↑ atorvastatin ↑ lovastatin ↑ simvastatin	Coadministration may increase the concentration of atorvastatin, lovastatin, and simvastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Coadministration with these statins is not recommended.
Pravastatin	↑ pravastatin	Coadministration may increase the concentration of pravastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Reduce pravastatin dose by 50% when coadministered with MAVYRET.
Rosuvastatin	↑ rosuvastatin	Coadministration may significantly increase the concentration of rosuvastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Rosuvastatin may be administered with MAVYRET at a dose that does not exceed 10 mg.
Fluvastatin Pitavastatin	↑ fluvastatin ↑ pitavastatin	Coadministration may increase the concentrations of fluvastatin and pitavastatin. Increased statin concentrations may increase the risk of myopathy, including rhabdomyolysis. Use the lowest approved dose of fluvastatin or pitavastatin. If higher doses are needed, use the lowest necessary statin dose based on a risk/benefit assessment.
Immunosuppressants:		
Cyclosporine	↑ glecaprevir ↑ pibrentasvir	MAVYRET is not recommended for use in patients requiring stable cyclosporine doses > 100 mg per day.

↑= increase; ↓= decrease; ↔ = no effect

Drugs with No Observed Clinically Significant Interactions with MAVYRET

No dose adjustment is required when MAVYRET is coadministered with the following medications: abacavir, amlodipine, buprenorphine, caffeine, dextromethorphan, dolutegravir, elvitegravir/cobicistat, emtricitabine, felodipine, lamivudine, lamotrigine, losartan, methadone, midazolam, naloxone, norethindrone or other progestin-only contraceptives, omeprazole, raltegravir, rilpivirine, sofosbuvir, tacrolimus, tenofovir alafenamide, tenofovir disoproxil fumarate, tolbutamide, and valsartan.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

No adequate human data are available to establish whether or not MAVYRET poses a risk to pregnancy outcomes. In animal reproduction studies, no adverse developmental effects were observed when the components of MAVYRET were administered separately during organogenesis at exposures up to 53 times (rats; glecaprevir) or 51 and 1.5 times (mice and rabbits, respectively; pibrentasvir) the human exposures at the recommended dose of MAVYRET *(see Data)*. No definitive conclusions regarding potential developmental effects of glecaprevir could be made in rabbits, since the highest achieved glecaprevir exposure in this species was only 7% (0.07 times) of the human exposure at the recommended dose. There were no effects with either compound in rodent pre/post-natal developmental studies in which maternal systemic exposures (AUC) to glecaprevir and pibrentasvir were approximately 47 and 74 times, respectively, the exposure in humans at the recommended dose *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Glecaprevir

Glecaprevir was administered orally to pregnant rats (up to 120 mg/kg/day) and rabbits (up to 60 mg/kg/day) during the period of organogenesis (gestation days (GD) 6 to 18, and GD 7 to 19, respectively). No adverse embryo-fetal effects were observed in rats at dose levels up to 120 mg/kg/day (53 times the exposures in humans at the recommended human dose (RHD)). In rabbits, the highest glecaprevir exposure achieved was 7% (0.07 times) of the exposure in humans at RHD. As such, data in rabbits during organogenesis are not available for glecaprevir systemic exposures at or above the exposures in humans at the RHD.

In the pre/post-natal developmental study in rats, glecaprevir was administered orally (up to 120 mg/kg/day) from GD 6 to lactation day 20. No effects were observed at maternal exposures 47 times the exposures in humans at the RHD.

Pibrentasvir

Pibrentasvir was administered orally to pregnant mice and rabbits (up to 100 mg/kg/day) during the period of organogenesis (GD 6 to 15, and GD 7 to 19, respectively). No adverse embryo-fetal effects were observed at any studied dose level in either species. The systemic exposures at the highest doses were 51 times (mice) and 1.5 times (rabbits) the exposures in humans at the RHD.

In the pre/post-natal developmental study in mice, pibrentasvir was administered orally (up to 100 mg/kg/day) from GD 6 to lactation day 20. No effects were observed at maternal exposures approximately 74 times the exposures in humans at the RHD.

Lactation

Risk Summary

It is not known whether the components of MAVYRET are excreted in human breast milk, affect human milk production, or have effects on the breastfed infant. When administered to lactating rodents, the components of MAVYRET were present in milk, without effect on growth and development observed in the nursing pups *(see Data)*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MAVYRET and any potential adverse effects on the breastfed child from MAVYRET or from the underlying maternal condition.

Data

No significant effects of glecaprevir or pibrentasvir on growth and post-natal development were observed in nursing pups at the highest doses tested (120 mg/kg/day for glecaprevir and 100 mg/kg/day for pibrentasvir). Maternal systemic exposure (AUC) to glecaprevir and pibrentasvir was approximately 47 or 74 times the exposure in humans at the RHD. Systemic exposure in nursing pups on post-natal day 14 was approximately 0.6 to 2.2 % of the maternal exposure for glecaprevir and approximately one quarter to one third of the maternal exposure for pibrentasvir.

Glecaprevir or pibrentasvir was administered (single dose; 5 mg/kg oral) to lactating rats, 8 to 12 days post parturition. Glecaprevir in milk was 13 times lower than in plasma and pibrentasvir in milk was 1.5 times higher than in plasma. Parent drug (glecaprevir or pibrentasvir) represented the majority (>96%) of the total drug-related material in milk.

Pediatric Use

Safety and effectiveness of MAVYRET in children less than 18 years of age have not been established.

Geriatric Use

In clinical trials of MAVYRET, 328 subjects were age 65 years and over (14% of the total number of subjects in the Phase 2 and 3 clinical trials) and 47 subjects were age 75 and over (2%). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects. No dosage adjustment of MAVYRET is warranted in geriatric patients.

Renal Impairment

No dosage adjustment of MAVYRET is required in patients with mild, moderate or severe renal impairment, including those on dialysis.

Hepatic Impairment

No dosage adjustment of MAVYRET is required in patients with mild hepatic impairment (Child-Pugh A). MAVYRET is not recommended in patients with moderate hepatic impairment (Child-Pugh B). Safety and efficacy have not been established in HCV-infected patients with moderate hepatic impairment. MAVYRET is contraindicated in patients with severe hepatic impairment (Child-Pugh C) due to higher exposures of glecaprevir and pibrentasvir *[see Contraindications]*.

OVERDOSAGE

In case of overdose, the patient should be monitored for any signs and symptoms of toxicities. Appropriate symptomatic treatment should be instituted immediately. Glecaprevir and pibrentasvir are not significantly removed by hemodialysis.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV

Inform patients that HBV reactivation can occur in patients coinfected with HBV during or after treatment of HCV infection. Advise patients to tell their healthcare provider if they have a history of hepatitis B virus infection *[see Warnings and Precautions]*.

Drug Interactions

Inform patients that MAVYRET may interact with some drugs; therefore, patients should be advised to report to their healthcare provider the use of any prescription, non-prescription medication or herbal products *[see Contraindications, Warnings and Precautions and Drug Interactions]*.

Administration

Advise patients to take MAVYRET recommended dosage (three tablets) once daily with food as directed. Inform patients that it is important not to miss or skip doses and to take MAVYRET for the duration that is recommended by the physician.

If a dose is missed and it is:

- Less than 18 hours from the usual time that MAVYRET should have been taken – advise the patient to take the dose as soon as possible and then to take the next dose at the usual time.
- More than 18 hours from the usual time that MAVYRET should have been taken – advise the patient not to take the missed dose and to take the next dose at the usual time.

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Preliminary Efficacy and Safety of 8-Week Glecaprevir/Pibrentasvir in Patients With HCV Genotype 1-6 Infection and Compensated Cirrhosis: The EXPEDITION-8 Study

The fixed-dose combination of glecaprevir plus pibrentasvir administered for 8 weeks is approved as therapy for treatment-naive patients with hepatitis C virus (HCV) genotypes 1 to 6, without cirrhosis.[1-3] This treatment has demonstrated high rates of sustained virologic response at week 12 (SVR12).[1-3] The 2-drug combination inhibits the activity of 2 nonstructural proteins—the NS3/4A protease and the NS5A protein—thus interfering with viral replication. In registrational clinical trials, an 8-week regimen of glecaprevir plus pibrentasvir was associated with an SVR12 rate of 98% in treatment-naive patients without cirrhosis.[4] In patients with cirrhosis, a 12-week regimen yielded an SVR12 rate of 99%.[5,6]

EXPEDITION-8 is an ongoing, single-arm, open-label, multicenter, phase 3b study evaluating the efficacy and safety of an 8-week regimen of glecaprevir plus pibrentasvir in treatment-naive patients with HCV infection and compensated cirrhosis.[7] Enrolled patients were adults with treatment-naive, chronic HCV genotype 1, 2, 4, 5, or 6, with cirrhosis and a Child-Pugh score of 6 or less. Patients with HCV genotype 3 were enrolled as part of a protocol amendment, and data from this cohort will be presented at a later date. Primary endpoint 1, based on per-protocol analysis, excluded patients in the intention-to-treat (ITT) population who experienced virologic breakthrough or treatment discontinuation prior to week 8 and those without data for the SVR12 analysis. The SVR12 rate for primary endpoint 1 was compared with a historical SVR12 rate of 100%, with a noninferiority margin of 6% and a lower bound of the 95% CI of greater than 94%. Primary endpoint 2, based on ITT analysis, included all patients who received at least 1 dose of the study drug. The SVR12 rate of primary endpoint 2 was compared with a historical SVR12 rate of 99%, with a noninferiority margin of 6% and a lower bound of the 95% CI of greater than 93%.

