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A SPECIAL MEETING REVIEW EDITION

Highlights in Hepatitis C Virus From the 2017 AASLD Liver Meeting

A Review of Selected Presentations From the 2017 AASLD Liver Meeting • October 20-24, 2017 • Washington, DC

Special Reporting on:

- Efficacy, Safety, and Pharmacokinetics of Glecaprevir/Pibrentasvir in Adults With Chronic Genotype 1-6 Hepatitis C Virus Infection and Compensated Cirrhosis: An Integrated Analysis
- Hepatitis C Virus Reinfection and Injecting Risk Behavior Following Elbasvir/Grazoprevir Treatment in Participants on Opiate Agonist Therapy: Co-STAR Part B
- Efficacy and Safety of Glecaprevir/Pibrentasvir for 8 or 12 Weeks in Treatment-Naive Patients With Chronic HCV Genotype 3: An Integrated Phase 2/3 Analysis
- SOF/VEL/VOX for 12 Weeks in NS5A-Inhibitor–Experienced HCV-Infected Patients: Results of the Deferred Treatment Group in the Phase 3 POLARIS-1 Study
- Adherence to Pangenotypic Glecaprevir/Pibrentasvir Treatment and SVR12 in HCV-Infected Patients: An Integrated Analysis of the Phase 2/3 Clinical Trial Program
- The C-BREEZE 1 and 2 Studies: Efficacy and Safety of Ruzasvir Plus Uprifosbuvir for 12 Weeks in Adults With Chronic Hepatitis C Virus Genotype 1, 2, 3, 4, or 6 Infection
- 100% SVR With 8 Weeks of Ledipasvir/Sofosbuvir in HIV-Infected Men With Acute HCV Infection: Results From the SWIFT-C Trial (Sofosbuvir-Containing Regimens Without Interferon for Treatment of Acute HCV in HIV-1–Infected Individuals)

PLUS Meeting Abstract Summaries

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FOR CHRONIC HCV

TREAT ALL GENOTYPES IN AS FEW AS 8 WEEKS

THE ONLY 8-WEEK PANGENOTYPIC REGIMEN FOR TREATMENT-NAÏVE, NON-CIRRHOTIC PATIENTS

Duration is dependent on treatment history, genotype, or the presence of compensated cirrhosis. Refer to the full Prescribing Information for further dosing information.

INDICATION[1]

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[1]

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[1]

MAVYRET is contraindicated:

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

WARNINGS AND PRECAUTIONS[1]

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[1]

Most common adverse reactions observed with MAVYRET:

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

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

Reference: 1. MAVYRET [package insert]. North Chicago, IL: AbbVie Inc.; 2017.

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 Interaction]*.

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 comparable 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%.

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.

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, 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]*.

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.

Manufactured by AbbVie Inc., North Chicago, IL 60064

MAVYRET is a trademark of AbbVie Inc.

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46A-1924296 **MASTER**

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Efficacy, Safety, and Pharmacokinetics of Glecaprevir/Pibrentasvir in Adults With Chronic Genotype 1-6 Hepatitis C Virus Infection and Compensated Cirrhosis: An Integrated Analysis

Dr Edward Gane and colleagues presented results from an integrated analysis of the efficacy, safety, and pharmacokinetics of the newly approved fixed-dose oral combination agent glecaprevir/pibrentasvir.[1] Both agents are direct-acting antivirals (DAAs) targeting nonstructural (NS) proteins. Glecaprevir is a pangenotypic NS3/4A protease inhibitor, and pibrentasvir is a pangenotypic NS5A inhibitor.[2] The glecaprevir/pibrentasvir combination is potent against several common polymorphisms found in hepatitis C virus (HCV), including Y93H in NS5A and Q80K in NS3.[3,4] In 2017, the US Food and Drug Administration (FDA) approved glecaprevir/pibrentasvir for treatment-naive adult patients with HCV genotype 1 to 6 infection.[2] An 8-week duration is approved for patients without cirrhosis, and a 12-week duration is approved for those with compensated cirrhosis

In phase 2 and 3 clinical trials, glecaprevir/pibrentasvir demonstrated an overall rate of sustained virologic response at 12 weeks (SVR12) of 98% in patients with HCV genotype 1 to 6.[2] The safety profile in these studies indicated that glecaprevir/pibrentasvir was well-tolerated regardless of baseline factors, such as the presence of compensated cirrhosis or advanced renal disease.

The phase 3 EXPEDITION-1 trial was part of a clinical development program that evaluated a 12-week duration of treatment with glecaprevir/pibrentasvir in patients with HCV genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis. (Patients with genotype 3 HCV infection and compensated cirrhosis were enrolled in a separate trial.) This study demonstrated an SVR12 rate of 99%.[5]

The integrated analysis presented by Dr Gane evaluated the efficacy, safety, and pharmacokinetic profiles of treatment with glecaprevir/pibrentasvir in patients with chronic HCV genotype 1 to 6 infection and compensated cirrhosis. The analysis included 308 patients enrolled in 4 open-label, phase 2 and 3 trials: EXPEDITION-1, EXPEDITION-4, SURVEYOR-II, and MAGELLAN-1. Glecaprevir/pibrentasvir was administered for 12 weeks in 245 patients and for 16 weeks in 63 patients. The primary efficacy endpoint was SVR12, which was assessed in the intent-to-treat population. An additional efficacy assessment was SVR12 in the modified intent-to-treat population, which excluded nonvirologic treatment failures.

Most patients were male (65%) and white (85%). The median age was 58.5 years (range, 26-88 years). All 6 HCV genotypes were represented; 40% of patients had genotype 1, 12% had genotype 2, 38% had genotype 3, 7% had genotype 4, 1% had genotype 5, and 2% had genotype 6. All patients were required to have compensated cirrhosis. The analysis excluded patients coinfected with HIV-1 or hepatitis B virus. Patients were either treatment-naive (59%) or had previously received antiviral therapy. Previous treatments could include interferon or pegylated interferon with or without ribavirin, sofosbuvir plus ribavirin with or without pegylated interferon, and HCV NS5A or protease inhibitors. Cirrhosis was confirmed at screening by 1 of 3 methods: a FibroTest score of 0.75 or higher plus a ratio of aspartate aminotransferase (AST) to platelets exceeding 2, a FibroScan score of 14.6 kPa or higher, or a liver biopsy. Most patients had a Child-Pugh score of 5 (86%) or 6 (13%), with no current or past clinical evidence of liver

ABSTRACT SUMMARY Eradication of HCV Induced by Direct-Acting Antivirals Is Associated With a 79% Reduction in HCC Risk

In the current treatment era, most patients chronically infected with HCV will receive antiviral therapy with DAAs. An SVR12 will occur in nearly all of these patients. Despite their widespread use, the impact of DAAs on the development of HCC is controversial. Dr George Ioannou and coworkers described data from a study performed within the National Veterans Affairs Healthcare system, which aimed to investigate this question (Abstract 142). The study showed that DAA-induced SVR was associated with a 71% reduction in the risk for developing HCC. Furthermore, the full eradication of HCV RNA levels was associated with a similar reduction in the risk for developing HCC, regardless of the DAA regimen used. The presence of cirrhosis did not significantly impact the association between SVR and HCC risk. The use of DAAs was not associated with a higher risk for HCC compared with the use of interferon therapy.

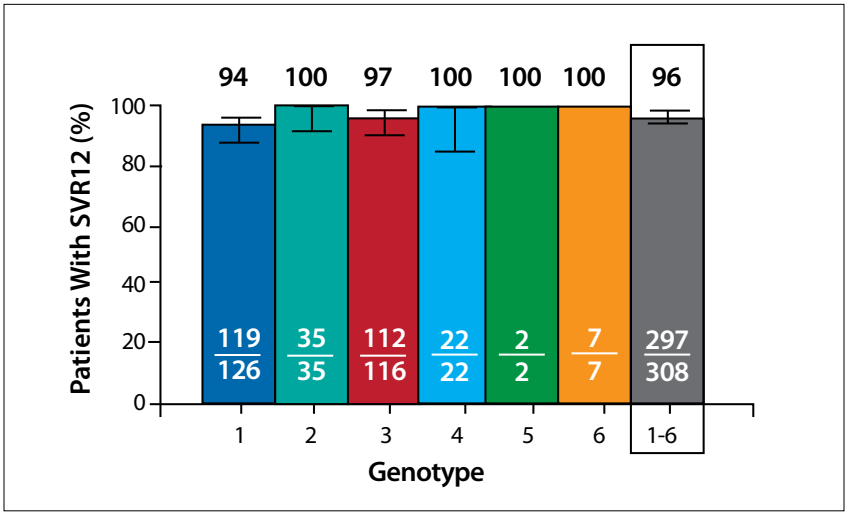

Figure 1. Rates of SVR12 among patients treated with glecaprevir/pibrentasvir among the intent-to-treat population. SVR12, sustained virologic response at week 12. Adapted from Gane EJ et al. AASLD Liver Meeting abstract 74. *Hepatology*. 2017;66(suppl 1).[1]

