GASTROENTEROLOGY & HEPATOLOGY
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A SPECIAL MEETING REVIEW EDITION

Highlights in the Treatment of Hepatitis C Virus From the 2016 AASLD Liver Meeting

A Review of Selected Presentations From the 2016 AASLD Liver Meeting • November 11-15, 2016 • Boston, Massachusetts

Special Reporting on:

- A Randomized Phase 3 Trial of Sofosbuvir/Velpatasvir/Voxilaprevir for 8 Weeks and Sofosbuvir/Velpatasvir for 12 Weeks for Patients With Genotype 3 HCV Infection and Cirrhosis: The POLARIS-3 Study
- SURVEYOR-II, Part 3: Efficacy and Safety of ABT-493/ABT-530 in Patients With Hepatitis C Virus Genotype 3 Infection With Prior Treatment Experience and/or Cirrhosis
- Sofosbuvir/Velpatasvir/Voxilaprevir for 12 Weeks as a Salvage Regimen in NS5A Inhibitor-Experienced Patients With Genotype 1-6 Infection: The Phase 3 POLARIS-1 Study
- The Fixed-Dose Combination Regimen of MK-3682/Grazoprevir/MK-8408 With or Without Ribavirin: Results From Parts B and C of C-CREST 1 & 2
- A Randomized, Controlled, Phase 3 Trial of Sofosbuvir/Velpatasvir/Voxilaprevir or Sofosbuvir/Velpatasvir for 12 Weeks in Direct Acting Antiviral Experienced Patients With Genotype 1-6 HCV Infection: The POLARIS-4 Study
- C-ISLE: Grazoprevir/Elbasvir Plus Sofosbuvir in Treatment-Naive and Treatment-Experienced HCV GT3 Cirrhotic Patients Treated for 8, 12 or 16 Weeks
- Eight Weeks Treatment Duration With Ledipasvir/Sofosbuvir (LDV/SOF) Is Effective for Appropriately Selected Patients With Genotype 1 Hepatitis C Virus (HCV) Infection: An Analysis of Multiple Real World Cohorts Totaling >6,500 Patients

PLUS Meeting Abstract Summaries

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GASTROENTEROLOGY & HEPATOLOGY
The Independent Peer-Reviewed Journal

Table of Contents

A CURE FOR **EVERY TYPE**

Patients of **any HCV genotype** can now be cured with a sofosbuvir-based, once-daily single-tablet regimen[1,2]

HARVONI is the #1 prescribed treatment for HCV GT 1 patients in the US[3,4,a]

NOW APPROVED EPCLUSA is the first and only pan-genotypic single-tablet regimen for patients with chronic HCV[2]

- **94%-99%** overall cure (SVR12) rates in **GT 1** subjects with HARVONI (ION-1, -2, -3)[1]
- **99%** and **95%** overall cure rates in **GT 2** and **GT 3** subjects, respectively, with EPCLUSA (ASTRAL-2, -3)[2]

INDICATIONS

HARVONI is indicated with or without ribavirin for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype **(GT) 1, 4, 5, or 6** infection.

EPCLUSA is indicated for the treatment of adult patients with chronic HCV **GT 1, 2, 3, 4, 5, or 6** infection without cirrhosis or with compensated cirrhosis and in combination with ribavirin for those with decompensated cirrhosis.

Study Designs[1,2]

The **HARVONI** clinical trial program evaluated the efficacy and safety of 8 or 12 weeks of HARVONI ± RBV in HCV GT 1 TN subjects without cirrhosis (ION-3; N=647) and 12 or 24 weeks of HARVONI ± RBV in GT 1 TN (ION-1; N=865) and GT 1 TE (ION-2; N=440) subjects with or without cirrhosis.

The **EPCLUSA** clinical trial program (ASTRAL-1, -2, -3; N=1558) evaluated the efficacy and safety of 12 weeks of EPCLUSA in TN and TE HCV GT 1-6 subjects with or without cirrhosis.

See full study information on following pages.

Cure = sustained virologic response (SVR). SVR12 was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the end of treatment in the HARVONI ION clinical trials and <15 IU/mL in the EPCLUSA ASTRAL clinical trials.[1,2,5]

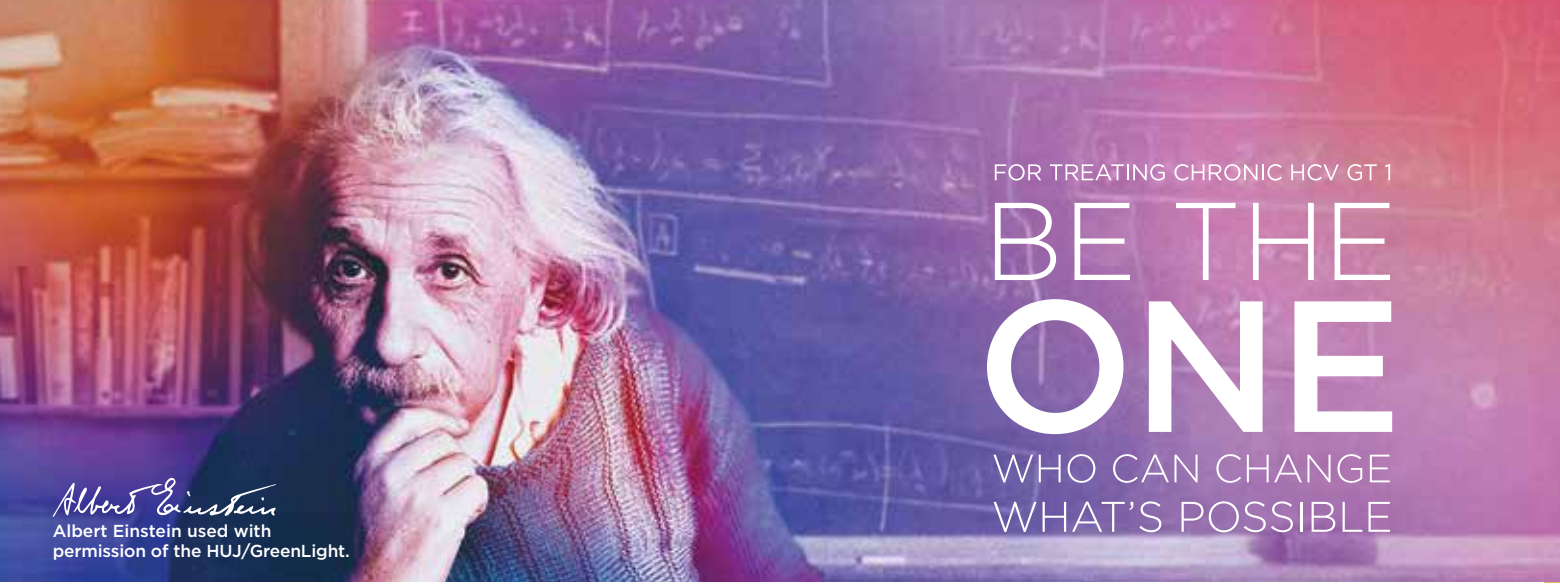
Cirrhosis = compensated cirrhosis (Child-Pugh A), RBV = ribavirin, TE = treatment-experienced (patients who have failed a peginterferon alfa + RBV–based regimen ± an HCV protease inhibitor), TN = treatment-naïve

[a]IMS Weekly NPA™ Market Dynamics™ from week-ending 11/14/14–4/1/16.