Among the 280 enrolled patients, the median age was 60 years (range, 34-88 years), and 60% were male. Most patients (83%) had HCV genotype 1 infection. The median concentration of HCV RNA at baseline was 6.3 $\log_{10}$ IU/mL (range, 3.4-7.5 $\log_{10}$ IU/mL), and the mean transient elastography score at baseline was 23.7 (standard deviation, 11.1). Nearly all patients (99%) had a Child-Pugh score of 5 or 6, and 26% had a history of injection drug use. Baseline polymorphisms included NS5A-only in 36% and NS3-only in 1%.

After 8 weeks of treatment with glecaprevir plus pibrentasvir, there were no virologic failures. Both primary endpoints were met, with SVR12 rates of 100% for the per-protocol analysis and 98% for the ITT analysis (Figure 1). The ITT analysis excluded 6 patients. One patient discontinued treatment prior to completing the 8-week regimen, but nonetheless achieved SVR12. Among the 5 patients who were lost to follow-up, all had no detectable viral load at their most recent visit. The per-protocol analysis excluded 6 patients from the ITT population who failed to respond and 1 patient who achieved SVR12 after less than 8 weeks of study treatment. The 2-drug combination was generally well-tolerated, and no new safety signals were observed.

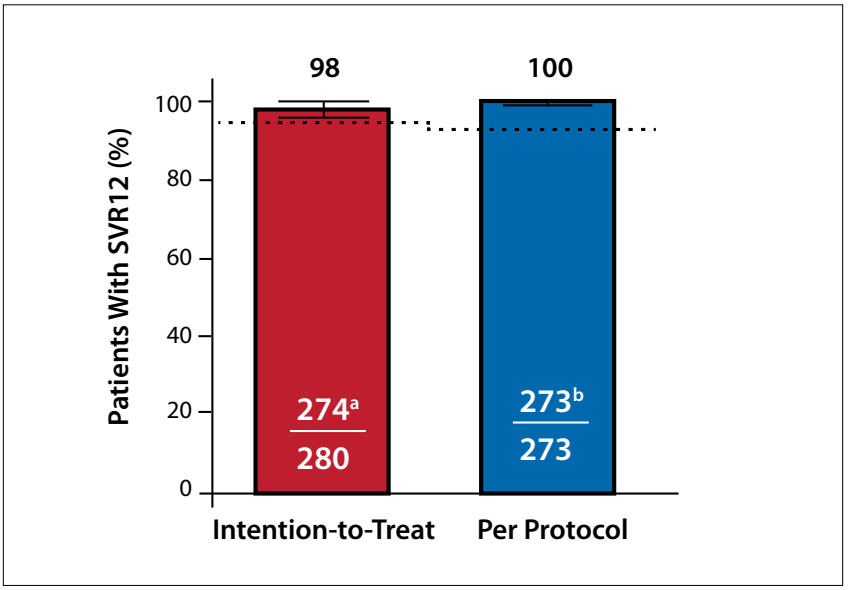

Figure 1. Efficacy in the EXPEDITION-8 study of 8-week glecaprevir/pibrentasvir in patients with hepatitis C virus genotype 1 to 6 infection and compensated cirrhosis. SVR12, sustained virologic response at week 12. [a]For 5 patients, SVR12 data were missing (all undetectable at last visit), and 1 patient prematurely discontinued treatment. [b]One patient dosed for <8 weeks who achieved SVR12, plus 6 nonresponders from the intention-to-treat population. Adapted from Brown RS Jr et al. AASLD Liver Meeting abstract LB-7. *Hepatology*. 2018;68(suppl 1).[7]

An adverse event (AE) of any grade occurred in 48% of patients, and a serious AE occurred in 2%. No patient discontinued treatment owing to an AE. No laboratory abnormalities were reported. Enrollment of patients with HCV genotype 3 infection is ongoing.

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Real-World Effectiveness of Sofosbuvir/Velpatasvir/Voxilaprevir in 573 Treatment-Experienced Patients With Hepatitis C

Few options are available for patients with HCV who require additional treatment after direct-acting antiviral agents. In clinical trials of this patient group, treatment with the combination of sofosbuvir, velpatasvir, and voxilaprevir yielded SVR12 rates of 95% to 100%.[1,2] The United States Department of Veterans Affairs conducted a study to evaluate the real-world efficacy of sofosbuvir, velpatasvir, and voxilaprevir in veterans with HCV who had received previous treatment.[3] The observational study included patients in the Veterans Affairs National HCV Clinical Case Registry. The primary endpoint was SVR assessed at least 12 weeks after the end of treatment, based on ITT analysis. Enrolled patients had HCV genotypes 1 to 4 and began treatment with sofosbuvir, velpatasvir, and voxilaprevir at any US Veterans Affairs facility, with treatment concluded by March 31, 2018. Among patients in the final SVR cohort, 490 had genotype 1, 20 had genotype 2, 51 had genotype 3, and 12 had genotype 4. Across the genotype cohorts, the patients' mean age was approximately 60 to 65 years. The proportion of patients with cirrhosis ranged from 30.0% to 58.3%. Treatment duration of 12 weeks was reported for 91.2% to 100% of patients; the remainder of patients were treated for less than 12 weeks. All of the patients had received prior treatment with an NS5A or NS5B inhibitor, and the most common prior treatment was ledipasvir plus sofosbuvir, with or without ribavirin.

The overall SVR rate was 90.7% for HCV genotype 1, 90.0% for genotype 2, 91.3% for genotype 3, and 100.0% for genotype 4. Similar SVR rates were observed regardless of race, the presence of cirrhosis, the level of fibrosis, and any history of decom-

ABSTRACT SUMMARY Improvements in Symptoms Shortly Following Viral Cure for Chronic Hepatitis C: A Large Multi-Site Clinical Cohort Study

The multicenter, observational PROP UP study (The Patient-Reported Outcomes Project of HCV-TARGET) evaluated changes in symptoms among HCV patients who achieved SVR and completed surveys at baseline and after treatment with direct-acting antiviral agents (Abstract 149). Patient-reported outcomes were available for 1248 participants and included neuropsychiatric, somatic, and gastrointestinal symptoms, as well as overall symptom burden and functional quality of life. The greatest mean change in patient-reported outcome scores for the entire cohort occurred in functional quality of life (–6.1), fatigue (–4.1), and sleep disturbance (–3.0). Patients ages 35 to 55 years experienced greater symptom reduction vs other age groups ($P<.05$), with the largest mean reductions in depression (–4.7), anger (–4.5), sleep disturbances (–4.4), pain (–4.2), and anxiety (–3.8). Reductions in fatigue were observed for all age groups, including those older than 55 years (–3.4), 35 to 55 years (–6.1), and younger than 35 years (–6.2). Patients with a higher number of comorbidities generally experienced the greatest improvement in symptoms, including depression, pain, sleep issues, and functional quality of life. Patients with mental health issues were most likely to show improvements in functional well-being and quality of life ($P<.01$; HR, –4.6; 95% CI, –7.5 to –1.7).