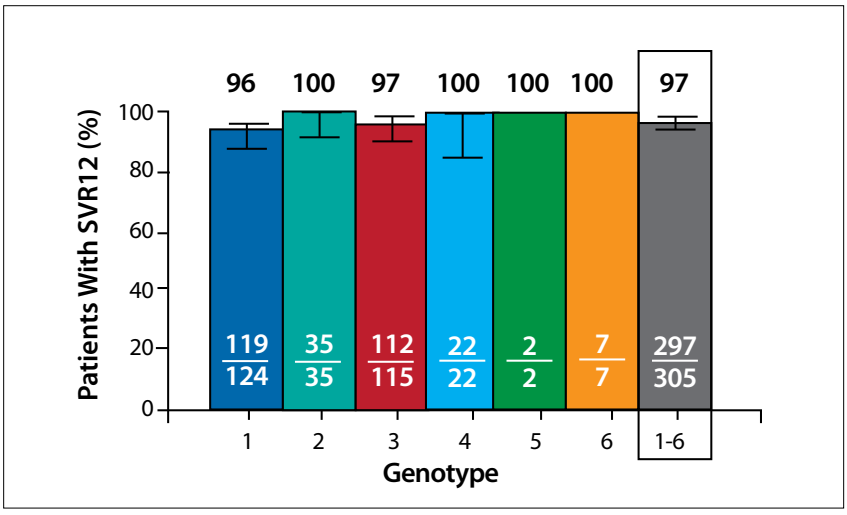

Figure 2. Rates of SVR12 among patients treated with glecaprevir/pibrentasvir among the modified intent-to-treat population. SVR12, sustained virologic response at week 12. Adapted from Gane EJ et al. AASLD Liver Meeting abstract 74. *Hepatology*. 2017;66(suppl 1).[1]

decompensation. The median HCV RNA level at baseline was 6.2 IU/mL. Approximately one-quarter of patients (23%) had low platelet counts (<100 × 10^9/L), and 7% had a low albumin level of less than 3.5 g/dL.

The rate of SVR12 in the intent-to-treat population was 96% across all HCV genotypes. Rates were 94% in patients with genotype 1, 97% in genotype 3, and 100% in genotype 2, 4, 5, and 6 (Figure 1). Treatment failed in 11 patients, owing to breakthrough (n=5), relapse (n=3), or treatment discontinuation (n=1). (The data were missing for the remaining 2 patients.) Five cases of treatment failure were attributed to viral breakthrough. Four of these patients had HCV genotype 1 and had been treated unsuccessfully with an NS5A regimen (2 of these patients had also received a protease inhibitor). The remaining case of treatment failure owing to viral breakthrough occurred in a patient with HCV genotype 3 who had previously failed treatment with pegylated interferon plus ribavirin.

The SVR12 rate in the modified intent-to-treat population (which excluded cases of nonvirologic treatment failures) was 97% overall. These rates were 96% in patients with genotype 1, 97% in patients with genotype 3, and 100% across the other genotypes (Figure 2).

A treatment-emergent adverse event was reported in 76% of patients overall; the majority of these events were mild or moderate. The most frequent adverse events were fatigue (19%), headache (16%), and nausea (10%). Serious adverse events occurred in 9% of patients; however, none were considered related to the study drug. Two patients discontinued treatment owing to adverse events: 1 patient with pruritus and 1 patient with diarrhea.

Two patients died after treatment, and both cases were deemed unrelated to the study drug. Additionally, 2 cases of treatment-emergent hepatocellular carcinoma (HCC) were reported, and 1 patient experienced adverse events that were consistent with hepatic decompensation.

There were no cases of alanine transaminase (ALT) or AST elevations that reached grade 3 or higher in severity. An elevation of total bilirubin reached grade 3 or higher in 3 patients (1%). These elevations were characterized as transient, asymptomatic, and predominantly indirect. The study investigators also noted that the elevations in total bilirubin levels were consistent with the known inhibition of bilirubin metabolism and/or transporters attributed to glecaprevir. Bilirubin elevations were not associated with ALT elevation or a worsening of hepatic function or hepatic failure, and they resolved without discontinuation of treatment.

An analysis of pharmacokinetic parameters showed that cirrhosis status impacted exposure to glecaprevir/pibrentasvir. Among the 308 patients with compensated cirrhosis included in this integrated analysis, glecaprevir exposure was approximately 2.2-fold

higher than in 2056 patients without cirrhosis enrolled in other clinical trials. Despite this increased exposure, the frequency and severity of adverse events were similar in patients with or without cirrhosis. In contrast, pibrentasvir exposure was similar between the 2 patient groups.

The authors of this integrated analysis concluded that the results supported a high efficacy and favorable safety profile for glecaprevir/pibrentasvir in HCV patients with genotype 1 to 6 and compensated cirrhosis. They noted that the glecaprevir/pibrentasvir fixed-dose combination was well-tolerated, with no serious adverse events related to the study drug.

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

Dr Gregory Dore and coworkers reported data from the Co-STAR Part B study, which evaluated HCV reinfection and injecting risk behavior after treatment with elbasvir/grazoprevir among patients receiving opiate agonist therapy.[1] Elbasvir/grazoprevir is a fixed-dose combination tablet administered orally once daily. It is approved by the FDA for the treatment of adults infected with HCV genotype 1 or 4.[2]

Elbasvir is an inhibitor of NS5A, and grazoprevir is an NS3/4A protease inhibitor.[2] In vitro studies have previously demonstrated that this treatment has activity against multiple clinically relevant resistance-associated substitutions, including first-generation protease inhibitor variants and variants associated with daclatasvir and ledipasvir treatment failures.[3-5] In clinical studies, elbasvir/grazoprevir was shown to be efficacious in both treatment-naive and previously treated patients, regardless of whether they had concomitant cirrhosis or HIV coinfection.[6-10] The safety and efficacy of elbasvir/grazoprevir have been demonstrated in special populations of HCV-infected patients, including those with stage 4 or 5 chronic kidney disease or inherited blood disorders.[7,10]

The phase 3 randomized Co-STAR study evaluated the efficacy and safety of a 12-week regimen of elbasvir/grazoprevir among patients who inject drugs and were receiving opiate agonist therapy. The study recruited participants infected with HCV genotype 1, 4, or 6, and who had been receiving opiate agonist therapy for at least 3 months. Coinfection with HIV was allowed.

In the first phase of the study (part A), 301 patients were randomly assigned to 1 of 2 arms: an immediate-treatment arm (n=201), in which patients received elbasvir/grazoprevir for the first 12 weeks of the study; and a deferred-treatment arm (n=100), in which patients received placebo for the first 12 weeks. After week 12, the treatments in each arm were unblinded for 4 weeks. Participants in the deferred-treatment arm then went on to receive 12 weeks of elbasvir/grazoprevir. The full analysis set included data for patients who experienced nonvirologic failures of treatment, and it categorized cases of reinfection as failures. The SVR12 rate was 90.9% in the combined treatment arms. The modified analysis set, which excluded 10 nonvirologic failures and categorized cases of reinfection as successes, showed an SVR12 of 95.8% in the combined treatment arms.

The report from Dr Dore provided interim results from part B of the study, which is ongoing. The analysis included a 3-year observational follow-up portion open to all participants who had received at least 1 dose of elbasvir/grazoprevir in part A. Assessments were performed every 6 months and included HCV RNA levels and urine drug screens. A behavioral questionnaire that included questions about drug use was administered to patients at each assessment. A total of 199 patients participated in Co-STAR part B. At the time of the interim analysis, follow-up was 6 months in 192 patients, 12 months in 179, 18 months in 173, and 24 months in 118.

The median age of the patients in part B was 48.6 years (range, 24-66 years) vs 44.1 years (range, 23-64 years) in the patients who did not enroll. In part B, most patients had HCV genotype 1, with 72% having 1a and 20% having 1b. Among

ABSTRACT SUMMARY Pan-Genotypic Hepatitis C Treatment With Glecaprevir/Pibrentasvir Achieves Greatest Improvements in Quality-Adjusted Life-Years and Lifetime Risk Reductions in Liver-Related Morbidity and Mortality vs Standards of Care: A Cost-Utility Analysis

Dr Sammy Saab and colleagues presented a cost-utility analysis that was performed in patients treated with the pangenotypic treatment regimen glecaprevir/pibrentasvir (Abstract 1578). This analysis compared glecaprevir/pibrentasvir with 2 standard-of-care strategies: sofosbuvir/ledipasvir or sofosbuvir/velpatasvir (strategy 1) or grazoprevir/elbasvir or sofosbuvir/velpatasvir (strategy 2). When compared with current standards of care, glecaprevir/pibrentasvir was associated with a more favorable improvement in quality-adjusted survival, better SVR rates, and a greater lifetime risk reduction in liver-related morbidity and mortality. Treatment with glecaprevir/pibrentasvir increased lifetime quality-adjusted life-years (18.2 years) vs both strategies (18.1 years with both strategies), at a lower lifetime cost ($34,703 for glecaprevir/pibrentasvir vs $80,169 with strategy 1 and $67,832 with strategy 2). The study authors concluded that among the treatment options analyzed, glecaprevir/pibrentasvir was associated with the most favorable patient outcomes as well as the lowest cost, calling it the "dominant treatment option."