HARVONI®
ledipasvir/sofosbuvir
90 mg/400 mg tablets

NOW APPROVED
EPCLUSA®
sofosbuvir/velpatasvir
400 mg/100 mg tablets

Please see Brief Summary of full Prescribing Information for HARVONI and EPCLUSA on the following pages.



HARVONI DELIVERED HIGH CURE (SVR12) RATES IN A BROAD RANGE OF GT 1 SUBJECTS[1]

97%

OVERALL CURE RATE ACROSS THREE HARVONI PHASE 3 TRIALS[1]
(n=1042/1079)

HARVONI IS THE ONLY HCV TREATMENT THAT OFFERS AN 8-WEEK COURSE OF THERAPY[1]

- The recommended treatment duration for HARVONI is 12 weeks for TN GT 1 patients with or without cirrhosis. Eight weeks can be considered for TN GT 1 patients without cirrhosis who have pre-treatment HCV RNA <6 million IU/mL[1]
- HARVONI is RBV-free, regardless of prior HCV treatment history, the presence of compensated cirrhosis, or GT 1a or 1b subtype[1]
- No baseline resistance testing is required with HARVONI[1]
- No hepatic or hematologic monitoring is required when HARVONI is used alone[1]
- Adverse reactions (all grades) reported in ≥5% of GT 1 subjects receiving 8, 12, or 24 weeks of treatment with HARVONI (in ION-3, ION-1, and ION-2): fatigue (13%-18%), headache (11%-17%), nausea (6%-9%), diarrhea (3%-7%), and insomnia (3%-6%)[1]

HARVONI Study Designs: randomized, open-label trials in GT 1 subjects[1]

ION-1: TN subjects (N=865) with or without cirrhosis were randomized to receive HARVONI for 12 weeks, HARVONI + RBV for 12 weeks, HARVONI for 24 weeks, or HARVONI + RBV for 24 weeks.

ION-2: TE subjects (N=440) with or without cirrhosis were randomized to receive HARVONI for 12 weeks, HARVONI + RBV for 12 weeks, HARVONI for 24 weeks, or HARVONI + RBV for 24 weeks.

ION-3: TN subjects (N=647) without cirrhosis were randomized to receive HARVONI for 8 weeks, HARVONI + RBV for 8 weeks, or HARVONI for 12 weeks.

These studies did not include subjects who were liver transplant recipients and/or with decompensated cirrhosis (Child-Pugh B or C). Sustained virologic response (SVR12) was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the cessation of treatment.[1] Achieving SVR is considered a virologic cure.[5]

Cirrhosis = compensated cirrhosis (Child-Pugh A), RBV = ribavirin, SOF = sofosbuvir, TE = treatment-experienced (patients who have failed a peginterferon alfa + RBV–based regimen with or without an HCV protease inhibitor), TN = treatment-naïve

IMPORTANT SAFETY INFORMATION FOR HARVONI AND EPCLUSA

CONTRAINDICATIONS

- If HARVONI or EPCLUSA is used in combination with ribavirin (RBV), all contraindications, warnings and precautions, in particular pregnancy avoidance, and adverse reactions to RBV also apply. Refer to RBV prescribing information.

WARNINGS AND PRECAUTIONS

- **Risk of Serious Symptomatic Bradycardia When Sofosbuvir Is Coadministered with Amiodarone and Another HCV Direct Acting Antiviral:** Amiodarone is not recommended for use with HARVONI or with EPCLUSA due to the risk of symptomatic bradycardia, particularly in patients also taking beta blockers or with underlying cardiac comorbidities and/or with advanced liver disease. In patients without alternative, viable treatment options, cardiac monitoring is recommended. Patients should seek immediate medical evaluation if they develop signs or symptoms of bradycardia.
- **Risk of Reduced Therapeutic Effect Due to Use with P-gp Inducers and/or Moderate to Potent Inducers of CYP:** Rifampin, St. John's wort and carbamazepine are not recommended for use with HARVONI or with EPCLUSA. P-gp inducers may significantly decrease ledipasvir, sofosbuvir and/or velpatasvir plasma concentrations. Moderate to potent inducers of CYP2B6, CYP2C8 or CYP3A4 may significantly decrease sofosbuvir and/or velpatasvir plasma concentrations.

HARVONI®
ledipasvir/sofosbuvir
90 mg/400 mg tablets

See what's possible at hcp.harvoni.com

NOW APPROVED

THE FIRST AND ONLY PAN-GENOTYPIC ONCE-DAILY SINGLE-TABLET REGIMEN FOR CHRONIC HCV PATIENTS[2]

EXPAND WHAT'S POSSIBLE

EPCLUSA FULFILLS A SIGNIFICANT UNMET NEED FOR GT 2 AND GT 3 PATIENTS, DELIVERING HIGH CURE (SVR12) RATES WITH A RBV-FREE SINGLE-TABLET REGIMEN[2]

99% **OF GT 2 SUBJECTS OVERALL ACHIEVED A CURE[2]**
(n=133/134; ASTRAL-2)

95% **OF GT 3 SUBJECTS OVERALL ACHIEVED A CURE[2]**
(n=264/277; ASTRAL-3)

98% OF GT 1-6 SUBJECTS OVERALL ACHIEVED A CURE ACROSS THREE PHASE 3 TRIALS[2] (n=1015/1035; ASTRAL-1, -2, -3)

- **GT 1-6 patients take 12 weeks of RBV-free EPCLUSA[2]**
- No baseline resistance testing is required with EPCLUSA[2]
- No hepatic or hematologic monitoring is required when EPCLUSA is used alone[2]
- Adverse reactions (all grades) reported in ≥5% of subjects receiving 12 weeks of treatment with EPCLUSA (ASTRAL-1): headache (22%), fatigue (15%), nausea (9%), asthenia (5%), and insomnia (5%)[2]
  - The adverse reactions observed in subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3 were consistent with those observed in ASTRAL-1. In ASTRAL-3, irritability was observed in ≥5% of subjects treated with EPCLUSA[2]

EPCLUSA Study Designs: randomized trials in TN and TE subjects without cirrhosis or with compensated cirrhosis[2]

ASTRAL-1: double-blind, placebo-controlled trial in GT 1, 2, 4, 5, or 6 subjects (N=740). GT 1, 2, 4, or 6 subjects were randomized 5:1 to receive EPCLUSA or placebo for 12 weeks; GT 5 subjects received EPCLUSA for 12 weeks. Overall SVR was 99% (n=618/624).