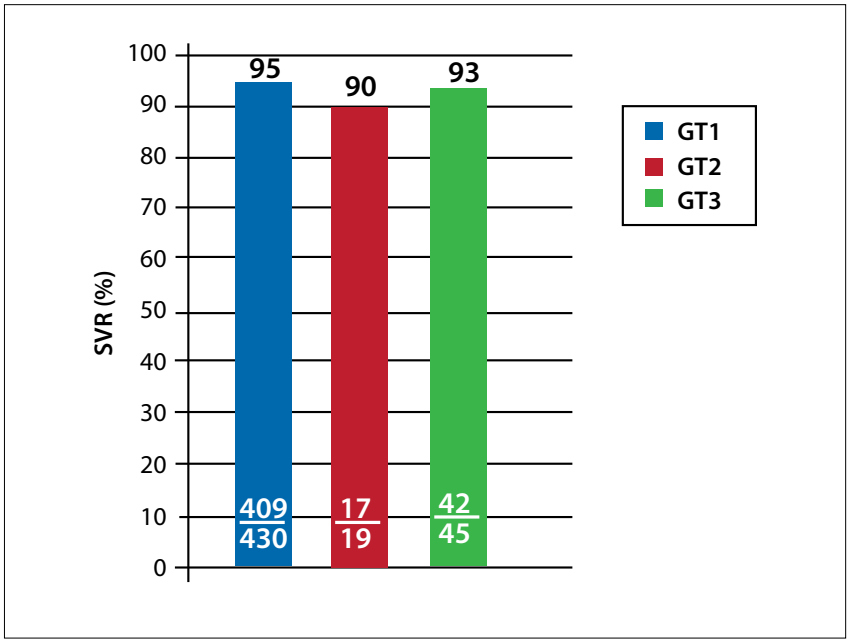

Figure 2. Overall SVR in a real-world analysis of previously treated patients with hepatitis C virus who received a 12-week regimen of sofosbuvir, velpatasvir, and voxilaprevir. GT, genotype; SVR, sustained virologic response. Adapted from Belperio P et al. AASLD Liver Meeting abstract 227. *Hepatology*. 2018;68(suppl 1).[3]

pensation. Among patients whose treatment duration lasted less than 12 weeks, SVR rates were 46.5% (20/43) for genotype 1, 100.0% (1/1) for genotype 2, and 0% (0/1) for genotype 3. Among patients who received the full 12 weeks of treatment, SVR rates were approximately 95% (409/430) for genotype 1, 90% (17/19) for genotype 2, and 93% (42/45) for genotype 3 (Figure 2). The SVR rate was 100.0% (12/12) for genotype 4. SVR rates of approximately 88% to 92% were observed in cohorts with more than 10 patients based on prior treatment class and HCV genotype. Among patients with HCV genotype 1 infection, most had received prior treatment with ledipasvir and sofosbuvir, with or without ribavirin. These patients had an SVR rate of 91% after treatment with sofosbuvir, velpatasvir, and voxilaprevir. In patients who received 12 weeks of treatment with the 3 drugs, subgroup analyses generally yielded high SVR rates for HCV genotypes 1, 2, and 3, regardless of race, cirrhosis, and fibrosis score.

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High Efficacy of Glecaprevir/Pibrentasvir in Patients With Chronic HCV GT1 Infection Who Failed Prior Treatment With NS5A-Inhibitor Plus Sofosbuvir Regimens

Sixteen weeks of therapy with the combination of glecaprevir plus pibrentasvir is approved by the US Food and Drug Administration (FDA) for the treatment of HCV genotype 1–infected patients with prior exposure to an NS5A inhibitor and without prior exposure to inhibitors of NS3/4A.[1] The drug approval was based on results from the phase 2 MAGELLAN-1 study, an open-label, randomized trial that demonstrated high rates of SVR12 in HCV patients with prior exposure to an inhibitor of NS5A.[2] The 16-week regimen is recommended as an alternative treatment option in guidelines from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America.[3]

In an effort to reduce the required treatment period, an open-label, multicenter, phase 3b trial compared 12 weeks vs 16 weeks of treatment with glecaprevir plus pibrentasvir in patients with chronic HCV genotype 1 infection.[4] Eligible patients had experienced treatment failure after at least 4 weeks of treatment with sofosbuvir plus an NS5A inhibitor, with or without ribavirin. Patients with decompensated cirrhosis and those with active hepatitis B virus were excluded from enrollment. Enrollment included patients who had undergone prior liver transplant and those infected with the human immunodeficiency virus (HIV) who were receiving antiretroviral therapy. Patients without cirrhosis (n=130) were randomly assigned in a 2:1 design to receive therapy for 12 weeks (arm A) or 16 weeks (arm B). Patients with

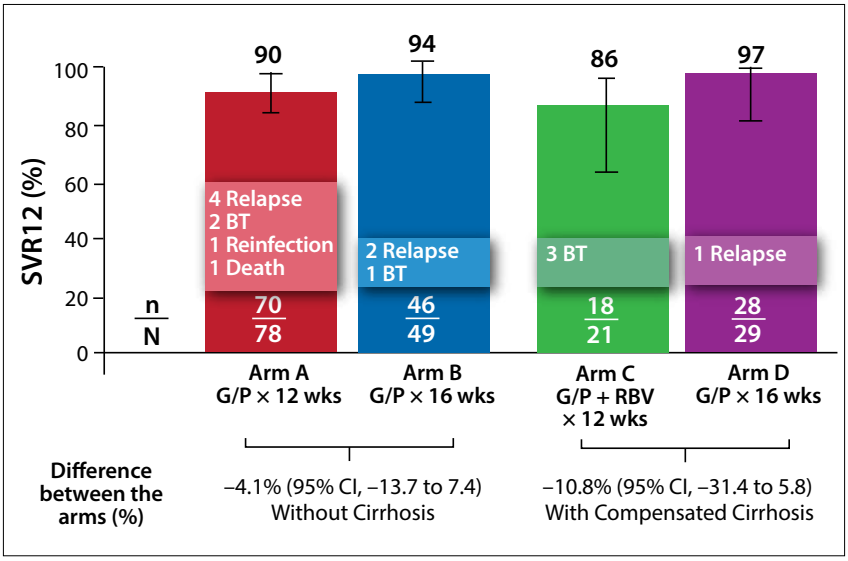

Figure 3. SVR12 in a study of glecaprevir/pibrentasvir in previously treated patients with chronic hepatitis C virus genotype 1 infection. BT, breakthrough; G/P, glecaprevir/pibrentasvir; RBV, ribavirin; SVR12, sustained virologic response at week 12; wks, weeks. Adapted from Sulkowski MS et al. AASLD Liver Meeting abstract 226. *Hepatology*. 2018;68(suppl 1).[4]

ABSTRACT SUMMARY Effectiveness of 8-Week Glecaprevir/Pibrentasvir for Treatment-Naive, Non-Cirrhotic Patients With HCV Infection in the Trio Health Network

A real-world study evaluated outcomes in 560 treatment-naive, noncirrhotic HCV patients who received 8 weeks of therapy with glecaprevir/pibrentasvir (Abstract 632). HCV genotypes included 1a (54%), 1b (15%), 2 (17%), 3 (9%), 4 (1%), and 6 (1%). Thirteen percent of patients had severe fibrosis, 6% had stage 4/5 chronic kidney disease, and 20% had a baseline viral load exceeding 6 million IU/mL. Overall, the SVR12 rate was 99% (537/540) in the per-protocol analysis and 96% (537/560) in the ITT population. When analyzed according to subtype, the SVR12 rate was 99% in genotype 1 and 100% in genotypes 2, 3, 4, and 6 in the per-protocol analysis. Among patients in the ITT group, the SVR12 rate was 95% in genotype 1, 98% in genotype 2, and 100% in genotypes 3, 4, and 6. The rate of virologic failure was 0.5% (3/560), and all cases occurred in patients with HCV genotype 1a. According to bivariate analyses, rates of SVR12 were not associated with sex, practice type, genotype, estimated glomerular filtration rate, fibrosis score, baseline HCV viral load, or type of insurance. The most common comorbidities were hypertension (32%), depression (20%), anxiety (18%), and diabetes (10%).

cirrhosis (n=50) were randomly assigned in a 1:1 manner to receive 12 weeks of therapy with weight-based ribavirin (arm C) or 16 weeks of therapy without ribavirin (arm D). The primary endpoint was the SVR12 rate.

Among 86 noncirrhotic patients in arm A, 3 withdrew consent prior to receiving treatment. After the FDA approval of glecaprevir plus pibrentasvir, the study protocol was amended. Five patients in arm A and 1 patient in arm C had received a protease inhibitor prior to their treatment with sofosbuvir plus an NS5A inhibitor. These patients were treated for 16 weeks, and included in the analysis of the 16-week treatment cohorts. The final cohorts included 78 patients in arm A, 49 in arm B, 21 in arm C, and 29 in arm D. Across the 4 arms, 76% to 82% of patients were male, and 38% to 51% were black. The median age ranged from 60 to 64 years. HCV genotype 1a was reported in 78% to 90% of patients. HIV infection was noted in 3% to 6%. Prior liver transplant was reported in 6% of arm A and 20% of arm B. The median number of days since exposure to an NS5A inhibitor was 505 in arm A, 355 in arm B, 499 in arm C, and 482 in arm D.