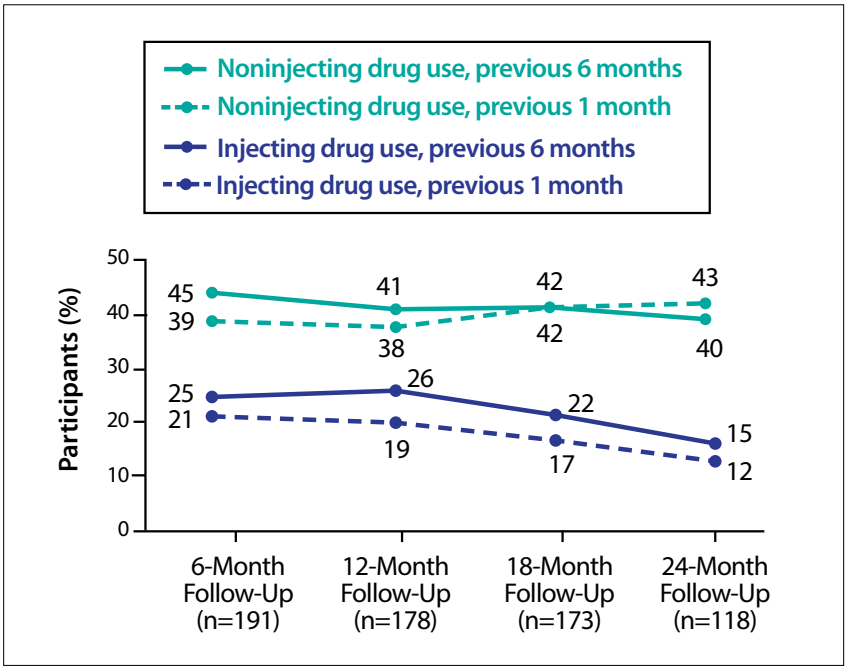

Figure 3. Reported drug use among patients treated with elbasvir/grazoprevir in the Co-STAR study. Adapted from Dore G et al. AASLD Liver Meeting abstract 195. *Hepatology*. 2017;66(suppl 1).[1]

participants who did not enroll in part B, genotype 1a accounted for 84% and genotype 1b for 5%. The remaining baseline characteristics were similar between the 2 groups. Most patients were male (76%) and white (79%). The rate of HIV-1 coinfection was 8%, and cirrhosis was present in 22%.

The incidence of ongoing risky behavior remained stable throughout part B. At the time of enrollment into part A, 59% of patients had a positive urine drug screen. The rate of positive drug screening at the time of enrollment into part B was 60%, and remained steady during follow-up at 6 months (59%), 12 months (62%), 18 months (59%), and 24 months (60%). Throughout follow-up, most positive urine drug screens were caused by the use of opioids (21% to 27%), benzodiazepines (21% to 24%), and cannabinoids (28% to 32%). Cocaine use (11% to 20%) and amphetamine use (2% to 8%) were less prevalent. Noninjecting drug use accounted for the majority of reported drug use throughout the follow-up period, with 39% of participants reporting noninjecting drug use during the previous month at the 6-month follow-up, and 40% reporting the same at the 24-month follow-up (Figure 3). Fewer participants reported injecting drug use during the previous month (21% at the 6-month follow-up, decreasing to 12% by the 24-month follow-up).

Ten cases of reinfection were reported from the end of treatment through 24 months of follow-up, which equated to 2.3 reinfections per 100 person-years (95% CI, 1.1-4.3). Among these, only 7 cases were found to be persistent, equating to 1.6 reinfections per 100 person-years (95% CI, 0.7-3.4). HCV RNA levels became detectable in these 7 participants during a wide range of follow-up periods, from week 9 to week 124, and subsequently persisted. Spontaneous clearance of reinfection was observed in the other 3 cases. HCV RNA levels became detectable at week 21 in 2 participants and at week 20 in 1 participant. Subsequently, HCV RNA levels became undetectable again at week 36 for 1 participant and at week 24 for the other 2 participants.

The use of injected drugs during follow-up seemed to be associated with an increased risk of reinfection. For example, among the 74 participants (37%) who self-reported injection drug use at any time during follow-up,

the rate of reinfection was 4.2 per 100 person-years (95% CI, 1.5-9.2). In contrast, among the 125 participants (63%) who did not self-report injection drug use at any time during the follow-up, the rate of reinfection was 0.4 per 100 person-years (95% CI, 0-2.3).

Dr Dore and colleagues concluded that HCV reinfection was uncommon after treatment with elbasvir/grazoprevir among patients receiving opiate agonist therapy. Results from an interim analysis suggested that ongoing injection drug use may be a risk factor for reinfection. However, even among patients who self-reported injection drug use, reinfection rates remained low.

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Efficacy and Safety of Glecaprevir/Pibrentasvir for 8 or 12 Weeks in Treatment-Naive Patients With Chronic HCV Genotype 3: An Integrated Phase 2/3 Analysis

Dr Steven Flamm and colleagues reported the results of an integrated analysis of glecaprevir/pibrentasvir.[1] This study focused on the efficacy and safety of glecaprevir/pibrentasvir in treatment-naive patients infected with HCV genotype 3 who had compensated liver disease (with or without cirrhosis).

HCV genotype 3 is more difficult to treat than the other genotypes. DAA therapies have reduced rates of SVR in patients infected with this genotype. Until recently, guidelines from the American Association for the Study of Liver Diseases (AASLD) recommended regimens of sofosbuvir plus daclatasvir for 24 or 12 weeks (for patients with or without cirrhosis, respectively) or sofosbuvir/velpatasvir for 12 weeks (regardless of cirrhosis status) for treatment-naive patients with HCV genotype 3. These guidelines were updated to reflect the 2017 FDA approval of glecaprevir/pibrentasvir, which is indicated in treatment-naive patients infected with HCV genotype 1 to 6.[2] Guidelines from the AASLD recommend an 8-week regimen of glecaprevir/pibrentasvir for patients without cirrhosis, and a 12-week regimen for patients with compensated cirrhosis. The guidelines also state that patients treated with glecaprevir/pibrentasvir can forgo testing for resistance-associated substitutions and skip concomitant administration with ribavirin.[3]

The integrated analysis included 571 patients enrolled in 7 phase 2 and 3 clinical trials. Among the 502 patients without cirrhosis, 208 were treated with glecaprevir/pibrentasvir for 8 weeks, and 294 were treated for 12 weeks. A total of 69 patients with cirrhosis received treatment with glecaprevir/pibrentasvir for 12 weeks.

Eligibility criteria for the analysis included chronic HCV infection with genotype 3. Coinfection with hepatitis B, but not HIV-1, was permitted. Patients were required to be treatment-naive, either with or without compensated cirrhosis (Child-Pugh class A). The analysis also included patients with chronic kidney disease (stage 4 or 5) or who had previously received a liver or kidney transplant.

The primary efficacy endpoint, SVR12, was assessed in the intent-to-treat population, which included all patients who had received at least 1 dose of the study drug. Additional efficacy assessments were SVR12, both overall and by patient subgroup, in the modified intent-to-treat population (which excluded nonvirologic treatment failures), and rates of on-treatment virologic failure and virologic relapse.

Overall, baseline characteristics were similar in the different treatment groups. Among the 208 patients without cirrhosis who received 8 weeks of glecaprevir/pibrentasvir treatment, 59%

ABSTRACT SUMMARY Evaluation of the Efficacy and Tolerability of JNJ-4178 (AL-335, Odalasvir, and Simeprevir) in Hepatitis C Virus–Infected Patients Without Cirrhosis: The Phase IIb OMEGA-1 Study

Dr Stefan Zeuzem and colleagues reported outcomes from the OMEGA-1 study, a phase 2b trial that evaluated 6 or 8 weeks of treatment with JNJ-4178, a combination of AL-335, odalasvir, and simeprevir (Abstract 65). This study enrolled 365 patients with chronic HCV infection with genotype 1, 2, 4, 5, and 6 who did not have cirrhosis. Patients were randomly assigned to 6 or 8 weeks of treatment. The SVR12 rates achieved were 99% with 6 weeks and 98% with 8 weeks of treatment. High SVR12 rates were observed across all genotypes, with the exception of genotype 2c, which was associated with an 83% SVR12 rate with 6 weeks of treatment and a 75% SVR12 rate with 8 weeks of treatment. JNJ-4178 was generally well-tolerated. Pruritus and rash were the most frequently reported adverse events. Cardiac events were reported in 3.3% of patients in the 6-week arm and 4.4% of patients in the 8-week arm. However, an extensive and thorough cardiac evaluation did not reveal any evidence of increased cardiac toxicity with the regimen.

were male and 87% were white. The median age was 46 years (range, 20-76 years). Among the 294 patients without cirrhosis who were treated with 12 weeks of glecaprevir/pibrentasvir, 57% were male and 88% were white. The median age was 49 years (range, 22-71 years). Although 11% of the 8-week treatment group had HIV-1 coinfection, none of the patients in the 12-week treatment group were coinfected with HIV-1. None of the patients in the 8-week group had chronic kidney disease or were post-transplant; in contrast, 4% of the 12-week group had chronic kidney disease and 8% were post-transplant. In the group of 69 patients with cirrhosis, 59% were male, 93% were white, and the median patient age was slightly older (56 years; range, 35-70 years). In this group, 6% were coinfected with HIV-1, 2% had chronic kidney disease, and none had undergone transplant.

Polymorphisms at baseline were found primarily in NS5A. Among patients without cirrhosis who were treated for 8 weeks, no patients had an NS3-only polymorphism, 28% had an NS5A-only polymorphism (10% with A30K and 6% with Y93H mutations), and 1% had polymorphisms in both. Among patients without cirrhosis who were treated for 12 weeks, 1% had an NS3-only polymorphism, 17% had an NS5A-only polymorphism (7% with A30K and 7% with Y93H mutations), and 1% had polymorphisms in both. In the group of patients with cirrhosis, 4% had an NS3-only polymorphism, and 19% had an NS5A-only polymorphism (3% with A30K and 10% with Y93H mutations). No patients had both polymorphisms.