ASTRAL-2: open-label trial in GT 2 subjects (N=266). Subjects were randomized to receive EPCLUSA or SOF + RBV for 12 weeks.

ASTRAL-3: open-label trial in GT 3 subjects (N=552). Subjects were randomized to receive EPCLUSA for 12 weeks or SOF + RBV for 24 weeks. SVR12 for EPCLUSA ranged from 89% (TE with cirrhosis) to 98% (TN without cirrhosis).

These studies did not include subjects with decompensated cirrhosis. Sustained virologic response (SVR12) was the primary endpoint and was defined as HCV RNA <15 IU/mL at 12 weeks after the cessation of treatment.[2] Achieving SVR is considered a virologic cure.[5]

IMPORTANT SAFETY INFORMATION FOR HARVONI AND EPCLUSA

ADVERSE REACTIONS

- The most common adverse reactions (≥10%, all grades) with HARVONI were fatigue, headache, and asthenia
- The most common adverse reactions (≥10%, all grades) with EPCLUSA were headache and fatigue; and when used with RBV in decompensated cirrhotics were fatigue, anemia, nausea, headache, insomnia, and diarrhea

DRUG INTERACTIONS

- Coadministration of HARVONI or EPCLUSA is not recommended with oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, and tipranavir/ritonavir due to decreased concentrations of sofosbuvir, ledipasvir and/or velpatasvir.
- Coadministration of EPCLUSA is not recommended with proton-pump inhibitors or efavirenz due to decreased concentrations of velpatasvir; or with topotecan due to increased concentrations of topotecan.
- Coadministration of HARVONI is not recommended with co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate due to increased concentrations of tenofovir; or with simeprevir due to increased concentrations of ledipasvir and simeprevir; or with rosuvastatin due to increased concentrations of rosuvastatin.

Consult the full Prescribing Information for HARVONI or for EPCLUSA for more information on potentially significant drug interactions, including clinical comments.

NOW APPROVED

EPCLUSA®
sofosbuvir/velpatasvir
400 mg/100 mg tablets

See what's possible at hcp.epclusainfo.com

Please see Brief Summary of full Prescribing Information for HARVONI and EPCLUSA on the following pages.

HARVONI® (ledipasvir 90 mg and sofosbuvir 400 mg) tablets, for oral use

Brief Summary of full Prescribing Information. See full Prescribing Information. Rx Only.

INDICATIONS AND USAGE: HARVONI is indicated with or without ribavirin for the treatment of patients with chronic hepatitis C virus (HCV) genotype (GT) 1, 4, 5, or 6 infection.

CONTRAINDICATIONS
If HARVONI is administered with ribavirin (RBV), the contraindications to RBV also apply to this combination regimen. Refer to RBV prescribing information.

WARNINGS AND PRECAUTIONS:

Serious Symptomatic Bradycardia When Coadministered with Amiodarone: Postmarketing cases of symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention, have been reported when amiodarone is coadministered with HARVONI. Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown. Coadministration of amiodarone with HARVONI is not recommended. For patients taking amiodarone who will be coadministered HARVONI and patients taking HARVONI who need to start amiodarone, who have no other alternative, viable treatment options; and due to amiodarone's long half-life for patients discontinuing amiodarone just prior to starting HARVONI: Counsel patients about the risk of serious symptomatic bradycardia; and cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment. Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion or memory problems.

Risk of Reduced Therapeutic Effect Due to Use With P-gp Inducers: Concomitant use may significantly decrease ledipasvir and sofosbuvir concentrations and may lead to a reduced HARVONI effect. Use of HARVONI with P-gp inducers (e.g., rifampin or St. John's wort) is not recommended.

Risks Associated with RBV Combination Treatment
If HARVONI is administered with RBV, the warnings and precautions for RBV, in particular pregnancy avoidance, apply to this combination regimen. Refer to the RBV prescribing information.

Related Products Not Recommended: Use of HARVONI with products containing sofosbuvir is not recommended.

ADVERSE REACTIONS:

Most common adverse reactions (incidence greater than or equal to 10%, all grades) were fatigue, headache and asthenia.

GT 1 Subjects with Compensated Liver Disease (With and Without Cirrhosis): The safety assessment of HARVONI was based on pooled data from three randomized, open-label Phase 3 clinical trials (ION-1, ION-3 and ION-2) in subjects who received HARVONI once for 8, 12 or 24 weeks. Adverse events led to permanent treatment discontinuation in 0%, less than 1% and 1% of subjects receiving HARVONI for 8, 12 and 24 weeks, respectively. Adverse Reactions (adverse events assessed as causally related by the investigator; all grades; majority Grade 1) observed in at least 5% of subjects receiving HARVONI for 8, 12 or 24 weeks, respectively, were: fatigue (16%, 13%, 18%), headache (11%, 14%, 17%), nausea (6%, 7%, 9%), diarrhea (4%, 3%, 7%), and insomnia (3%, 5%, 6%). Direct comparison across trials should not be made due to differing trial designs.

GT 4, 5 or 6 Subjects with Compensated Liver Disease (With or Without Cirrhosis): The safety assessment of HARVONI was also based on pooled data from three open-label trials (Study 1119, ION-4 and ELECTRON-2) in 118 subjects who received HARVONI once daily for 12 weeks. The safety profile in these subjects was similar to that observed in subjects with chronic HCV GT 1 infection with compensated liver disease. The most common adverse reactions occurring in at least 10% of subjects were asthenia (18%), headache (14%) and fatigue (10%).

GT 1 Treatment-Experienced Subjects with Cirrhosis (SIRIUS): The safety assessment of HARVONI with or without RBV was based on a randomized, double-blind and placebo-controlled trial. Subjects were randomized to receive HARVONI once daily for 24 weeks without RBV or 12 weeks of placebo followed by 12 weeks of HARVONI + RBV. Adverse reactions (all grades; majority Grade 1 or 2) observed in at least 5% greater frequency reported in subjects receiving HARVONI for 24 weeks or HARVONI + RBV for 12 weeks compared to placebo for 12 weeks, respectively, were: asthenia (31% or 36% vs 23%); headache (29% or 13% vs 16%); fatigue (18% or 4% vs 1%); cough (5% or 11% vs 1%); myalgia (9% or 4% vs 0%); dyspnea (3% or 9% vs 1%); irritability (8% or 7% vs 1%); and dizziness (5% or 1% vs 0%).