The SVR12 rates were 90% in arm A (70/78), 94% in arm B (46/49), 86% in arm C (18/21), and 97% in arm D (28/29; Figure 3). All 8 patients with early exposure to sofosbuvir plus an NS5A inhibitor achieved SVR12. In arm A, 4 patients relapsed, 2 experienced a virologic breakthrough, 1 was reinfected, and 1 patient died. In arm B, 2 patients relapsed and 1 patient had a virologic breakthrough. Three patients in arm C had a virologic breakthrough, and 1 patient in arm D relapsed. The difference in SVR12 rates for 12 vs 16 weeks of treatment was –4.1% for arm A vs arm B (95% CI, –13.7% to 7.4%) and –10.8% for arm C vs arm D (95% CI, –31.4% to 5.8%). Among the cohort of patients treated for 12 weeks, the overall SVR12 rate was 89% (88/99), with a higher rate observed in patients with HCV genotype 1b infection vs 1a infection (95% vs 87%; Figure 4). Among the cohort of patients treated for 16 weeks, the SVR12 rate was 95%, with rates of 100% (13/13) in patients with HCV genotype 1b infection vs 94% (61/65) in those with HCV genotype 1a infection. Baseline polymorphisms observed across the 4 arms included NS5A (76%-81%), NS3 residue 80 (33%-48%), and NS3 residues 155, 156, and 168 (0% to 14%). Among the 6 patients who developed virologic failure while on treatment, all

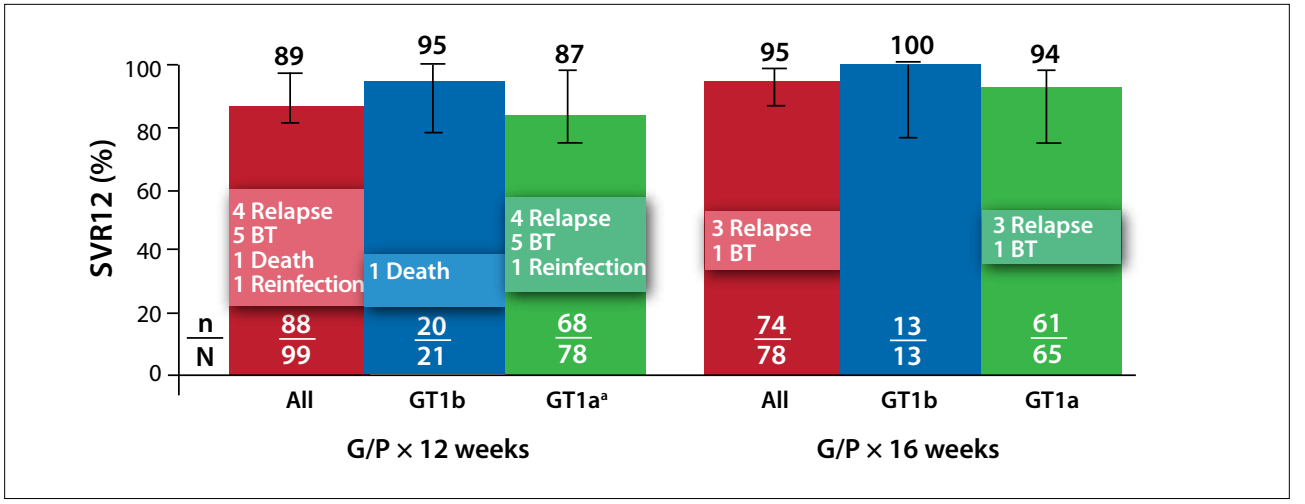

Figure 4. Efficacy according to treatment duration and subtype in a study of glecaprevir/pibrentasvir in previously treated patients with chronic hepatitis C virus genotype 1 infection. BT, breakthrough; G/P, glecaprevir/pibrentasvir; GT, genotype; SVR12, sustained virologic response at week 12. [a]Includes 4 patients with non-1a/non-1b genotype. Adapted from Sulkowski MS et al. AASLD Liver Meeting abstract 226. *Hepatology*. 2018;68(suppl 1).[4]

ABSTRACT SUMMARY Improved Graft Survival After Liver Transplantation for Recipients With Hepatitis C in the Direct-Acting Antiviral Era

In light of the availability of direct-acting antiviral agents, a study evaluated longer-term outcomes in HCV-positive liver transplant recipients (Abstract 228). The analysis included adults from one US registry who were single-organ recipients of a liver from a deceased donor from January 1, 2008 to January 31, 2018. Data were available for 47,662 transplant recipients. Among these patients, 18,348 were positive for HCV (R+) and received an organ from a donor who was negative for HCV (D–). Both the donor and the recipient were HCV-negative for 29,314 transplants (D–/R–). The number of D–/R+ transplants decreased from 2010 in 2008 to 1329 in 2017, whereas the number of D–/R– transplants rose from approximately 2400 to 4000 during the same time. For patients treated before vs after November 24, 2013, graft survival significantly improved in all groups after the introduction of direct-acting antiviral agents. The most dramatic improvement was associated with transplants with an HCV-positive recipient (83.3% vs 77.7%; *P*<.001). For the cohort of D–/R+ transplants, the availability of direct-acting antiviral agents was also associated with decreased creatinine (*P*=.003), decreased posttransplant diabetes (*P*<.001), decreased rehospitalization (*P*<.001), and decreased rejection (*P*<.001) at 1 year after transplant. The authors concluded that the results support the use of grafts from deceased donors in patients with HCV.

had HCV genotype 1a infection. None of these patients had baseline resistance-associated substitutions (RAS) in NS3 at baseline, and 5 of these patients had RAS observed after virologic failure. All of these patients had RAS in NS5A at baseline, and 4 of the 6 patients had additional treatment-emergent RAS after virologic failure. One patient who developed reinfection had no RAS in either NS3 or NS5A at baseline or at failure.

Across the 4 arms, the proportion of patients with any AE ranged from 55% in arm D to 81% in arm C. The most commonly observed AEs were fatigue, headache, and nausea. Serious AEs were observed in 0% to 6% of patients, but no events were related to treatment with a direct-acting antiviral agent. No patient discontinued study treatment owing to an AE related to treatment with glecaprevir plus pibrentasvir. AEs during treatment with ribavirin led 7 patients (33%) to reduce the dose and 1 patient (5%) to discontinue treatment. One patient in arm A who received 11.5 weeks of study treatment later presented with advanced hepatocellular carcinoma and subsequently died. Laboratory abnormalities were observed in 6% of patients in arm A, 10% in arm B, 10% in arm C, and 8% in arm D.

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Hepatitis C Virus Reinfection and Injecting Risk Behavior Following Elbasvir/Grazoprevir Treatment in Participants on Opiate Agonist Therapy: C-EDGE CO-STAR Part B

The combination of elbasvir plus grazoprevir is available as a once-daily, fixed-dose combination tablet for the treatment of HCV genotypes 1 and 4.[1] The therapy has shown in vitro activity against many clinically relevant RAS, and efficacy has been demonstrated in various patient settings.[2,3] The phase 3 CO-STAR trial compared 12 weeks of elbasvir plus grazoprevir vs placebo in patients with HCV genotype 1, 4, or 6 infection who had been receiving opioid agonist therapy for at least 3 months. In part A of the trial, the SVR12 rate was 90.9% in the full analysis set and 95.8% in the modified full analysis set.[4] Adherence to treatment was high, with 97% of patients demonstrating adherence exceeding 95%.

CO-STAR Part B was a 3-year observational trial that was open to all participants who received at least 1 dose of elbasvir plus grazoprevir in CO-STAR Part A.[5] Every 6 months, patients underwent assessment for HCV RNA levels and urine drug screening, and they completed a behavioral questionnaire about drug use. If HCV RNA was detected, DNA sequencing was performed. Among the 301 patients who enrolled in part A of the study, 199 enrolled in part B. Follow-up visits were completed by 192 patients at 6 months, 179 at 12 months, 173 at 18 months, 155 at 24 months, and 148 at 30 months. Baseline characteristics were generally similar in patients who enrolled in part B vs those who participated only in part A. In part B, the patients' median age was 48.6 years (range, 24-66 years), and 76% were male. Eight percent were HCV/HIV coinfected. Opioid agonist treatment included methadone (80%) and buprenorphine (20%). Ninety-two percent of patients had HCV genotype 1a or 1b infection. Among patients in part B, 59% had a positive urine drug test upon enrollment in part A. Positive results were observed for the use of benzodiazepines (24%), cannabinoids (23%), opiates (22%), cocaine (10%), and amphetamines (7%). The proportion of positive urine drug test results remained fairly constant, ranging from 53% to 62% throughout the 30 months of follow-up.

Self-reported drug use also remained fairly steady during follow-up. At any time point throughout 6 to 30 months of follow-up, the proportion of patients reporting noninjecting drug use during the previous 6 months ranged from 39% to 45% (Figure 5). Noninjecting drug use during the previous month was reported by 36% to 42%. Injecting drug use during the previous 6 months occurred in 20% to 26%. Injecting drug use during the previous month ranged from 15% to 21%.

Reinfections were observed in 6 patients during CO-STAR part A and in 4 patients during part B, consistent with a rate of 1.8 reinfections per 100 person-years. In part B, the reinfection rate was higher in patients who reported injecting drug use (2.8 reinfections per 100 person-years [95% CI, 1.0-6.2]) compared with those who did not report injecting drug use (0.3 reinfections per 100 person-years [95% CI, 0.0-1.8]).