In the intent-to-treat analysis of all patients who had received at least 1 dose of glecaprevir/pibrentasvir, the SVR12 rates were 95% in patients without cirrhosis (treated for 8 or 12 weeks) and 97% in patients with cirrhosis. The modified intent-to-treat analysis, which excluded patients with nonvirologic treatment failures, showed an SVR12 rate of 98% for patients without cirrhosis treated for 8 weeks, 99% for patients without cirrhosis treated for 12 weeks, and 100% for patients with cirrhosis treated for 12 weeks.

When the modified intent-to-treat analysis was performed according to patient characteristics in the noncirrhosis arm, no statistically significant differences were noted between the 8-week and 12-week treatment groups for any subgroup (Figure 4). The SVR12 rate was 100% for patients of black race in both the 8-week and 12-week treatment groups. The degree of fibrosis did not significantly affect the SVR12 rate. Among patients with F0 to F2 fibrosis, 98% achieved SVR12 in both the 8-week and 12-week treatment groups. Among patients with F3 fibrosis, 94% achieved SVR12 in the 8-week group and 100% achieved SVR12 in the 12-week group. For patients receiving opioid substitution therapy, SVR12 was reported in 100% of the 8-week group and 98% of the 12-week group. Recent drug use did not affect the SVR12 rate in the 8-week group (100%) or the 12-week group (94%), nor did history of intravenous drug use (SVR12 of 98% in both the 8-week and 12-week groups).

Viral characteristics also did not significantly impact the SVR12 rates in the 8-week vs 12-week treatment groups for patients without cirrhosis. A similar SVR12 rate was achieved in the 8-week and 12-week treatment groups for patients with a baseline HCV RNA level of less than 800,000 IU/mL (99% vs 100%) or 800,000 IU/mL or higher (97% vs 98%). Additionally, the presence or absence of polymorphisms at baseline had no effect. Among patients with no baseline polymorphisms, the SVR12 rate was 99%, regardless of treatment duration. The SVR12 rates in the 8-week vs 12-week treatment groups were 95% vs 94% for those with a baseline NS5A polymorphism, 84% vs 94% for those with the A30K mutation, and 100% vs 90% for those with the Y93H mutation.

Overall, adverse events were similar in the different patient groups treated with glecaprevir/pibrentasvir. Among patients without cirrhosis, an adverse event occurred in 65% of the 8-week treatment group and 77% of the 12-week treatment group. Among patients with cirrhosis, 84% experienced an adverse event. In the 3 groups (8-week noncirrhotic group, 12-week noncirrhotic group, and

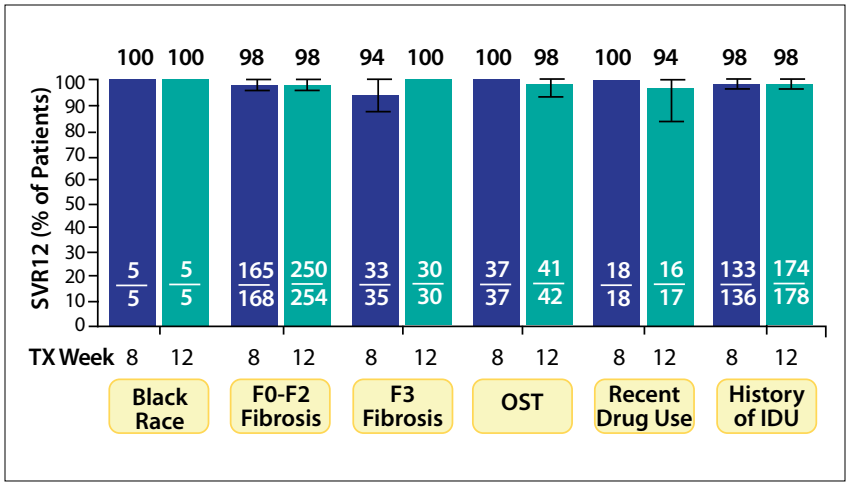

Figure 4. Rates of SVR12 across subgroups in an integrated analysis of patients treated with glecaprevir/pibrentasvir. Data for the modified intent-to-treat population are shown. F, fibrosis stage; IDU, injection drug use; OST, opioid substitution therapy; SVR12, sustained virologic response at week 12; TX, treatment. Adapted from Flamm SL et al. AASLD Liver Meeting abstract 62. *Hepatology*. 2017;66(suppl 1).[1]

12-week group with cirrhosis), the most commonly reported adverse events were headache (19%, 24%, and 19%, respectively), fatigue (14%, 19%, and 10%), and nausea (12%, 13%, and 10%).

Serious adverse events were reported by 1% of patients in the 8-week noncirrhotic group and 3% in the other groups. However, none of these serious adverse events were deemed related to the study drug. Three patients without cirrhosis who were treated with 12 weeks of glecaprevir/pibrentasvir discontinued treatment owing to an adverse event; only 1 of these cases was deemed by the investigator to be related to the study drug.

No grade 3 or higher elevations in ALT were reported. A grade 3 or higher AST elevation occurred in 1 patient (who did not have cirrhosis and who was treated with 12 weeks of glecaprevir/pibrentasvir). Additionally, 1 patient in each of the treatment groups experienced a grade 3 or higher increase in total bilirubin level.

The study investigators concluded that the results of this integrated analysis showed high efficacy of glecaprevir/pibrentasvir in treatment-naive patients with chronic HCV genotype 3 infection, regardless of cirrhosis status. Glecaprevir/pibrentasvir was associated with high rates of SVR12. In most cases where SVR12 was not achieved, nonvirologic failure was the reason. Subgroup analyses demonstrated no significant difference in efficacy between 8 weeks and 12 weeks of treatment with glecaprevir/pibrentasvir among these patients with HCV genotype 3 infection.

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SOF/VEL/VOX for 12 Weeks in NS5A-Inhibitor–Experienced HCV-Infected Patients: Results of the Deferred Treatment Group in the Phase 3 POLARIS-1 Study

In a poster presentation, Dr Marc Bourlière and colleagues reported on a POLARIS-1 substudy that evaluated treatment with sofosbuvir/velpatasvir/voxilaprevir.[1] This once-daily, oral single-tablet regimen is indicated for the treatment of adult patients with chronic HCV infection with or without compensated cirrhosis. It was approved by the FDA in November 2017 for patients with HCV genotype 1 to 6 who had previously been treated with an HCV regimen containing an NS5A inhibitor, and in patients with HCV genotype 1a or 3 infection who had previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.[2] This approval was based, in part, on results from the randomized, double-blind POLARIS-1 study, which demonstrated an SVR12 rate of 96% among patients who had previously been treated with an NS5A inhibitor.[3] In POLARIS-1, patients infected with HCV genotype 1 at screening were randomly assigned to treatment with sofosbuvir/velpatasvir/voxilaprevir or placebo. Patients with all other HCV genotypes were treated with sofosbuvir/velpatasvir/voxilaprevir. Patients in the placebo arm were then eligible for a deferred treatment

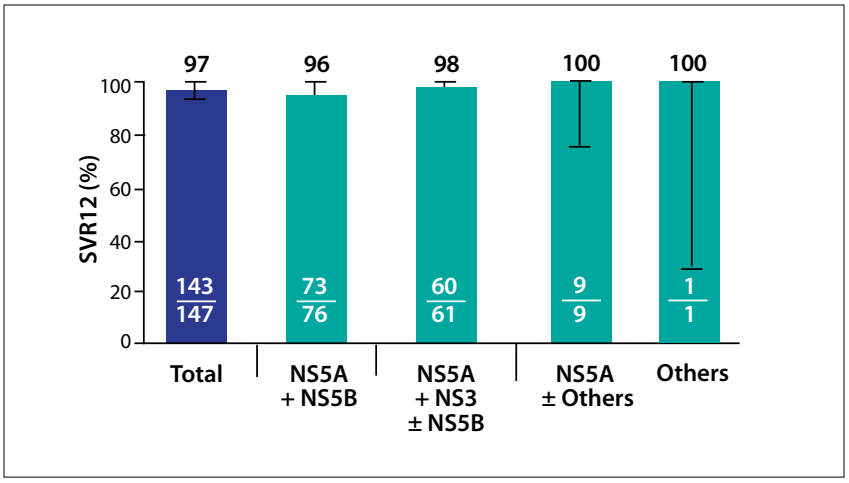

Figure 5. Rates of SVR12 according to previous treatment with direct-acting antiviral therapy among patients treated with sofosbuvir/velpatasvir/voxilaprevir. NS3, nonstructural protein 3; NS5A, nonstructural protein 5A; NS5B, nonstructural protein 5B; SVR12, sustained virologic response at week 12. Adapted from Bourlière M et al. AASLD Liver Meeting abstract 1178. *Hepatology*. 2017;66(suppl 1).[1]

ABSTRACT SUMMARY Survival Benefit of Direct-Acting Antiviral Therapy in Patients With Decompensated Cirrhosis

In a late-breaking abstract, Dr W. Ray Kim and colleagues reported on a study comparing the observed incidence of deaths among patients with hepatic decompensation enrolled in the SOLAR studies vs the mortality rate predicted by survival models in patients with HCV infection and hepatic decompensation in the pre-DAA treatment era (Abstract LB-27). The analysis evaluated data from 212 patients with Child-Pugh class B or C cirrhosis. Within 1 year of therapy, 15 deaths were reported. The observed-vs-expected survival was not different for the first 100 days (standardized mortality ratio of 0.57). However, by the ninth death that had occurred (at 124 days), the standardized mortality ratio reached 0.50 (95% CI, 0.26-0.97), and the reduction in observed-vs-expected survival became statistically significant. By 1 year, the standardized mortality ratio had decreased to 0.39 (95% CI, 0.24-0.65). Among patients with chronic HCV infection and decompensated cirrhosis, DAA use was associated with a decrease of approximately 60% in the observed-vs-expected mortality rate within the first year of treatment.

substudy, in which they could receive 12 weeks of open-label treatment with sofosbuvir/velpatasvir/voxilaprevir.