Liver Transplant Recipients and/or Subjects with Decompensated Cirrhosis: The safety assessment of HARVONI + RBV in liver transplant recipients and/or those who had decompensated liver disease was based on pooled data from two Phase 2 open-label clinical trials including 336 subjects who received HARVONI + RBV for 12 weeks. Subjects with Child-Pugh-Turcotte (CPT) scores greater than 12 were excluded from the trials. The adverse events observed were consistent with the expected clinical sequelae of liver transplantation and/or decompensated liver disease, or the known safety profile of HARVONI and/or RBV. Decreases in hemoglobin to less than 10 g/dL and 8.5 g/dL during treatment were observed in 38% and 13% of subjects treated with HARVONI + RBV for 12 weeks, respectively. RBV was permanently discontinued in 11% of subjects treated with HARVONI + RBV for 12 weeks.

Liver Transplant Recipients with Compensated Liver Disease: Among the 174 liver transplant recipients with compensated liver disease who received HARVONI + RBV for 12 weeks, 2 (1%) subjects permanently discontinued HARVONI due to an adverse event. *Subjects with Decompensated Liver Disease:* Among the 162 subjects with decompensated liver disease (pre- or post-transplant) who received HARVONI + RBV for 12 weeks, 7 (4%) subjects died, 4 (2%) subjects underwent liver transplantation, and 1 subject (<1%) underwent liver transplantation and died during treatment or within 30 days after discontinuation of treatment. Because these events occurred in patients with advanced liver disease who are at risk of progression of liver disease including liver failure and death, it is not possible to reliably assess the contribution of drug effect to outcomes. A total of 4 (2%) subjects permanently discontinued HARVONI due to an adverse event.

GT 1 or 4 Subjects with HCV/HIV-1 Co-infection (ION-4): The safety assessment of HARVONI was based on an open-label clinical trial in 335 subjects who were on stable antiretroviral therapy. The safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects. The most common adverse reactions occurring in at least 10% of subjects were headache (20%) and fatigue (17%).

Less Common Adverse Reactions Reported in Clinical Trials (less than 5% of subjects receiving HARVONI in any one trial): These events have been included because of their seriousness or assessment of potential causal relationship. *Psychiatric disorders*: depression (including in subjects with pre-existing history of psychiatric illness). Depression, particularly in subjects with pre-existing history of psychiatric illness, occurred in subjects receiving sofosbuvir containing regimens. Suicidal ideation and suicide have occurred in less than 1% of subjects treated with sofosbuvir in combination with RBV or pegylated interferon/RBV in other clinical trials.

Laboratory Abnormalities: *Bilirubin Elevations:* Elevations of greater than 1.5x ULN were observed in 3%, <1% and 2% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively and in the SIRIUS trial, 3%, 11% and 3% of subjects with compensated cirrhosis treated with placebo, HARVONI + RBV for 12 weeks and HARVONI for 24 weeks, respectively. *Lipase Elevations:* Transient, asymptomatic elevations of greater than 3x ULN were observed in less than 1%, 2% and 3% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively and in the SIRIUS trial, 1%, 3% and 9% of subjects with compensated cirrhosis treated with placebo, HARVONI + RBV for 12 weeks and HARVONI for 24 weeks, respectively. *Creatine Kinase:* was not assessed in Phase 3 trials ION-1, ION-3 or ION-2 of HARVONI but was assessed in the ION-4 trial. Isolated, asymptomatic creatine kinase elevations of greater than or equal to 10xULN was observed in 1% of subjects treated with HARVONI for 12 weeks in ION-4 and has also been previously reported in subjects treated with sofosbuvir in combination with RBV or peginterferon/RBV in other clinical trials.

Brief Summary (cont.)

Postmarketing Experience: Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Cardiac Disorders:* Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiate treatment with HARVONI during post approval use of HARVONI. *Skin and Subcutaneous Tissue Disorders:* Skin rashes, sometimes with blisters or angioedema-like swelling

DRUG INTERACTIONS:

Ledipasvir is an inhibitor of the drug transporters P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters. Ledipasvir and sofosbuvir are substrates of P-gp and BCRP while the inactive sofosbuvir metabolite GS-331007 is not. P-gp inducers (e.g. rifampin or St. John's wort) may decrease ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect; use of HARVONI with P-gp inducers is not recommended.

Established and Potentially Significant Drug Interactions: The drug interactions described are based on studies conducted in healthy adults with either HARVONI, the components of HARVONI as individual agents, or are predicted drug interactions that may occur with HARVONI. This list includes potentially significant interactions but is not all inclusive.

Alteration in dose or regimen may be recommended for the following drugs when coadministered with HARVONI:

Acid Reducing Agents: Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease ledipasvir concentration. *Antacids:* Separate HARVONI and antacid administration by 4 hours. *H_2-receptor antagonists*: Doses comparable to famotidine 40 mg twice daily or lower may be administered simultaneously with or 12 hours apart from HARVONI. *Proton-pump inhibitors:* Doses comparable to omeprazole 20 mg or lower can be administered simultaneously with HARVONI under fasted conditions.

Antiarrhythmics (amiodarone; digoxin) *Amiodarone:* Coadministration of amiodarone with HARVONI may result in serious symptomatic bradycardia and is not recommended. Mechanism of effect is unknown. If coadministration is required, cardiac monitoring is recommended. *Digoxin:* Increased digoxin concentration. Monitor digoxin therapeutic concentration during coadministration with HARVONI.

Anticonvulsants (carbamazepine; phenytoin; phenobarbital; oxcarbazepine): Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.

Antimycobacterials (rifabutin; rifampin; rifapentine): Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.

HIV Antiretrovirals:

Regimens containing tenofovir disoproxil fumarate (DF) without a HIV protease inhibitor/ritonavir or cobicistat: Due to increased tenofovir concentrations, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for renal monitoring recommendations.

Regimens containing tenofovir DF and a HIV protease inhibitor/ritonavir or cobicistat (e.g., atazanavir/ritonavir or cobicistat + emtricitabine/tenofovir DF, darunavir/ritonavir or cobicistat + emtricitabine/tenofovir DF, lopinavir/ritonavir + emtricitabine/tenofovir DF): The safety of increased tenofovir concentrations has not been established. Consider alternative HCV or antiretroviral therapy to avoid increases in tenofovir exposures. If coadministration is necessary, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for renal monitoring recommendations.

Elvitegravir/cobicistat/emtricitabine/tenofovir DF: The safety of increased tenofovir concentrations has not been established. Coadministration is not recommended.

Tipranavir/ritonavir: Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.

HCV Products (simeprevir): Increased ledipasvir and simeprevir concentrations. Coadministration is not recommended.

Herbal Supplements (St. John's wort): Decreased ledipasvir and sofosbuvir concentrations. Coadministration is not recommended.

HMG-CoA Reductase Inhibitors (rosuvastatin): Significant increase in rosuvastatin concentrations and risk of rosuvastatin associated myopathy, including rhabdomyolysis. Coadministration is not recommended.