Two study participants had recurrent viremia followed by spontaneous clearance. The first patient had HCV genotype 1a at baseline. After treatment with elbasvir plus grazoprevir, the patient was found to be reinfected

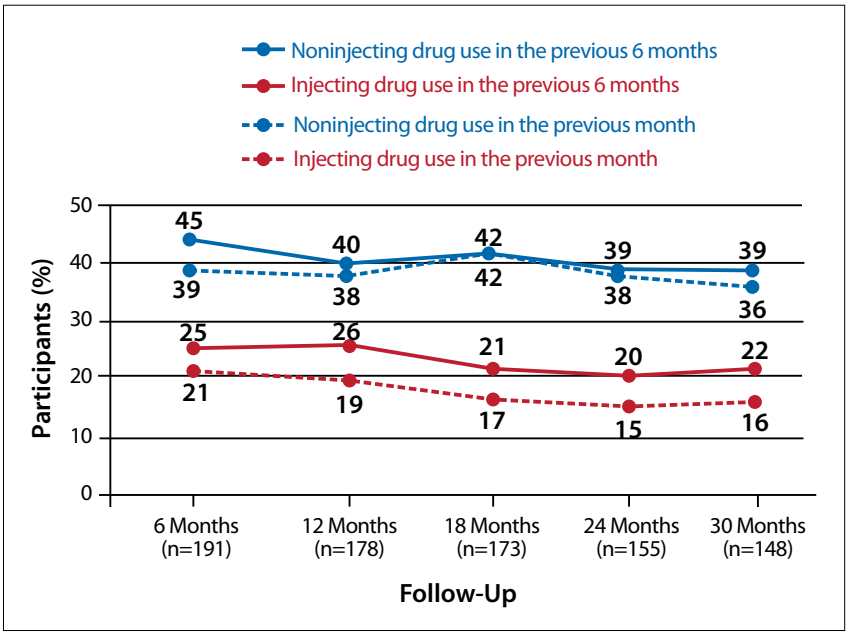

Figure 5. Reported drug use among patients treated with elbasvir/grazoprevir in the C-EDGE CO-STAR Part B trial. Patients were receiving opiate agonist therapy. Adapted from Grebely J et al. AASLD Liver Meeting abstract 52. *Hepatology*. 2018;68(suppl 1).[5]

with HCV genotype 6a at follow-up week 8. The reinfection spontaneously cleared and remained undetectable for approximately 2 years, but the patient was reinfected at week 170 with HCV genotype 2a. This patient's urine drug tests were positive for benzodiazepines and opiates at several time points. The second patient was infected with HCV genotype 6a at baseline. After successful viral clearance with elbasvir plus grazoprevir, the patient was reinfected with HCV genotype 1a. This patient did not enroll in part B of the study. Among the 10 patients who were reinfected, 8 had persistent reinfection. Four of the latter patients were successfully treated outside of the clinical trial.

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Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Pediatric Patients With Genotypes 1-6 Chronic HCV Infection: Part 1 of the DORA Study

Worldwide, approximately 13.2 million children ages 1 to 15 years are chronically infected with HCV.[1] For children older than 12 years, the combinations of sofosbuvir plus ledipasvir and sofosbuvir plus ribavirin are the only approved, interferon-free, direct-acting antiviral agents. The phase 2/3 DORA trial (A Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Pediatric Subjects With Genotypes 1-6 Chronic Hepatitis C Virus [HCV] Infection) is an ongoing study evaluating the pharmacokinetics, safety, and efficacy of glecaprevir plus pibrentasvir in pediatric patients with chronic HCV infection.[2] Part 1 of the study was conducted in adolescents ages 12 to 17 years, all of whom received the adult formulation of the 2-drug combination. Part 2 of the study is evaluating a pediatric formulation of glecaprevir plus pibrentasvir in children ages 3 to 11 years.

DORA Part 1 enrolled patients ages 12 through 17 years. Patients had chronic infection with any HCV genotype, including mixed genotypes. HIV-1 coinfection was allowed with stable, concomitant antiretroviral therapy compatible with study treatment. Patients with compensated cirrhosis were permitted to enroll. The treatment duration was 8 weeks in 44 treatment-naive patients, including 2 with HIV coinfection. Three treatment-experienced patients with HCV genotype 3 infection received 16 weeks

ABSTRACT SUMMARY Glecaprevir/Pibrentasvir for the Treatment of Patients With Chronic Hepatitis C Virus Infection: Updated Real-World Data From the German Hepatitis C Registry

The DHC-R study (German Hepatitis C Registry) is accumulating real-world data on outcomes in German patients with HCV (Abstract 611). This noninterventional, multicenter, prospective registry study analyzed data collected between July 28, 2017 and April 9, 2018 from 118 sites. This analysis evaluated whether on-label or off-label use of glecaprevir plus pibrentasvir impacted outcome. On-label use followed recommendations from the European Medicines Agency label. Off-label use encompassed patients who had received nonindicated prior HCV treatments, such as sofosbuvir; patients with liver decompensation; and treatment duration that was shorter or longer than 12 weeks. Among 1333 enrolled patients, 1242 received on-label treatment with glecaprevir plus pibrentasvir and had a documented baseline visit. Most patients (89%) were treatment-naive. Compensated cirrhosis was reported in 7%. In the ITT population, the SVR12 rate was 97.2% (592/609) with on-label use vs 100% (34/34) with off-label use. Among on-label patients in the ITT population, SVR12 rates were 97.6% (319/327) for genotype 1, 97.4% (37/38) for genotype 2, 96.5% (192/199) for genotype 3, 96.8% (30/31) for genotype 4, and 100% (14/14) for genotypes 5, 6, and mixed or unknown. The rates of AEs were 26% with on-label treatment vs 35% with off-label treatment.

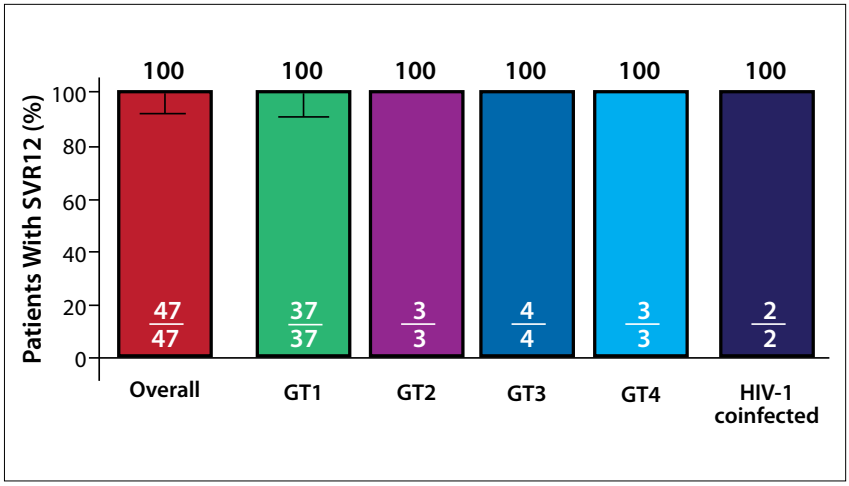

Figure 6. Efficacy among pediatric patients treated with glecaprevir/pibrentasvir in the phase 2/3 DORA trial. Confidence intervals were not calculated for subgroups with fewer than 10 patients. GT, genotype; HIV, human immunodeficiency virus; SVR12, sustained virologic response at week 12. Adapted from Jonas MM et al. AASLD Liver Meeting abstract 2379. *Hepatology*. 2018;68(suppl 1).[2]

ABSTRACT SUMMARY The Impact of HCV Sustained Virologic Response From Direct-Acting Antiviral and Interferon-Based Treatments on Mortality in a Large Population-Based Cohort Study

A retrospective study examined mortality among patients who achieved an SVR with direct-acting antiviral agents or interferon-based treatment (Abstract 145). The analysis included 15,895 patients with or without cirrhosis from the British Columbia Hepatitis Testers Cohort. Among 13,127 patients who achieved SVR, 6551 were treated with interferon and 6576 were treated with direct-acting antiviral agents. Mortality was lowest in patients without cirrhosis who achieved SVR and highest in cirrhotic patients who did not achieve SVR ($P<.0001$). Among patients treated with direct-acting antiviral agents, noncirrhotic patients who achieved SVR had the lowest mortality rate ($P<.001$). Compared with patients who failed to achieve SVR, patients who did achieve SVR experienced a reduction in the HR for mortality, both with interferon-based therapy (HR, 0.20; 95% CI, 0.18-0.22) and with direct-acting antiviral agents (HR, 0.14; 95% CI, 0.11-0.18). Among patients who achieved SVR, the HR for mortality was lower in noncirrhotic vs cirrhotic patients with direct-acting antiviral therapy (0.13 vs 0.14) and with interferon-based treatment (0.19 vs 0.31).

of study drug. The primary endpoint was the steady-state area under the curve values for each study drug.