A total of 147 patients were enrolled into the substudy, and all completed deferred treatment. In these patients, the mean age was 59 years (range, 29-80 years), 79% were male, and 82% were white. One-third (33%) had cirrhosis. Most patients had HCV genotype 1a (77%) or 1b (20%), and 4 patients had a different HCV genotype. Approximately half of patients (52%) had prior treatment experience with NS5A and NS5B inhibitors; 41% had prior treatment experience with NS5A and NS3 inhibitors (with or without an NS5B inhibitor). At baseline, 41% of patients showed an NS5A-only polymorphism, 41% had both NS3 and NS5A polymorphisms, and 7% had an NS3-only polymorphism. No polymorphisms at baseline were reported in 10% of patients.

The SVR12 rate was 97%. High SVR12 rates were achieved regardless of the HCV genotype. SVR12 rates were 97% in patients with HCV genotype 1 overall, 95% in those with HCV genotype 1a, and 100% in those with HCV genotype 1b. Additionally, SVR12 rates were high regardless of the patient's prior DAA regimen. SVR12 was 96% in patients with prior exposure to NS5A plus NS5B inhibitors, and 98% in patients with prior exposure to NS5A plus NS3, with or without NS5B inhibitors (Figure 5). SVR12 rates were not affected by baseline polymorphisms; they were 100% in patients with no resistance-associated substitutions vs 97% in patients with any. Among 4 patients who showed virologic failure, 2 had developed treatment-emergent resistance mutations.

An adverse event occurred in 76% of patients. The most common adverse events were fatigue (21%), headache (20%), diarrhea (19%), and nausea (14%). Grade 3 or 4 adverse events occurred in 5% of patients. No patients discontinued treatment because of an adverse event.

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Adherence to Pangenotypic Glecaprevir/Pibrentasvir Treatment and SVR12 in HCV-Infected Patients: An Integrated Analysis of the Phase 2/3 Clinical Trial Program

Dr Ashley Brown and colleagues presented data from an integrated analysis of glecaprevir/pibrentasvir.[1] This analysis examined the factors associated with nonadherence to glecaprevir/pibrentasvir, and their impact on SVR12 rates. Previous studies of anti-HCV regimens suggested that adherence to DAA regimens was good overall. There is an association between lower treatment adherence and reduced SVR rates.[2] Therefore, this analysis aimed to assess the factors associated with nonadherence to glecaprevir/pibrentasvir.

Data from 2091 patients were pooled from 8 phase 3 clinical trials (ENDURANCE-1, ENDURANCE-2, ENDURANCE-3, ENDURANCE-4, EXPEDITION-1, EXPEDITION-4, SURVEYOR-II, and MAGELLAN-1). All patients were treated with glecaprevir/pibrentasvir. The treatment durations were 8 weeks (n=711), 12 weeks (n=1264), and 18 weeks (n=116). Patients had chronic HCV infection with genotype 1 to 6, either with or without compensated cirrhosis. (Patients with decompensated cirrhosis were excluded.) Patients with HIV-1 coinfection were permitted to enroll in the study, but patients with hepatitis B coinfection were excluded. Both treatment-naive and treatment-experienced patients were enrolled. Previously treated patients had prior exposure to interferon or pegylated interferon with or without ribavirin, or to sofosbuvir plus ribavirin with or without pegylated interferon. Prior treatment experience with protease inhibitors and/or NS5A inhibitors was allowed for patients enrolled in the MAGELLAN-1 study.

The primary study endpoint was SVR12 assessed in the intent-to-treat population. Other efficacy endpoints included SVR12 in the modified intent-to-treat population (this group excluded cases of non-virologic failures). A multivariable logistic regression model was used to assess the interaction of nonadherence with treatment outcome, controlling for baseline demographic and clinical characteristics. Adherence was measured via pill count. Adherent patients were those who took between 80% to 120% of the assigned pills given at each treatment visit. Accordingly, non-adherent patients were those who took less than 80%, or more than 120%, of the assigned pills in at least 1 of the study visits.

Overall, 89% of patients (1851 of 2091) were adherent to glecaprevir/

Table 1. Multivariable Logistic Regression for Prediction of Nonadherence to Treatment With Glecaprevir/Pibrentasvir in Patients With HCV

Characteristic	Odds Ratio	95% CI	*P* Value
Alcohol use: drinker vs nondrinker	2.0	1.3-3.0	.002
Alcohol use: ex-drinker vs nondrinker	1.9	1.2-2.9	.005
Compensated cirrhosis	1.6	1.1-2.3	.026
HCV genotype 3 vs genotype 1	2.2	1.5-3.0	<.001
Severe renal impairment	2.8	1.6-5.0	<.001
Tobacco use	1.5	1.0-2.2	.037

HCV, hepatitis C virus.

Adapted from Brown AS et al. AASLD abstract 198. *Hepatology*. 2017;66(suppl 1).[1]

ABSTRACT SUMMARY Impact of Hepatitis C Treatment With Glecaprevir + Pibrentasvir on Patient's Health Related Quality of Life: Results From Phase 3 CERTAIN Trials

Dr Hiromitsu Kumada and colleagues (Abstract 1187) reported from a study that assessed the impact of treatment with glecaprevir/pibrentasvir on patient-reported function and quality of life. Data were pooled from 2 Japanese clinical studies (CERTAIN I and CERTAIN II), in which patients received glecaprevir/pibrentasvir for either 8 weeks or 12 weeks. The study authors concluded that treatment with glecaprevir/pibrentasvir for either duration resulted in no worsening or improvement in patient-reported health-related quality of life. For both the 8-week and 12-week treatment groups, all glecaprevir/pibrentasvir-treated patients experienced statistically significant improvements in health-related quality of life compared with baseline. The authors also found that these patient-reported outcomes did not seem to be affected by a patient's treatment history, as both treatment-naive and treatment-experienced patients showed statistically significant improvements in health-related quality of life.

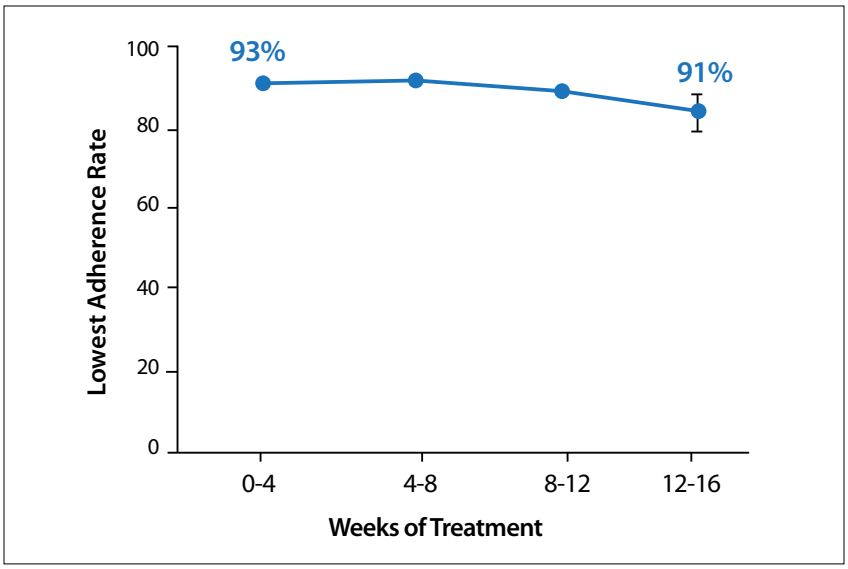

Figure 6. Treatment duration as a factor of nonadherence among patients treated with glecaprevir/pibrentasvir. Adapted from Brown AS et al. AASLD Liver Meeting abstract 198. *Hepatology*. 2017;66(suppl 1).[1]

ABSTRACT SUMMARY Sofosbuvir/Velpatasvir for 12 Weeks in Genotype 1-4 HCV-Infected Liver Transplant Recipients

Dr Kosh Agarwal and coworkers reported outcomes from a study that evaluated the safety and efficacy of sofosbuvir/velpatasvir among 79 liver transplant recipients with recurrent chronic HCV genotype 1 to 6 infection (Abstract 1069). Overall, the SVR12 rate was 96%. SVR12 rates were 95% in genotype 1, 93% in genotype 1a, 96% in genotype 1b, 100% in genotype 2, 97% in genotype 3, and 100% in genotype 4. High SVR12 rates were achieved regardless of the presence of cirrhosis and prior history of treatment failure. Two patients with baseline resistance-associated substitutions in NS5A failed to achieve SVR12. However, 4 patients who had a Y93 mutation at baseline all went on to achieve SVR12. Based on these data, the investigators concluded that a 12-week regimen of sofosbuvir/velpatasvir was highly effective for achieving SVR12 in liver transplant recipients. Furthermore, the regimen appeared to be well-tolerated, although 23% of patients required adjustments to their immunosuppression regimen (primarily owing to local institutional guidelines).

pibrentasvir at all consecutive treatment intervals. Nonadherence to treatment was reported in 240 patients. Nearly all of these patients (98%) were considered nonadherent because they took less than 80% of the assigned pill count.