Drugs without Clinically Significant Interactions with HARVONI: Based on drug interaction studies conducted with HARVONI or its components, no clinically significant drug interactions have been observed or are expected when used with the following drugs: abacavir, atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, dolutegravir, efavirenz, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, lamivudine, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, tacrolimus, or verapamil.

Consult the full Prescribing Information prior to and during treatment with HARVONI for potential drug interactions and use with certain HIV antiretroviral regimens; this list is not all inclusive.

USE IN SPECIFIC POPULATIONS:

Pregnancy: If HARVONI is administered with RBV, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the RBV prescribing information for more information on use in pregnancy. No adequate human data are available to establish whether or not HARVONI poses a risk to pregnancy outcomes.

Lactation: It is not known whether ledipasvir or sofosbuvir, the components of HARVONI, or their metabolites are present in human breast milk, affect human milk production or have effects on the breastfed infant. Studies in rats have demonstrated that ledipasvir and GS-331007 are secreted in milk without clear effect on nursing pups. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for HARVONI and any potential adverse effects on the breastfed infant from HARVONI or from the underlying maternal condition. If HARVONI is administered with RBV, the lactation information for RBV also applies to this combination regimen. Refer to the RBV prescribing information.

Females and Males of Reproductive Potential: If HARVONI is administered with RBV, the information for RBV with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to RBV prescribing information.

Pediatric Use: Safety and effectiveness of HARVONI have not been established in pediatric patients.

Geriatric Use: Clinical trials of HARVONI included 225 subjects aged 65 and over (9% of total number of subjects in the clinical studies). 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 patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of HARVONI is warranted in geriatric patients.

Renal Impairment: No dosage adjustment of HARVONI is required for patients with mild or moderate renal impairment. The safety and efficacy of HARVONI have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD. Refer to RBV prescribing information regarding use in patients with renal impairment.

Hepatic Impairment: No dosage adjustment of HARVONI is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B, or C). Clinical and hepatic laboratory monitoring, as clinically indicated, is recommended for patients with decompensated cirrhosis receiving treatment with HARVONI and RBV.

References:

1. HARVONI US full Prescribing Information. Gilead Sciences, Inc. Foster City, CA. June 2016.
2. EPCLUSA US full Prescribing Information. Gilead Sciences, Inc. Foster City, CA. June 2016.
3. Data on file. IMS Weekly National Prescription Audit (NPA) Market Dynamics, 11/14/14–4/1/16. Gilead Sciences, Inc.
4. Data on file. HCV Weekly Sales Reports, 11/14/14–1/1/16. Gilead Sciences, Inc.
5. US Department of Health and Human Services, Center for Drug Evaluation and Research. Draft Guidance for Industry. Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment. May 2016.

EPCLUSA® (sofosbuvir 400 mg and velpatasvir 100 mg) tablets, for oral use

Brief Summary of full Prescribing Information. See full Prescribing Information. Rx Only.

INDICATIONS AND USAGE: EPCLUSA 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
- With decompensated cirrhosis for use in combination with ribavirin

CONTRAINDICATIONS

EPCLUSA and ribavirin (RBV) combination regimen is contraindicated in patients for whom RBV is contraindicated. Refer to the RBV prescribing information.

WARNINGS AND PRECAUTIONS:

Serious Symptomatic Bradycardia When Sofosbuvir is Coadministered with Amiodarone and Another HCV Direct-Acting Antiviral: Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with sofosbuvir in combination with daclatasvir or simeprevir. A fatal cardiac arrest was reported in a patient taking amiodarone who was coadministered a sofosbuvir-containing regimen (HARVONI (ledipasvir/sofosbuvir)). Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown. Coadministration of amiodarone with EPCLUSA is not recommended. For patients taking amiodarone who have no other alternative viable treatment options and who will be coadministered EPCLUSA: Counsel patients about the risk of serious symptomatic bradycardia; and cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment. Patients who are taking EPCLUSA who need to start amiodarone therapy due to no other alternative viable treatment options should undergo similar cardiac monitoring as outlined. Due to amiodarone's long half-life, patients discontinuing amiodarone just prior to starting EPCLUSA should also undergo similar cardiac monitoring as outlined. Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion, or memory problems.

Risk of Reduced Therapeutic Effect Due to Concomitant Use of EPCLUSA With Inducers of P-gp and/or Moderate to Potent Inducers of CYP: Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine) may significantly decrease plasma concentrations of sofosbuvir and/or velpatasvir leading to potentially reduced therapeutic effect of EPCLUSA. The use of these agents with EPCLUSA is not recommended.

Risks Associated with RBV and EPCLUSA Combination Treatment If EPCLUSA is administered with RBV, the warnings and precautions for RBV apply to this combination regimen. Refer to the RBV prescribing information.

ADVERSE REACTIONS:

Most common adverse reactions (greater than or equal to 10%, all grades) with EPCLUSA for 12 weeks were headache and fatigue; EPCLUSA and RBV for 12 weeks in patients with decompensated cirrhosis were fatigue, anemia, nausea, headache, insomnia, and diarrhea.

Subjects without Cirrhosis or with Compensated Cirrhosis: The adverse reactions data for EPCLUSA in patients without cirrhosis or with compensated cirrhosis were derived from three Phase 3 clinical trials (ASTRAL-1, ASTRAL-2, and ASTRAL-3) which evaluated a total of 1035 subjects infected with genotype 1, 2, 3, 4, 5, or 6 HCV, who received EPCLUSA for 12 weeks. The proportion of subjects who permanently discontinued treatment due to adverse events was 0.2% for subjects who received EPCLUSA for 12 weeks. The most common adverse reactions (at least 10%) were headache and fatigue in subjects treated with EPCLUSA for 12 weeks. Adverse reactions (all grades) reported in ≥5% of subjects receiving 12 weeks of treatment with EPCLUSA in ASTRAL-1 were: headache (22%), fatigue (15%), nausea (9%), asthenia (5%), and insomnia (5%). Of subjects receiving EPCLUSA who experienced these adverse reactions, 79% had an adverse reaction of mild severity (Grade 1). The adverse reactions observed in subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3 were consistent with those observed in ASTRAL-1. Irritability was also observed in greater than or equal to 5% of subjects treated with EPCLUSA in ASTRAL-3.