Among 47 patients, 21 (45%) were male and 35 (74%) were white. The median age was 14 years (range, 12-17 years), and patients had a median weight of 58 kg (range, 32-109 kg). The majority of patients (79%) were infected with HCV genotype 1a or 1b, and the remaining patients were infected with genotype 2 (6%), 3 (9%), or 4 (6%). The median level of HCV RNA was 6.2 $\log_{10}$ IU/mL (range, 4.6-7.2 $\log_{10}$ IU/mL). None of the patients had cirrhosis, 23% were treatment-experienced, and 4% were coinfected with HIV. Among 44 patients with available data, 25% had baseline polymorphisms in NS5A only, and the remaining patients had no polymorphisms in NS3 or NS5A.

Based on the area under the curve at 24 hours, the steady-state exposures of glecaprevir and pibrentasvir observed in HCV-infected adolescents were similar to those observed in HCV-infected adults. Specifically, levels of glecaprevir were 4380 ng·h/mL in adolescents vs 4800 ng·h/mL in adults, and levels of pibrentasvir were 1440 ng·h/mL vs 1430 ng·h/mL, respectively. Neither patient weight nor patient age appeared to have a clinically meaningful relationship with study drug exposure. The study yielded an SVR12 rate of 100%. Viral remissions were seen across all genotypes and in the 2 patients coinfected with HIV (Figure 6).

Among the 47 patients in both treatment arms, 87% had an AE of any grade, with no serious AEs and no AEs leading to discontinuation of the study drug. The most common AEs of any grade were nasopharyngitis (26%), upper respiratory tract infection (19%), and headache (17%). Most AEs were mild and unrelated to treatment with glecaprevir plus pibrentasvir. There were no reports of clinically significant laboratory abnormalities, liver-related toxicities, or drug-induced liver injury. In both patients with HIV-1 coinfection, the infection remained suppressed during treatment.

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Sustained Virologic Response Reduces the Incidence of Extrahepatic Manifestations in Chronic Hepatitis C Infection

Cirrhosis and liver cancer are commonly observed in patients with chronic HCV infection. In addition, a large proportion of HCV patients experience extrahepatic manifestations (EHMs), such as diabetes and chronic kidney disease, which are associated with substantial cost and use of health care resources.[1] A longitudinal cohort study evaluated the relationship between SVR10 and the incidence of EHMs among patients in the British Columbia Hepatitis Testers Cohort.[2] Eligible patients had initiated interferon-based treatment for their HCV infection between January 1999 and July 2014 and had a documented treatment response. EHM outcomes included diabetes, chronic kidney disease/end-stage renal disease, ischemic heart disease, mood and anxiety disorders, and rheumatoid arthritis. The follow-up duration extended from the SVR testing date until the development of a specific EHM, death, retreatment or reinfection, or December 31, 2015 (whichever occurred first). All hazard ratio (HR) analyses were adjusted for factors such as age, sex, and injection drug use.

Among the 10,823 patients who received interferon-based treatment, 1352 had no measurement of HCV RNA at 10 or more weeks after cessation of HCV treatment. After exclusion of prevalent EHMs, the sample sizes for each EHM were 9413 for stroke, 9261 for rheumatoid arthritis, 9241 for chronic kidney disease, 9084 for diabetes, 8981 for heart disease, and 3777 for mood and anxiety disorders. Among the initial study population of 9471 patients, 5930 achieved an SVR. Baseline patient characteristics for the 2 cohorts were generally similar. The median age was 50 to 51 years (range, 42-56 years), and 66% to 70% of patients were male. Injection drug use was reported by 21% to 22% of patients, and 18% to 20% had problematic alcohol use. One-fourth of the patients in each cohort had a major mental illness. Rates of hypertension were 18% to 20%, and diabetes was noted in 3% to 6% of patients.

For each EHM, the crude incidence rate per 1000 person-years was lower in the cohort of patients who achieved SVR. The difference was significant for diabetes, chronic kidney disease/end-stage renal disease, hemorrhagic or ischemic stroke, and mood and anxiety disorders (Table). However, the difference was not significant for ischemic heart disease (P=.3523; adjusted HR, 1.06; 95% CI, 0.88-1.28) or rheumatoid arthritis (P=.98; adjusted HR, 0.83; 95% CI, 0.54-1.27). The study also identified a significant relationship between SVR24 and diabetes (adjusted HR, 0.51; 95% CI, 0.43-0.61), chronic kidney disease or end-stage renal disease (adjusted HR, 0.48; 95% CI, 0.37-0.61), and mood or anxiety disorders (adjusted HR, 0.70; 95% CI, 0.60-0.81). However, there was no significant relationship between SVR24 and ischemic heart disease (adjusted HR, 1.09; 95% CI, 0.90-1.32) or rheumatoid arthritis (adjusted HR, 0.82; 95% CI, 0.53-1.26). The findings are consistent with those observed in studies from Japan, Taiwan, and a US veterans cohort.

Table. The Effect of SVR on Extrahepatic Manifestations

Extrahepatic Manifestation Outcome	Adjusted HR[a] (95% CI)	SVR24 (95% CI)
Diabetes	0.53 (0.45-0.64)	0.51 (0.43-0.61)
Chronic kidney disease or end-stage renal disease	0.48 (0.38-0.61)	0.48 (0.37-0.61)
Stroke	0.67 (0.44-1.02)	0.73 (0.48-1.12)
Ischemic heart disease	1.06 (0.88-1.28)	1.09 (0.90-1.32)
Mood and anxiety disorders	0.71 (0.61-0.83)	0.70 (0.60-0.81)
Rheumatoid arthritis	0.83 (0.54-1.27)	0.82 (0.53-1.26)

HR, hazard ratio; SVR, sustained virologic response.

[a]The HR was adjusted for age, sex, injection drug use, alcohol use, mental health, social/material deprivation, coinfection with hepatitis B virus and human immunodeficiency virus, statin use, diabetes, hypertension, hepatitis C virus genotype, cirrhosis, and treatment year.

Data from Rossi C et al. AASLD Liver Meeting abstract 148. *Hepatology*. 2018;68(suppl 1).[2]

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Quality of Life in Patients With Psychiatric Disorders: Pooled Analysis From Glecaprevir/Pibrentasvir Registrational Studies

Psychiatric disorders are common among patients with chronic HCV infection, affecting as many as half of these patients.[1] In a study of 168 HCV patients, achievement of SVR with interferon-based treatment led to long-term improvements in neurocognitive performance.[2] However, psychiatric comorbidities are associated with a lower likelihood of receiving treatment for HCV infection. A retrospective study evaluated the relationship between HCV treatment and quality of life in patients with or without psychiatric comorbidities.[3] Data were pooled from 8 clinical trials: SURVEYOR -I and -II; ENDURANCE -2, -3, and -4; and EXPEDITION -1, -2, and -4. The study enrolled patients who were infected with chronic HCV, genotypes 1 to 6. Patients did not have cirrhosis or had compensated liver disease. Patients in the trials received daily glecaprevir plus pibrentasvir for 8, 12, or 16 weeks. Patients with psychiatric disorders were identified by medical history or concomitant use of antidepressants or antipsychotics. Patient-reported outcomes were collected by means of the Short Form 36 Health Survey (SF-36), the EuroQOL 5D questionnaire (EQ-5D), and the Fatigue Severity Scale (FSS). Patient-reported outcomes were recorded at baseline, end of treatment, and posttreatment week 12. Meaningful change was defined as one-half of the pooled standard deviation at baseline, and this measurement was then used to indicate whether the outcome was improved, stable, or deteriorated.

Among 2570 patients, 809 (31%) had a psychiatric disorder, including depression (65.4%), anxiety (27.8%), cognitive disorder (10.4%), and bipolar disorder (7.4%). Overall, patients with psychiatric disorders had a greater benefit from treatment as assessed by quality-of-life questionnaires. All domain scores from SF-36 showed a greater improvement in patients with psychiatric disorders compared with those without (Figure 7).