Baseline characteristics did not markedly differ between the adherent vs nonadherent groups. In the adherent population, 54% were male and 79% were white. The median age was 54 years (range, 19-84 years). In the nonadherent population, 66% were male and 82% were white. The median age was 53 years (range, 20-88 years). All 6 HCV genotypes were represented in both the adherent and nonadherent groups. In the adherent group, 47% of patients had genotype 1, 19% had genotype 2, 23% had genotype 3, 8% had genotype 4, 1% had genotype 5, and 2% had genotype 6. In the nonadherent group, these rates were 33%, 12%, 44%, 8%, 2%, and 3%, respectively. Most patients were treatment-naive (68% in the adherent group and 72% in the nonadherent group). Approximately three-quarters of patients had fibrosis stage F0 to F2 (77% in the adherent group and 71% in the nonadherent group). Fibrosis stage F3 was reported in 10% of the adherent group and 9% of the nonadherent group.

More patients in the nonadherent group than in the adherent group had compensated cirrhosis (20% vs 13%, respectively), had severe renal impairment or end-stage renal disease (9% vs 4%), or were on opiate substitution therapy (13% vs 6%).

Polypharmacy was reported in 38% of the nonadherent group and 31% of the adherent group. Tobacco use was more common in the nonadherent group vs the adherent group (50% vs 35%). Similar trends were also apparent for current alcohol drinkers (38% vs 32%) and former alcohol drinkers (44% vs 32%). In the nonadherent group, 18% of patients were nondrinkers vs 35% in the adherent group. Among patients in the adherent group, the duration of treatment was 8 weeks in 34%, 12 weeks in 61%, and 16 weeks in 5%. These rates were 34%, 56%, and 10% in the nonadherent group.

Adherence was found to be high at all treatment intervals. It was slightly lower during weeks 0 to 4 (93%) and weeks 12 to 16 (91%; Figure 6). Among 23 independent variables assessed using the multivariable logistic regression model, 6 were significantly associated with nonadherence: alcohol use in drinkers vs nondrinkers (odds ratio [OR], 2.0; 95% CI, 1.3-3.0; P=.002), alcohol use in former drinkers vs nondrinkers (OR, 1.9; 95% CI, 1.2-2.9; P=.005), compensated cirrhosis (OR, 1.6; 95% CI, 1.1-2.3; P=.026), HCV genotype 3 vs genotype 1 (OR, 2.2; 95% CI, 1.5-3.0; P<.001), severe renal impairment (OR, 2.8; 95% CI, 1.6-5.0; P<.001),

ABSTRACT SUMMARY Analysis of SVR12 Efficacy Data for Grazoprevir/Elbasvir

Two studies reported on the efficacy of treatment with grazoprevir/elbasvir. Interim results from the STREAGER study, reported by Dr Armand Abergel and colleagues, showed an SVR12 rate of 98% in treatment-naive patients infected with HCV genotype 1b (Abstract LB-5). The second, an analysis from the Veterans Affairs System reported by Dr Jennifer Kramer and coworkers, evaluated the real-world effectiveness and use of grazoprevir/elbasvir for the treatment of patients with chronic HCV infection and chronic kidney disease (Abstract 1113). In this analysis, grazoprevir/elbasvir was associated with high SVR12 rates both overall (96.3%) and in patients with stage 3 (97.1%) or stages 4 to 5 (95.6%) chronic kidney disease. Additionally, SVR12 rates remained high across multiple patient subgroups regardless of chronic kidney disease stage, including across HCV genotype 1, 1a, 1b, and 4, age (≤65 vs >65 years), race, prior treatment exposure, and degree of cirrhosis (compensated vs decompensated).

and tobacco use (OR, 1.5; 95% CI, 1.0-2.2; *P*=.037; Table 1).

Adherence had no significant impact on SVR12 rates. Adherence rates as low as 50% still correlated with at least a 90% chance of achieving SVR12. In the intent-to-treat population, 98% of patients in the adherent group and 95% of patients in the nonadherent group achieved SVR12. In the modified intent-to-treat population, the SVR12 rate was 99% regardless of whether patients were in the adherent or nonadherent group.

The adverse event profile was similar in patients who were adherent vs nonadherent (overall adverse events reported: 66% vs 73%, respectively). An adverse event leading to discontinuation of treatment was slightly more common in the nonadherent group (2%) vs the adherent group (0.4%).

The study authors concluded that in this integrated analysis of HCV-infected patients treated with the glecaprevir/pibrentasvir regimen for 8, 12, or 16 weeks, overall adherence was high. Importantly, nonadherence did not correlate with lower SVR12 rates, and patients retained an excellent chance (>90%) of achieving SVR12 even with 50% adherence to their prescribed regimen. The investigators noted that these data provide further support for the high SVR rates, regardless of patient characteristics, observed in clinical studies of glecaprevir/pibrentasvir.

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The C-BREEZE 1 and 2 Studies: Efficacy and Safety of Ruzasvir Plus Uprifosbuvir for 12 Weeks in Adults With Chronic Hepatitis C Virus Genotype 1, 2, 3, 4, or 6 Infection

Dr Eric Lawitz and coworkers reported on data from the C-BREEZE 1 and 2 studies, which evaluated a 2-drug combination of ruzasvir plus uprifosbuvir.[1,2] Ruzasvir is a pangenotypic NS5A inhibitor that has shown in vitro activity against resistance-associated substitutions selected by other first-generation NS5A inhibitors. Uprifosbuvir is a pangenotypic NS5B inhibitor shown to have a high barrier to resistance in in vitro studies.

The phase 2 C-BREEZE 1 trial found that uprifosbuvir (450 mg) coadministered with a lower dose of ruzasvir (60 mg) had suboptimal efficacy in patients infected with HCV genotype 3.[1] This 12-week, open-label, single-arm study enrolled 160 patients infected with genotype 1 to 6. SVR12 rates were highest in patients with genotype 1, 2, and 4, and efficacy was lowest in patients with genotype 3 and 1a. Prior treatment history did not seem to impact the efficacy of the 2-drug combination. Baseline mutation status, particularly Y93, may have affected the efficacy rate.

The aim of C-BREEZE 2 was to assess the efficacy and safety of uprifosbuvir (450 mg) coadministered with a higher dose of ruzasvir (180 mg).[2] C-BREEZE 2 was an open-label, single-arm study with 2 cohorts of patients. The initial cohort consisted of 50 patients who began treatment. After safety was confirmed, a second cohort of 200 patients was enrolled. In both cohorts, treatment was administered for 12 weeks, after which patients underwent a 24-week follow-up period.

The study enrolled patients with HCV genotype 1 to 6. They could be treatment-naive or treatment-

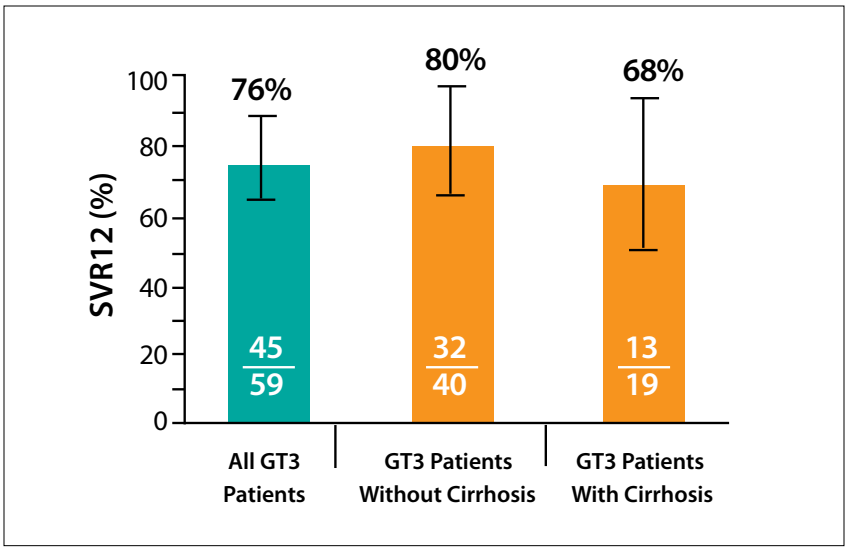

Figure 7. Rates of SVR12 among patients with GT3 treated with ruzasvir and uprifosbuvir. GT3, genotype 3; SVR12, sustained virologic response at week 12. Adapted from Lawitz E et al. AASLD Liver Meeting abstract 61. *Hepatology*. 2017;66(suppl 1).[2]

ABSTRACT SUMMARY Safety and Efficacy of Glecaprevir/Pibrentasvir in Patients Aged 65 Years or Older With Chronic Hepatitis C: A Pooled Analysis of Phase 2 and 3 Clinical Trials

Dr Graham Foster and colleagues presented data that demonstrated the safety and efficacy of glecaprevir/pibrentasvir in elderly patients (≥65 years) with chronic HCV (Abstract 1188). Among 328 older patients pooled from several phase 2 and 3 studies, glecaprevir/pibrentasvir was found to be effective, with an overall SVR12 rate of 97.9%. Among 7 elderly patients who did not achieve SVR12, 3 discontinued treatment and 2 had on-treatment virologic failure. (SVR12 data were missing for 2 patients.) SVR12 rates were comparable and were not significantly affected by HCV genotype, fibrosis stage, or duration of glecaprevir/pibrentasvir treatment. Overall, 64% of this elderly population experienced an adverse event, most commonly headache and fatigue. Serious adverse events, which were more common in patients with renal impairment, were only rarely associated with glecaprevir/pibrentasvir. Laboratory abnormalities were infrequent in this elderly population. Thus, the study authors concluded that glecaprevir/pibrentasvir was safe and effective in elderly patients with chronic HCV infection, and achieved similar SVR12 rates and safety outcomes as has been observed in the nonelderly patient population.

experienced. However, the only prior treatment could be interferon; patients with prior DAA exposure were not eligible. Other key eligibility criteria included HCV monoinfection or HIV-1 coinfection. (Hepatitis B coinfection was not allowed.) The HCV RNA viral load was at least 10,000 IU/L. Patients with or without compensated cirrhosis were enrolled, but decompensated liver disease or evidence of HCC was exclusionary. Patients with significant laboratory abnormalities (eg, low platelet levels or a low estimated glomerular filtration rate) were also excluded from the study.