Subjects with Decompensated Cirrhosis: The safety assessment of EPCLUSA in subjects infected with genotype 1, 2, 3, 4, or 6 HCV with decompensated cirrhosis was based on one Phase 3 trial (ASTRAL-4) including 87 subjects who received EPCLUSA with RBV for 12 weeks. All 87 subjects had Child-Pugh B cirrhosis at screening. On the first day of treatment with EPCLUSA with RBV, 6 subjects and 4 subjects were assessed to have Child-Pugh A and Child-Pugh C cirrhosis, respectively. The most common adverse reactions (all grades with frequency of 10% or greater) in the 87 subjects who received EPCLUSA with RBV for 12 weeks were fatigue (32%), anemia (26%), nausea (15%), headache (11%), insomnia (11%), and diarrhea (10%). Of subjects who experienced these adverse reactions, 98% had adverse reactions of mild to moderate severity. A total of 4 (5%) subjects permanently discontinued EPCLUSA with RBV due to an adverse event; there was no adverse event leading to discontinuation that occurred in more than 1 subject. Decreases in hemoglobin to less than 10 g/dL and 8.5 g/dL during treatment were observed in 23% and 7% subjects treated with EPCLUSA with RBV for 12 weeks, respectively. RBV was permanently discontinued in 17% of subjects treated with EPCLUSA with RBV for 12 weeks due to adverse reactions.

Less Common Adverse Reactions Reported in Clinical Trials: *Rash:* In ASTRAL-1, rash occurred in 2% of subjects without cirrhosis or with compensated cirrhosis treated with EPCLUSA for 12 weeks and in 1% of subjects treated with placebo. In ASTRAL-4, rash occurred in 5% of subjects with decompensated cirrhosis treated with EPCLUSA with RBV for 12 weeks. No serious adverse reactions of rash occurred in either studies and all rashes were mild or moderate in severity. *Depression:* In ASTRAL-1, depressed mood occurred in 1% of subjects without cirrhosis or with compensated cirrhosis treated with EPCLUSA for 12 weeks and was not reported by any subject taking placebo. No serious adverse reactions of depressed mood occurred and all events were mild or moderate in severity.

Laboratory Abnormalities: *Lipase Elevations:* In ASTRAL-1, isolated, asymptomatic lipase elevations of greater than 3xULN were observed in 3% and 1% of subjects treated with EPCLUSA and placebo for 12 weeks, respectively and in 6% and 3% of subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3, respectively. In the Phase 3 trial of subjects with decompensated cirrhosis (ASTRAL-4), lipase was assessed when amylase values were ≥1.5xULN. Isolated, asymptomatic lipase elevations of greater than 3xULN were observed in 2% of subjects treated with EPCLUSA with RBV for 12 weeks. *Creatine Kinase:* In ASTRAL-1, isolated, asymptomatic creatine kinase elevations of greater than or equal to 10xULN was observed in 1% and 0% of subjects treated with EPCLUSA and placebo for 12 weeks, respectively; and in 2% and 1% of subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3, respectively. In ASTRAL-4, isolated, asymptomatic creatine kinase elevations greater than or equal to 10xULN were reported in 1% of subjects treated with EPCLUSA with RBV for 12 weeks. *Indirect Bilirubin:* Increases in indirect bilirubin up to 3 mg/dL above baseline were noted among HIV-1/HCV coinfected subjects treated with EPCLUSA and an atazanavir/ritonavir-based antiretroviral regimen. The elevated indirect bilirubin values were not associated with clinical adverse events and all subjects completed 12 weeks of EPCLUSA without dose adjustment or treatment interruption of either EPCLUSA or HIV antiretroviral agents.

Postmarketing Experience: Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Cardiac Disorders:* Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiated treatment with sofosbuvir in combination with another HCV direct-acting antiviral.

Brief Summary (cont.)

DRUG INTERACTIONS:

Sofosbuvir and velpatasvir are substrates of P-gp and breast cancer resistance protein (BCRP) while GS-331007 (the predominant circulating metabolite of sofosbuvir) is not. Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine) may decrease plasma concentrations of sofosbuvir and/or velpatasvir, leading to reduced therapeutic effect of EPCLUSA. The use of these agents with EPCLUSA is not recommended. EPCLUSA may be coadministered with P-gp, BCRP, and CYP inhibitors. Velpatasvir is an inhibitor of drug transporters P-gp, BCRP, OATP1B1, OATP1B3, and OATP2B1. Coadministration of EPCLUSA with drugs that are substrates of these transporters may increase the exposure of such drugs.

Established and Potentially Significant Drug Interactions: The drug interactions are based on studies conducted with either EPCLUSA, the components of EPCLUSA (sofosbuvir and velpatasvir) as individual agents, or are predicted drug interactions that may occur with EPCLUSA. This list includes potentially significant interactions but is not all inclusive.

Alteration in Dose or Regimen May Be Recommended For The Following Drugs When Coadministered With EPCLUSA:

Acid Reducing Agents: Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of velpatasvir. *Antacids:* Separate antacid and EPCLUSA administration by 4 hours. *H_2-receptor antagonists:* Doses comparable to famotidine 40 mg twice daily or lower may be administered simultaneously with or 12 hours apart from EPCLUSA. *Proton-pump inhibitors:* Coadministration of omeprazole or other proton pump inhibitors is not recommended. If considered medically necessary to coadminister, EPCLUSA should be administered with food and taken 4 hours before omeprazole 20 mg. Use with other proton pump inhibitors has not been studied.

Antiarrhythmics (amiodarone; digoxin): *Amiodarone:* Coadministration of amiodarone with EPCLUSA may result in serious symptomatic bradycardia and is not recommended. Mechanism of effect is unknown. If coadministration is required, cardiac monitoring is recommended. *Digoxin:* Increased concentration of digoxin. Monitor digoxin therapeutic concentration during coadministration with EPCLUSA. Refer to digoxin prescribing information for monitoring and dose modification recommendations for concentration increases of less than 50%.

Anticancers (topotecan): Increased concentration of topotecan. Coadministration is not recommended

Anticonvulsants (carbamazepine; phenytoin; phenobarbital; oxcarbazepine): Decreased sofosbuvir and velpatasvir concentrations leading to reduced EPCLUSA effect. Coadministration is not recommended.

Antimycobacterials (rifabutin; rifampin; rifapentine): Decreased sofosbuvir and velpatasvir concentrations leading to reduced EPCLUSA effect. Coadministration is not recommended.

HIV Antiretrovirals (efavirenz; regimens containing tenofovir DF; tipranavir/ritonavir): *Efavirenz:* Decreased concentration of velpatasvir. Coadministration of EPCLUSA with efavirenz-containing regimens is not recommended. *Regimens containing tenofovir disoproxil fumarate (DF):* Due to increased tenofovir concentrations, monitor for tenofovir-associated adverse reactions. Refer to the prescribing information of the tenofovir DF-containing product for renal monitoring recommendations. *Tipranavir/ritonavir:* Decreased sofosbuvir and velpatasvir concentrations leading to reduced EPCLUSA effect. Coadministration is not recommended.

Herbal Supplements (St. John's wort): Decreased sofosbuvir and velpatasvir concentrations. Coadministration is not recommended.