Patients with psychiatric disorders also demonstrated a greater mean change in improvement from baseline based on the EQ-5D health state index (0.03 vs 0.02), the EQ-5D visual analog scale (8.21 vs 5.14), and the FSS (–0.50 vs –0.29; Figure 8). For each domain in the SF-36 questionnaire, patients with psychiatric disorders were more likely to show improvement than those without psychiatric disorders, including for physical function; role, physical; bodily pain; general health; vitality; social function; role, emotional; and mental health (P<.0001 for each). The proportions of patients with an improvement in the FSS score were similar in both cohorts (P=.4356). However, patients with psychiatric disorders were again more likely to show improvement in the EQ-5D health state index (24% vs

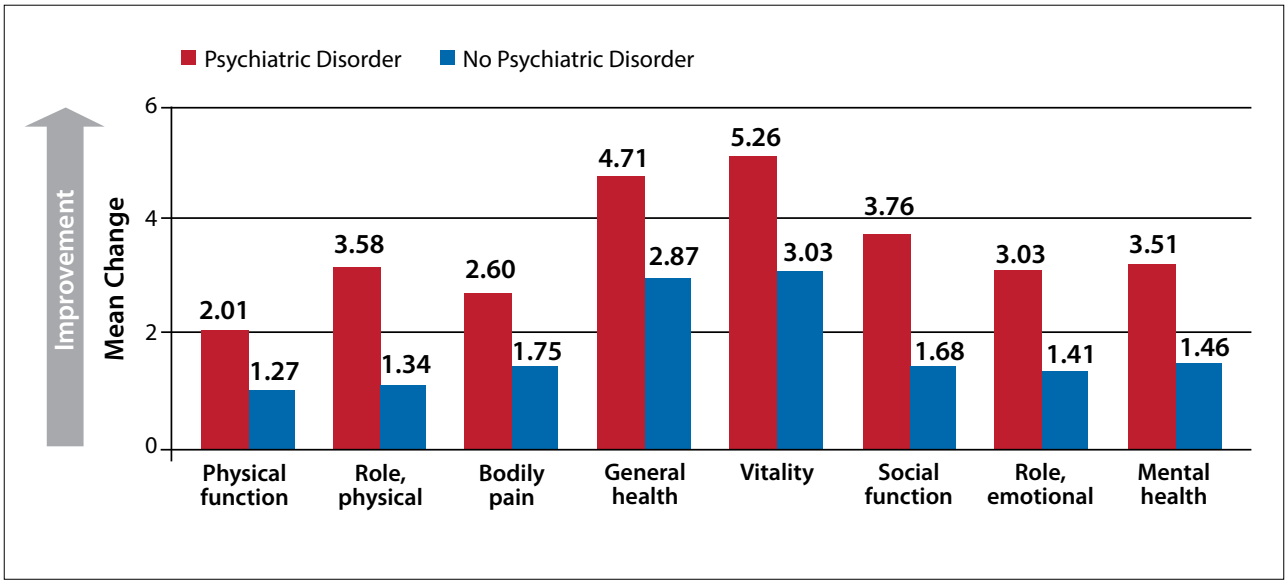

Figure 7. Improvement in SF-36 domain scores among patients treated with glecaprevir/pibrentasvir in a pooled analysis of data from registrational studies. SF-36, Short Form 36 Health Survey. Adapted from Cacoub P et al. AASLD Liver Meeting abstract 150. *Hepatology*. 2018;68(suppl 1).[3]

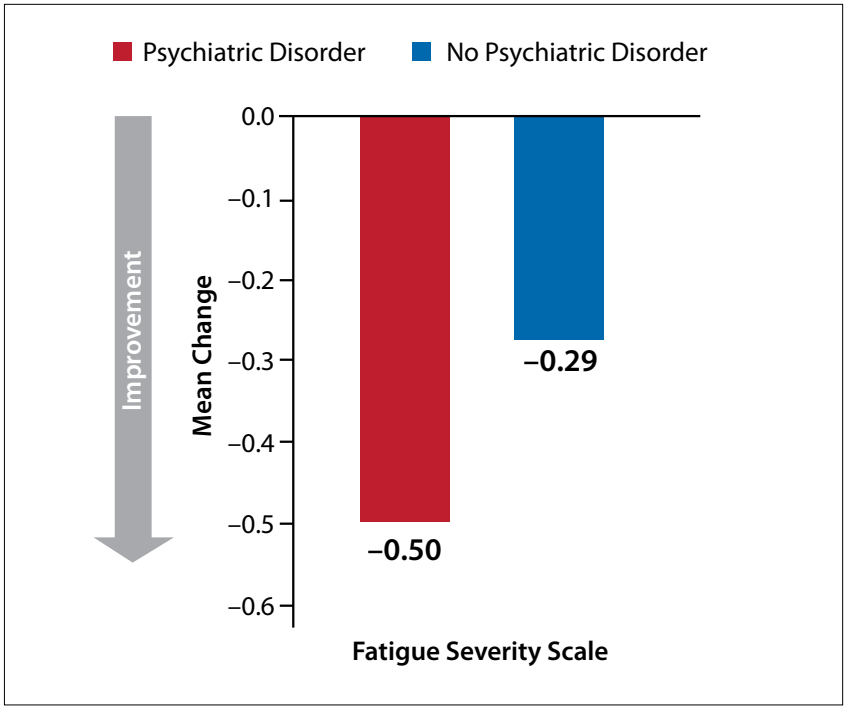

Figure 8. Improvement in fatigue among patients treated with glecaprevir/pibrentasvir in a pooled analysis of data from registrational studies. Adapted from Cacoub P et al. AASLD Liver Meeting abstract 150. *Hepatology*. 2018;68(suppl 1).[3]

19%; *P*=.0049) and the EQ-5D visual analog scale (40% vs 30%; *P*<.0001).

The study is limited by the fact that the analyses were not prespecified in the respective trials. In the cohort with psychiatric disorders, 81 patients were included based on concomitant medication use, which may have led to an overestimation of the number of patients with psychiatric disorders. The pooled analysis included data from registrational clinical studies; therefore, the findings may not reflect real-world outcomes.

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High SVR in People Who Inject Drugs With HCV Despite Imperfect Medication Adherence: Data From the ANCHOR Study

High rates of HCV acquisition and transmission have been observed among people who inject drugs.[1] These people may be denied treatment with direct-acting antiviral agents, based in part on concerns regarding lack of adherence to treatment regimens. The single-center ANCHOR study (Hepatitis C Treatment to Prevent HIV, Initiate Opioid Substitution Therapy, and Reduce Risky Behavior) evaluated the use of direct-acting antiviral agents in patients with opioid use disorder and chronic HCV infection.[2] The study evaluated adherence to treatment and the impact on SVR. Enrolled patients received sofosbuvir plus velpatasvir for 12 weeks, with medication dispensed monthly. Patients also received buprenorphine and medication to prevent possible infection with HIV. All study participants were treated at a harm reduction drop-in center in Washington, DC. They reported injection of an opioid within the prior 3 months. Exclusion criteria included decompensated cirrhosis and contraindicated drug-drug interactions. Adherence to treatment was assessed at weeks 4, 8, and 12 after initiation.

The study screened 160 people and enrolled 100 for the data analysis. Patients who were not enrolled were not eligible for the study (53%), lost to follow-up (35%), or excluded for another reason (12%). Patients had a median age of 57 years (range, 53-62 years), and 76% were male. Ninety-three percent of patients were black, one-third had cirrhosis, and half had unstable housing. More than 90% of patients had previously been incarcerated. The mean age at first intravenous drug use was 21 years (range, 17-30.5 years), and 58% injected opioids daily or more frequently. One-third had received medication-assisted treatment, 40% reported a hazardous level of alcohol consumption, and 29% had shared drug injection equipment within the prior 3 months.

Medication was dispensed to 97% of participants at week 4 and 92% at

ABSTRACT SUMMARY Durability of Sustained Virologic Response and Liver Safety in Patients Treated With Glecaprevir/Pibrentasvir: A Long-Term Follow-Up Study

An ongoing, noninterventional study is evaluating the durability of SVR, the occurrence of RAS in patients who did not achieve SVR12, and liver-related safety outcomes in patients treated with glecaprevir plus pibrentasvir in phase 2/3 clinical trials (Abstract 602). Patients will be followed for 3 years after their final dose of treatment. In the full analysis set population, 373 patients had a median follow-up of 792 days. All of the 87 patients treated with the 8-week course of glecaprevir plus pibrentasvir maintained SVR. All 370 patients with an SVR at enrollment into this study maintained the SVR throughout the last follow-up analysis. Viral suppression was maintained in 99.5% of patients. Among 2 patients with viral failure, 1 patient with HCV genotype 3 infection reported injection drug use and was reinfected with HCV genotype 1a. The second patient relapsed after SVR24. Two patients had liver-related AEs: 1 patient had hepatocellular carcinoma that occurred after achieving SVR12, and 1 patient developed a regenerative liver node after achieving SVR24.