Most patients were male (55%) and white (78%). The mean patient age was 49.5 years. A total of 21% of patients had cirrhosis, and 56% of patients had a baseline viral HCV load exceeding 2,000,000 IU/mL. A small number of patients (16%) had received previous treatment with interferon. All HCV genotypes were represented; 17% of patients had genotype 1a, 11% had genotype 1b, 17% had genotype 2, 22% had genotype 3, 21% had genotype 4, 6% had genotype 5, and 8% had genotype 6.

The primary study endpoint was SVR12. It was assessed in both the full analysis set (all patients who received a minimum of 1 dose of the study drug) and in the modified full analysis set (which excluded patients with nonvirologic failures). The SVR12 rate in the full analysis set reached 90%. This rate improved to 92% in the modified full analysis set. The SVR12 rate was relatively similar across most HCV genotypes, with the exception of genotype 3, in which the SVR12 decreased to 76% in the modified full analysis set (Figure 7). The SVR12 rates (in the modified full analysis set) across the remainder of the HCV genotypes were 91% in genotype 6, 93% in genotype 1a, 96% in genotype 2, and 100% in genotype 1b, 4, and 5.

In the group of patients with genotype 3 infection, the SVR12 rate (in the modified full analysis set) was affected by the presence of cirrhosis (80% in patients without cirrhosis vs 68% in patients with cirrhosis). Additionally, among the genotype 3 patients, the combination treatment showed lower efficacy in those who had resistance-associated substitutions at baseline. SVR12 was 86% among patients without mutations vs 74% in patients with a mutation at any of the 7 analyzed positions. This observation held true when the SVR12 rate was assessed at each particular mutation site, such as A30 (SVR12 of 79% vs 57% in patients without vs with a mutation), S62 (SVR12 of 82% vs 69% in patients without vs with a mutation), and Y93 (SVR12 of 80% vs 40% in patients without vs with a mutation).

ABSTRACT SUMMARY HCV Reinfection in At-Risk Populations

Two studies investigated the rates of HCV reinfection in at-risk populations. Dr Diana Sylvestre and colleagues found that there was no evidence of reinfection 1 year after treating HCV among individuals enrolled in a methadone program (Abstract LB-18). In fact, these data showed that effective opiate treatment appeared to lower the risk of reinfection. Dr David Wyles and colleagues found similar rates of HCV recurrence in HCV/HIV and HCV monoinfected patients who had achieved SVR with DAA treatment (Abstract 978). In 287.5 person-years of follow-up for the HCV/HIV group, 1 recurrence was reported (incidence rate of 0.35 per 100 person-years; 95% CI, 0.01-1.94). In 190.6 person-years of follow-up for the HCV monoinfected group, 1 recurrence was also reported (incidence rate of 0.52 per 100 person-years; 95% CI, 0.01-2.92).

Accordingly, a total of 19 patients showed virologic failure; 14 of these had HCV genotype 3 and the rest had genotype 1 (n=3), genotype 2 (n=1), or genotype 6 (n=1). Among the 14 patients with HCV genotype 3, all the virologic failures were caused by relapsed disease. Of these, 8 occurred in patients without cirrhosis and 6 occurred in patients with cirrhosis. Among the 3 patients with HCV genotype 1, all treatment failures were caused by relapse as well. Notably, 2 of these relapses occurred in patients with a mutation at Y93. In contrast, neither cirrhosis nor baseline mutation status impacted efficacy in patients with HCV genotype 1b, 2, 4, 5, or 6.

An adverse event occurred in 61% of patients. In 33.3% of patients, the adverse events were deemed related to the study treatment. The most common adverse events related to study treatment were fatigue (7.8%) and headache (7.4%). Two patients discontinued the study treatment owing to adverse events. Serious adverse events were reported in 2.5% of patients.

The C-BREEZE 2 study investigators concluded that uprifosbuvir at 450 mg coadministered with a higher dose of ruzasvir, 180 mg, remained suboptimal as a pangenotypic regimen. This conclusion was supported by the low SVR12 rate reported in patients infected with HCV genotype 3, several of whom showed virologic relapse.

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100% SVR With 8 Weeks of Ledipasvir/Sofosbuvir in HIV-Infected Men With Acute HCV Infection: Results From the SWIFT-C Trial (Sofosbuvir-Containing Regimens Without Interferon for Treatment of Acute HCV in HIV-1–Infected Individuals)

A shortened duration of treatment with ledipasvir/sofosbuvir was evaluated in the SWIFT-C trials.[1] Ledipasvir/sofosbuvir is FDA-approved as a once-daily fixed-dose combination regimen indicated for the treatment of adult patients with chronic HCV infection in several settings: for patients with genotype 1, 4, 5, or 6 without cirrhosis or with compensated cirrhosis; those with genotype 1 with decompensated cirrhosis (in combination with ribavirin); and those with genotype 1 or 4 who are liver transplant recipients without cirrhosis or with compensated cirrhosis (in combination with ribavirin).[2]

Historically, early identification and treatment during the acute phase of HCV infection has been shown to result in higher response rates with a shortened course of pegylated interferon-based antiviral therapies. Guidelines from the European Association for the Study of the Liver (EASL) recommend 8 weeks of DAA therapy for acute-phase HCV infection, with certain caveats (including no coinfection with HIV-1 and a baseline HCV RNA level <1 million IU/mL).[3]

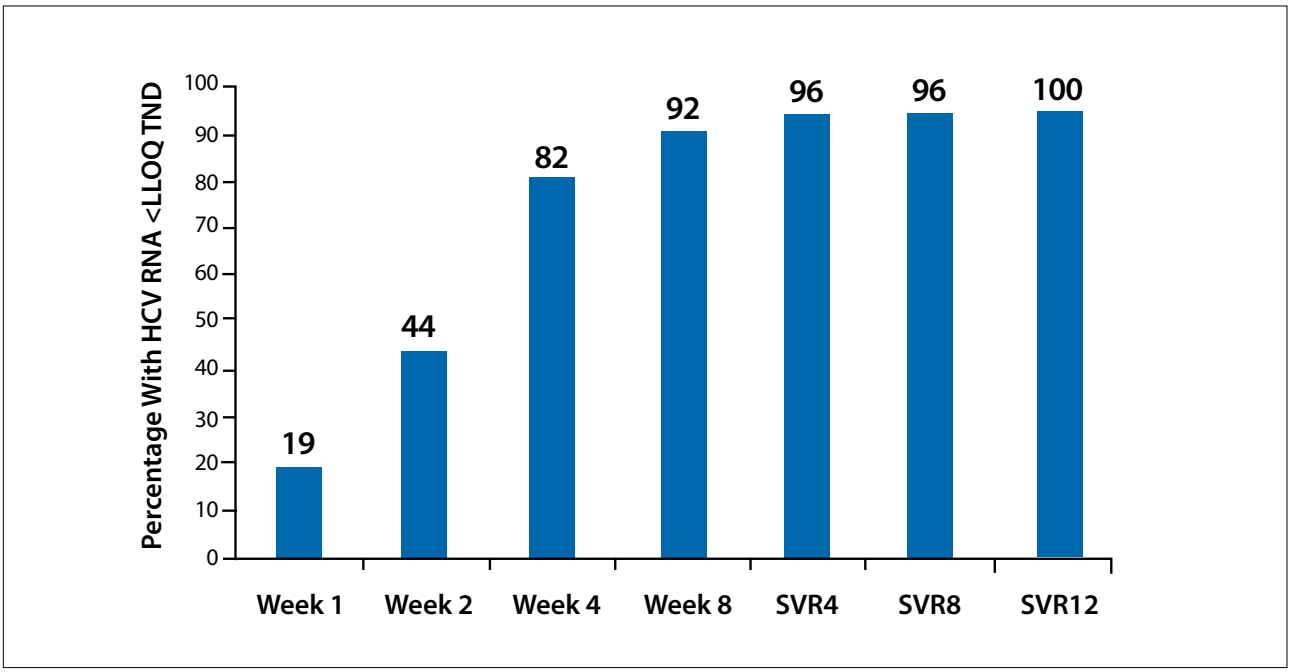

Figure 8. Rates of SVR among men with HIV and acute HCV infection treated with ledipasvir/sofosbuvir. HCV, hepatitis C virus; LLOQ, lower limit of quantitation; SVR, sustained virologic response; TND, target not detectable. Adapted from Naggie S et al. AASLD Liver Meeting abstract 196. *Hepatology*. 2017;66(suppl 1).[1]