HMG-CoA Reductase Inhibitors (rosuvastatin; atorvastatin): *Rosuvastatin:* Significant increase in rosuvastatin concentrations and risk of rosuvastatin associated myopathy, including rhabdomyolysis. Rosuvastatin may be administered with EPCLUSA at a dose that does not exceed 10 mg. *Atorvastatin*: Expected increase in atorvastatin concentrations and risk of atorvastatin associated myopathy, including rhabdomyolysis. Monitor closely for HMG-CoA reductase inhibitor-associated adverse reactions, such as myopathy and rhabdomyolysis.

Drugs without Clinically Significant Interactions with EPCLUSA: Based on drug interaction studies conducted with the components of EPCLUSA (sofosbuvir or velpatasvir) or EPCLUSA, no clinically significant drug interactions have been observed with the following drugs. *EPCLUSA*: atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, dolutegravir, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, raltegravir, or rilpivirine; *Sofosbuvir*: ethinyl estradiol/norgestimate, methadone, or tacrolimus; *Velpatasvir*: ethinyl estradiol/norgestimate, ketoconazole, or pravastatin.

Consult the full Prescribing Information prior to and during treatment with EPCLUSA for potential drug interactions and use with certain HIV antiretroviral regimens; this list is not all inclusive.

USE IN SPECIFIC POPULATIONS:

Pregnancy: If EPCLUSA is administered with RBV, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the RBV prescribing information for more information on RBV-associated risks of use during pregnancy. No adequate human data are available to establish whether or not EPCLUSA poses a risk to pregnancy outcomes.

Lactation: It is not known whether the components of EPCLUSA and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed infant. When administered to lactating rats, velpatasvir was detected in the milk of lactating rats and in the plasma of nursing pups without effects on the nursing pups. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for EPCLUSA and any potential adverse effects on the breastfed infant from EPCLUSA or from the underlying maternal condition. If EPCLUSA is administered with RBV, the lactation information for RBV also applies to this combination regimen. Refer to the RBV prescribing information.

Females and Males of Reproductive Potential: If EPCLUSA is administered with RBV, the information for RBV with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to RBV prescribing information.

Pediatric Use: Safety and effectiveness of EPCLUSA have not been established in pediatric patients.

Geriatric Use: Clinical trials of EPCLUSA included 156 subjects aged 65 and over (12% of total number of subjects in the Phase 3 clinical studies). 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 patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of EPCLUSA is warranted in geriatric patients.

Renal Impairment: No dosage adjustment of EPCLUSA is required for patients with mild or moderate renal impairment. The safety and efficacy of EPCLUSA have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD. Refer to RBV prescribing information regarding use of RBV in patients with renal impairment.

Hepatic Impairment: No dosage adjustment of EPCLUSA is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C). Clinical and hepatic laboratory monitoring (including direct bilirubin), as clinically indicated, is recommended for patients with decompensated cirrhosis receiving treatment with EPCLUSA and RBV.

GILEAD

A Randomized Phase 3 Trial of Sofosbuvir/Velpatasvir/Voxilaprevir for 8 Weeks and Sofosbuvir/Velpatasvir for 12 Weeks for Patients With Genotype 3 HCV Infection and Cirrhosis: The POLARIS-3 Study

Sofosbuvir is a nucleotide analogue inhibitor of NS5B polymerase with activity against hepatitis C virus (HCV) genotypes 1 through 6. Velpatasvir is a pangenotypic NS5A inhibitor. The 2 drugs are approved as a once-daily, fixed-dose combination administered for 12 weeks for the treatment of HCV genotype 3 infection in patients with cirrhosis who have not received prior treatment with direct-acting antiviral (DAA) agents.[1] Voxilaprevir (GS-9857) is a pangenotypic NS3/4A protease inhibitor and has demonstrated activity against most resistance-associated substitutions (RASs). In phase 2 studies, the combination of sofosbuvir/velpatasvir plus voxilaprevir administered daily for 8 weeks yielded high rates of sustained virologic response at 12 weeks post-treatment (SVR12) in patients with HCV genotype 3 infection, including those with cirrhosis.[2] HCV genotype 3 accounts for approximately 30% of infections worldwide and is associated with high rates of hepatocellular carcinoma and rapid development of cirrhosis.[3]

Dr Graham Foster presented results of the international, open-label, randomized, phase 3 POLARIS-3 study (Safety and Efficacy of SOF/VEL/VOX FDC for 8 Weeks and SOF/VEL for 12 Weeks in Adults With Chronic Genotype 3 HCV Infection and Cirrhosis), which investigated 8 weeks of treatment with the once-daily, fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) vs 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) in patients with HCV genotype 3 infection and compensated cirrhosis.[4] Treatment-naive and treatment-experienced patients were eligible. Patients were stratified based on prior interferon exposure and were randomly assigned to the 2 treatment arms. HCV RNA levels were assessed by quantitative polymerase chain reaction with a lower limit of quantification of 15 IU/mL. Deep sequencing of HCV was performed using a 15% cutoff. Cirrhosis was determined by liver biopsy, blood biomarker testing, or transient elastography. The primary endpoint was SVR12, with additional safety and laboratory endpoints.

Sofosbuvir/velpatasvir/voxilaprevir was administered to 110 patients for 8 weeks. Sofosbuvir/velpatasvir was given to 109 patients for 12 weeks. Patients had a median age of 55 years (range, 25-75 years), and most were male. In the experimental vs the control arm, the mean platelet count was 140 × 10^3/μL (range, 37-351 × 10^3/μL) vs 130 × 10^3/μL (range, 51-292 × 10^3/μL). The proportion of patients with a platelet count below 100 × 10^3/μL was 29% vs 19%. The mean transient elastography score was 23 (range,

ABSTRACT SUMMARY A Randomized Phase 3 Trial of Sofosbuvir/Velpatasvir/Voxilaprevir for 8 Weeks Compared to Sofosbuvir/Velpatasvir for 12 Weeks in DAA-Naive Genotype 1-6 HCV-Infected Patients: The POLARIS-2 Study

The phase 3 POLARIS-2 study (A Phase 3, Global, Multicenter, Randomized, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir/GS-9857 Fixed-Dose Combination for 8 Weeks Compared to Sofosbuvir/Velpatasvir for 12 Weeks in Direct-Acting Antiviral-Naive Subjects With Chronic HCV Infection) evaluated the once-daily, fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) for 8 weeks vs daily sofosbuvir/velpatasvir for 12 weeks in 941 patients infected with HCV genotypes 1 to 6 (Abstract LB-12). Patients did not have prior exposure to DAA therapy. The presence of compensated cirrhosis was permitted, except in patients with genotype 3 infection. Patients with genotype 1 to 4 infection were stratified based on HCV genotype, prior treatment with interferon, and cirrhosis followed by 1:1 randomization to treatment. Patients with genotype 5 or 6 were enrolled in the sofosbuvir/velpatasvir/voxilaprevir arm. The SVR12 rates were 95% after 8 weeks of treatment with sofosbuvir/velpatasvir/voxilaprevir, and 98% after 12 weeks of treatment with sofosbuvir/velpatasvir. The trial failed to demonstrate noninferiority based on the virologic failure rates of 4.2% in the 3-drug treatment arm vs 0.7% in the comparator arm. In the sofosbuvir/velpatasvir/voxilaprevir vs the comparator arm, SVR12 rates in patients without cirrhosis were 96% vs 98%, including 14 vs 2 relapses, respectively. SVR12 rates in patients with cirrhosis were 91% vs 99%, including 7 vs 1 relapses, respectively. Both treatment regimens were generally well-tolerated.