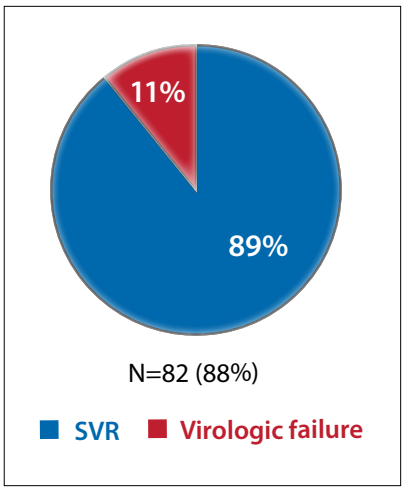

Figure 9. Rates of SVR among patients with hepatitis C virus who inject drugs. Data are shown for the per-protocol analysis. SVR, sustained virologic response. Adapted from Kattakuzhy S et al. AASLD Liver Meeting abstract 18. *Hepatology*. 2018;68(suppl 1).[2]

week 8. Visit adherence was 88% at week 4, 83% at week 8, 70% at week 12, and 88% at week 24. Among 95 patients, 89% had an HCV viral load of less than 200 IU/mL, and 11% had a higher HCV level. Treatment interruptions were reported for 13 patients, owing to stolen medication (n=3), failure to take medication (n=3), hospitalization (n=2), inpatient drug treatment (n=2), incarceration (n=2), or lost medication (n=1). Eighty-seven patients completed 12 weeks of anti-HCV treatment, represented by 3 bottles of 28 pills each. Seven patients completed 2 to 3 bottles, 5 patients completed 1 to 2 bottles, and 1 patient completed less than 1 bottle. Among 80 patients with known end-of-treatment timing, 46 patients finished after 12 weeks, 21 patients finished on time, and 13 patients did not complete treatment.

Among 93 patients in the ITT population, 78% achieved SVR, 10% experienced virologic failure, 9% were lost to follow-up, and 3% died. In the per-protocol population of 82 patients, 89% achieved SVR and 11% had a virologic failure (Figure 9). No baseline factor, including daily injection, unstable housing, or hazardous drinking, was associated with SVR. HCV viral load of less than 200 IU/mL at week 4 was associated with SVR (P<.001). Among 76 patients without treatment interruption, the SVR rate was 86%, whereas 12 patients with treatment interruption had an SVR rate of 67%. Completion of at least 8 weeks of treatment was strongly associated with SVR (P<.001), whereas completing treatment on time did not affect the SVR rate (P=.65).

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Highlights in Hepatitis C Virus From the 2018 AASLD Liver Meeting: Commentary

Fred Poordad, MD

Professor of Medicine
Chief, Hepatology
University Transplant Center
The University of Texas Health, San Antonio
San Antonio, Texas

Studies presented at the 2018 American Association for the Study of Liver Diseases (AASLD) Liver Meeting provided interesting new data regarding the treatment of patients with hepatitis C virus (HCV). One late-breaking abstract, and several other presentations, focused on glecaprevir and pibrentasvir. New data were also presented on the sofosbuvir, velpatasvir, and voxilaprevir regimen. Studies examined outcomes among patients who use drugs, and the use of deceased donor grafts was also evaluated.

Glecaprevir and Pibrentasvir

Dr Robert S. Brown Jr. and colleagues presented a late-breaking abstract on the EXPEDITION-8 study, which evaluated glecaprevir and pibrentasvir given for 8 weeks to treatment-naive patients with compensated cirrhosis.[1] Patients with cirrhosis typically receive 12 weeks of treatment, and this duration was used in the registration trial for glecaprevir and pibrentasvir.[2] The current analysis aimed to determine whether patients with compensated cirrhosis could receive treatment for a shorter duration. The analysis provided data for 280 patients with HCV genotype 1, 2, 4, 5, or 6; most patients had genotype 1. There were no reports of virologic failure, and 98% of patients in the intention-to-treat population achieved a sustained virologic response (SVR). This outcome is consistent with the SVR data for the 12-week regimen. It therefore appears that 8 weeks of glecaprevir plus pibrentasvir among treatment-naive patients with non–genotype 3 HCV and compensated cirrhosis is comparable with 12 weeks.

Patients with HCV genotype 3 were introduced into the study at a later date. Data for these patients were not presented at the AASLD meeting, and they are eagerly awaited. It should be noted that the approval of glecaprevir plus pibrentasvir by the US Food and Drug Administration does not include patients with decompensated cirrhosis. All of the patients in the EXPEDITION-8 trial had well-compensated disease.

Dr Mark S. Sulkowski and colleagues from the Hepatitis C Target Network presented results of a study that evaluated glecaprevir and pibrentasvir in patients with HCV genotype 1 who had failed prior treatment with an NS5A inhibitor plus sofosbuvir.[3] The study included regimens of 12 and 16 weeks; ribavirin was added to the 12-week regimen in patients with cirrhosis. The analysis provided data for 127 patients without cirrhosis and 50 patients with compensated disease. The study found that 16 weeks of treatment was better than 12 weeks, with SVR rates of 95% vs 89%, respectively. The addition of ribavirin to the 12-week regimen did not improve efficacy. The data therefore support the use of 16 weeks of glecaprevir and pibrentasvir for patients without cirrhosis or with compensated cirrhosis who require further treatment after receiving an NS5A inhibitor and sofosbuvir.

Dr Franco Felizarta and colleagues provided long-term follow-up data for 377 patients who had been treated in phase 2 or 3 studies of glecaprevir plus pibrentasvir.[4] After a mean follow-up of 792 days, the SVR rate was 99.5%. Therefore, there were very few reports of late relapses, even among the 90 patients who had been treated with the 8-week regimen.

A study from the German Hepatitis C Registry evaluated real-world data for glecaprevir and pibrentasvir.[5] The analysis showed an SVR rate of 99%. Similarly, a study by Dr Steven L. Flamm and colleagues examined data from the Trio Health Network.[6] Among 478 treatment-naive, noncirrhotic patients with HCV genotypes 1 to 6, treatment with glecaprevir and pibrentasvir for 8 weeks was associated with an SVR rate of 100%.

Dr Maureen M. Jonas and colleagues presented results from the DORA study, which focused on children with HCV.[7] Worldwide, approximately 13 million children ages 1 through 15 years are infected with HCV.[8] Two regimens—sofosbuvir plus

ledipasvir and sofosbuvir plus ribavirin—are now approved for children older than 12 years. The DORA study evaluated the use of glecaprevir plus pibrentasvir in children ages 12 to 17 years. Most patients received 8 weeks of treatment; 16 weeks were given to treatment-experienced patients with genotype 3. The SVR rate was 100%.

Sofosbuvir, Velpatasvir, and Voxilaprevir

Dr Pamela Belperio and colleagues evaluated treatment of HCV among patients in the US Department of Veterans Affairs HCV clinical case registry.[9] The study examined data for 573 treatment-experienced patients, genotypes 1 through 4. Most of the patients had genotype 1 and had received prior treatment with an NS5A inhibitor. They were treated with sofosbuvir, velpatasvir, and voxilaprevir. Among patients with genotype 1 who completed therapy, the SVR rate was 95.1%. In contrast, the SVR rate was 46.5% among patients with genotype 1 who did not complete therapy. This study underscores the fact that adherence is absolutely necessary during treatment with the triple regimen of sofosbuvir, velpatasvir, and voxilaprevir.

Patients With Hepatitis C Virus Who Use Drugs

Dr Jason Grebely and colleagues presented results from the C-EDGE CO-STAR Part B study.[10] Part A of this study assessed 12 weeks of elbasvir and grazoprevir in patients with HCV genotypes 1 through 6 who had received opioid agonist therapy for more than 3 months.[11] This treatment was associated with a good SVR rate of 96%. The Part B analysis showed that high-risk behavior continued in spite of the SVR. In approximately 60% of patients, drug screening was positive for amphetamines, cocaine, opioids, benzodiazepines, or cannabinoids over a 30-month follow-up period. In addition, up to 26% of patients reported injection drug use in the previous 6 months. Interestingly, the reinfection rate throughout the 30-month follow-up period was 1.8 per 100 person-years in the overall population. This rate was somewhat higher, 2.8 per 100 person-years, among patients who reported intravenous drug use. Overall, the analysis shows that the majority of these patients will remain virus-free in spite of ongoing high-risk behavior.

A study by Dr Sarah Kattakuzhy and coworkers also evaluated outcome among patients with HCV who inject drugs.[12] In the per-protocol group, treatment with 12 weeks of sofosbuvir and velpatasvir yielded an SVR12 rate of 89%. In spite of missing doses, problems with housing, issues with adherence, and interruptions in treatment, these patients still were able to achieve high rates of SVR, particularly if they completed all 12 weeks of therapy. This study shows that it is necessary to treat the population of patients who inject drugs in order to eradicate HCV. These patients still achieve very respectable SVR rates, even if some have poor adherence to treatment.

Donor Grafts

Dr Thomas G. Cotter and colleagues evaluated whether the advent of direct-acting antiviral (DAA) therapy has impacted graft survival after liver transplant.[13] The study addressed the question of whether deceased donor grafts placed into patients with HCV would lead to reasonable survival outcomes. It found that HCV-positive recipients had better outcomes in the post-DAA era than before. In fact, their outcomes were similar to non-HCV recipients of deceased organ grafts. Based on this finding, the study authors concluded that it is viable to use organ grafts from deceased donors in patients with or without HCV.

Disclosure

Dr Poordad is on the speakers bureaus/advisory boards of and receives educational and research grants from Gilead Sciences, Merck, Bristol-Myers Squibb, AbbVie, and Intercept Pharmaceuticals.

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