Ledipasvir/sofosbuvir is approved for a 12-week treatment duration, but there is potential that a shorter duration regimen may be used in certain cases. Two studies have examined a 6-week regimen of ledipasvir/sofosbuvir for the treatment of patients in the acute phase of HCV infection. The HepNet Acute HCV IV study included 20 patients, of whom 55% had genotype 1a and 45% had genotype 1b. Coinfection with hepatitis B or HIV-1 was not allowed. The acute phase was defined as 4 months. The median HCV viral load in these patients was 4 $\log_{10}$ IU/mL, and 60% had the *IL28B* CC genotype. In this study, the SVR12 rate was 100%.[4] The HIV/HCV cohort study included 26 patients, all of whom were coinfected with HIV-1; 69% had HCV genotype 1a and 31% had genotype 4. The acute phase was defined as 6 months. The mean viral load was 5.4 $\log_{10}$ IU/mL, and 46% had the *IL28B* CC genotype. In this study, the SVR12 rate was 77%.[5]

SWIFT-C is a single-arm, multicenter trial investigating the use of shortened, interferon-sparing regimens to treat acute HCV infection. The patients described here (n=27) were treated with a shortened 8-week ledipasvir/sofosbuvir regimen and evaluated for the potential to achieve noninferior SVR12 rates and an improved safety profile vs the standard of care (as assessed by historical control) for the treatment of acute HCV in patients

ABSTRACT SUMMARY Efficacy and Safety of Sofosbuvir/Velpatasvir Plus Ribavirin for 12 or 24 Weeks in Genotype 1 or 2 HCV-Infected Japanese Patients With Prior Treatment Failure to DAA-Based Regimens

Dr Namiki Izumi and colleagues presented data from a phase 3 study in treatment-experienced Japanese patients with chronic HCV genotype 1 or 2 infection who were treated with sofosbuvir/velpatasvir plus ribavirin for 12 or 24 weeks (Abstract 194). This combination led to SVR12 rates of 82% in patients treated with 12 weeks and 97% in patients treated for 24 weeks. Although resistance-associated substitutions in NS5A were common at baseline, they did not significantly impact treatment outcomes. Additionally, no resistance-associated substitutions were found to be treatment-emergent in patients with virologic relapse. Cirrhosis status also did not affect the SVR12 rates achieved with either 12 or 24 weeks of treatment. The sofosbuvir/velpatasvir plus ribavirin regimen was well-tolerated; the most commonly reported adverse events were viral upper respiratory infection, anemia, and headache. Few patients discontinued treatment owing to adverse events. The study investigators concluded that the 24-week duration was associated with the best outcomes and provided an effective salvage regimen for this patient population.

with HCV/HIV coinfection. Acute HCV was defined as the first 24 weeks of HCV infection after diagnosis.

Key eligibility criteria included HIV-1 coinfection (hepatitis B coinfection was not permitted), infection with HCV genotype 1 or 4, and study enrollment between 12 and 24 weeks from the first laboratory evidence of HCV infection. The primary endpoint was SVR12.

All 27 patients were male, and 67% were white. Their median age was 46 years (range, 38-50 years). All but 1 patient (96%) had genotype 1 HCV infection, and the median HCV RNA level was 6.17 $\log_{10}$ IU/mL. Just over half (59%) had the *IL28B* CC genotype. At screening, all patients were receiving HIV-directed therapy, including boosted protease inhibitors (26%), non-nucleoside reverse transcription inhibitors (30%), integrase inhibitors (52%), and nucleoside reverse transcription inhibitors (100%).

All patients achieved an SVR12 (100%). This 100% SVR12 rate was superior to the control rate of 60%, which was drawn from historical studies of interferon-based regimens. The level of viral load at baseline was associated with the time it took to achieve an undetectable HCV RNA level; the higher the viral load, the longer it took to achieve undetectable levels (Figure 8). Ledipasvir/sofosbuvir was well-tolerated, with no treatment-related serious adverse events.

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Highlights in Hepatitis C Virus From the 2017 AASLD Liver Meeting: Commentary

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Presentations at the American Association for the Study of Liver Diseases (AASLD) 2017 Liver Meeting provided new insight into the optimal management of patients with hepatitis C virus. Data were presented for regimens such as glecaprevir/pibrentasvir; the triplet combination of AL-335, odalasvir, and simeprevir; ruzasvir plus uprifosbuvir; and sofosbuvir/velpatasvir/voxilaprevir. An analysis also evaluated the risk of hepatocellular carcinoma among patients treated with direct-acting antiviral (DAA) agents.

Glecaprevir/Pibrentasvir

Dr Steven Flamm presented data from an integrated analysis of glecaprevir/pibrentasvir in treatment-naive patients with hepatitis C virus (HCV) genotype 3, with or without cirrhosis.[1] The analysis showed that 8 weeks was as effective as 12 weeks in treatment-naive, genotype 3 patients without cirrhosis. The modified intent-to-treat analysis showed rates of sustained virologic response at 12 weeks (SVR12) of 98% in patients without cirrhosis treated for 8 weeks, 99% in patients without cirrhosis treated for 12 weeks, and 100% in patients with cirrhosis treated for 12 weeks. The one potential caveat may be that patients with baseline A30K variants had a lower SVR12 rate at 8 weeks (84%) compared with 12 weeks (94%). However, the number of patients in these subsets was small. Larger, real-world data sets will be needed to validate these data.

A study from Dr Edward Gane and colleagues evaluated glecaprevir/pibrentasvir in patients with cirrhosis, across all genotypes.[2] Patients were treatment-naive or had received treatment with interferon or pegylated interferon, with or without ribavirin; or with sofosbuvir plus ribavirin, with or without pegylated interferon. Treatment was administered for 12 weeks. The overall SVR12 rate was 96%, with the lowest SVR12, 94%, reported in patients with genotype 1. This study hints that 12 weeks, and not 8 weeks, is most likely the appropriate duration of glecaprevir/pibrentasvir for patients with cirrhosis. An 8-week regimen of glecaprevir/pibrentasvir in cirrhotic patients will have to be prospectively assessed to determine if all patients need 12 weeks of therapy.

AL-335, Odalasvir, and Simeprevir

The OMEGA-1 trial evaluated the nucleotide analogue AL-335, odalasvir, and simeprevir given for 6 or 8 weeks.[3] The study showed excellent results with both durations, yielding SVR12 rates of 99% and 98%, respectively. Patients with genotype 2C had SVR12 rates of only 75% with 8 weeks of treatment and 83% with 6 weeks, indicating a chink in the armor of this regimen. SVR12 rates were particularly low among patients who had baseline F28C resistance-associated substitutions and simeprevir resistance-associated substitutions. Unfortunately, this triplet combination will not undergo further assessment. However, a proof-of-concept finding is that 6 weeks of treatment worked for most patients, at least those with minimal fibrosis.

Ruzasvir and Uprifosbuvir

The C-BREEZE studies evaluated ruzasvir and uprifosbuvir given for 12 weeks in patients with genotype 1 to 6. Dr Eric Lawitz presented data for the modified full analysis set.[4,5] The regimen did well in patients with genotype 1, 2, and 4, but it faltered in patients with genotype 3. Rates of SVR12 were 100% in patients with genotype 1b, 4, or 5; 96% in genotype 2; 93% in genotype 1a; 91% in genotype 6; and 76% in genotype 3. This 2-drug combination will not be competitive in today's market, where there are several effective pangenotypic regimens.

Salvage Therapy

Dr Marc Bourlière and colleagues analyzed data from the deferred treatment group of the POLARIS-1 study, which

assessed the regimen of sofosbuvir/velpatasvir/voxilaprevir in patients with HCV genotype 1 to 6 who had received previous treatment with a nonstructural protein 5A (NS5A) inhibitor.[6] The new analysis included patients who had received placebo during the initial study. These patients were treated with sofosbuvir/velpatasvir/voxilaprevir for 12 weeks. Overall SVR12 rates ranged from 96% to 100% across all genotypes. The presence of baseline resistance-associated substitutions had no impact. Sofosbuvir/velpatasvir/voxilaprevir is the salvage regimen of choice for patients who need further treatment after DAA therapy, and it does not require testing of baseline-resistance. In the United States, this regimen is currently approved as a salvage therapy for patients who require treatment after failing a DAA regimen. Interestingly, the European Union indication allows this regimen to be used as first-line therapy.

Previous data have shown the efficacy of glecaprevir/pibrentasvir in patients with HCV genotype 1 infection. The phase 2 MAGELLAN-1 trial evaluated a 12-week regimen in patients with genotype 1 without cirrhosis, who required retreatment after failing a DAA regimen.[7] An SVR12 was reported in 100% of patients treated with 200-mg glecaprevir plus 80-mg pibrentasvir, 95% of patients treated with 300-mg glecaprevir plus 120-mg pibrentasvir with 800-mg once-daily ribavirin, and 86% of patients treated with 300-mg glecaprevir plus 120-mg pibrentasvir without ribavirin.

Risk of Hepatocellular Carcinoma

Dr George Ioannou and coworkers analyzed data from the National Veterans Affairs Healthcare System for more than 62,000 patients with HCV, with or without cirrhosis, who were treated with interferon-based and DAA-based therapies.[8] The analysis evaluated the incidence of de novo cases of hepatocellular carcinoma. Importantly, there was no signal that DAA therapy led to a higher rate of de novo hepatocellular carcinoma compared with interferon-based therapies. In fact, an SVR with DAA therapy led to a 71% reduction in overall HCC risk. This analysis suggests that clinicians should treat patients with cirrhosis, and continue to check them for liver cancer every 6 months with imaging and measurement of the serum marker alpha-fetoprotein (AFP). Although the risk of liver cancer decreases in these patients, it does not reach zero, and indefinite surveillance for hepatocellular carcinoma is recommended.

Disclosure

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