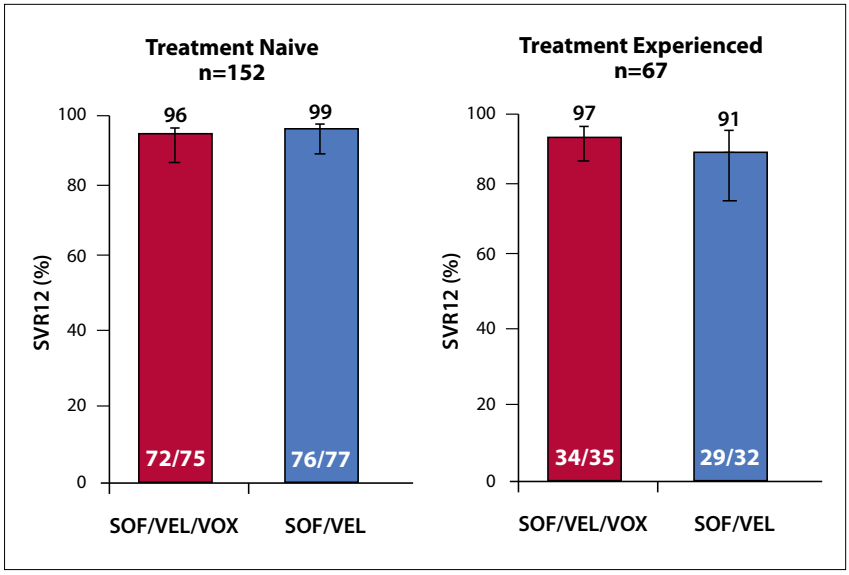


Figure 1. SVR12 according to previous treatment experience in the phase 3 POLARIS-3 study. POLARIS-3, Safety and Efficacy of SOF/VEL/VOX FDC for 8 Weeks and SOF/VEL for 12 Weeks in Adults With Chronic Genotype 3 HCV Infection and Cirrhosis; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SOF/VEL, sofosbuvir/velpatasvir; SVR12, sustained virologic response at 12 weeks posttreatment. Adapted from Foster GR et al. AASLD abstract 258. *Hepatology*. 2016;64(suppl 1):125A.[4]

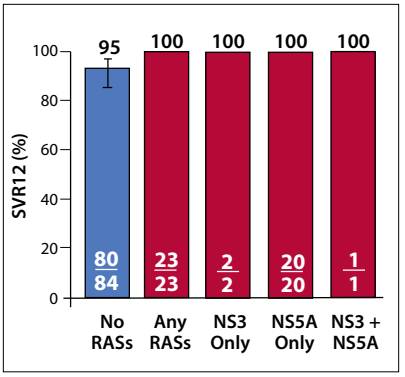


Figure 2. SVR12 according to baseline RASs among patients who received sofosbuvir/velpatasvir/voxilaprevir in the phase 3 POLARIS-3 study. POLARIS-3, Safety and Efficacy of SOF/VEL/VOX FDC for 8 Weeks and SOF/VEL for 12 Weeks in Adults With Chronic Genotype 3 HCV Infection and Cirrhosis; RASs, resistance-associated substitutions; SVR12, sustained virologic response at 12 weeks posttreatment. Adapted from Foster GR et al. AASLD abstract 258. *Hepatology*. 2016;64(suppl 1):125A.[4]

13-75) vs 22 (range, 13-75), reflecting a population with advanced cirrhosis. Approximately one-third of patients in each arm had received prior treatment with interferon, and the mean HCV RNA concentration was 6.0 $\log_{10}$ IU/mL (range, 1.6-7.6 $\log_{10}$ IU/mL) vs 6.3 $\log_{10}$ IU/mL (range, 4.1-7.5 $\log_{10}$ IU/mL). Patient compliance was 100% in the sofosbuvir/velpatasvir/voxilaprevir arm and 98% in the sofosbuvir/velpatasvir arm.

The SVR12 rate was 96% in both arms. In the sofosbuvir/velpatasvir/voxilaprevir arm, 2 patients relapsed, 1 patient withdrew consent, and 1 patient died. In the sofosbuvir/velpatasvir arm, 1 patient experienced on-treatment failure, 1 patient relapsed, 1 patient discontinued treatment owing to an adverse event (AE), and 1 patient was lost to follow-up. In treatment-naive patients, the SVR12 rate was 96% (72/75) with sofosbuvir/velpatasvir/voxilaprevir vs 99% (76/77) with sofosbuvir/velpatasvir (Figure 1). The addition of voxilaprevir improved the outcome in treatment-experienced patients, yielding an SVR12 rate of 97% (34/35) compared with 91% (29/32) in the treatment-experienced patients who received sofosbuvir/velpatasvir alone.

Baseline RASs were not associated with resistance to the combination of sofosbuvir/velpatasvir/voxilaprevir (Figure 2). The Y93H RAS was present in 6 patients in the voxilaprevir-containing arm and 4 patients in the sofosbuvir/velpatasvir arm, and all of these patients achieved SVR12. No treatment-emergent RASs were observed in the patients who received the voxilaprevir-containing regimen, and both patients with virologic failure in the sofosbuvir/velpatasvir arm had treatment-emergent Y93H mutations.

In the voxilaprevir-containing arm vs the control arm, the most common AEs included headache (25% vs 29%), fatigue (25% vs 28%), nausea (21% vs 9%), and diarrhea (15% vs 5%). Grade 3/4 AEs occurred in 3% and 4% of patients, and serious AEs occurred in 2% and 3%, respectively. No serious AEs were considered treatment-related.

References

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SURVEYOR-II, Part 3: Efficacy and Safety of ABT-493/ABT-530 in Patients With Hepatitis C Virus Genotype 3 Infection With Prior Treatment Experience and/or Cirrhosis

Current treatment recommendations from the American Association for the Study of Liver Diseases for patients with HCV genotype 3 infection include sofosbuvir plus daclatasvir or sofosbuvir plus velpatasvir, with the addition of ribavirin for patients with cirrhosis and/or prior treatment.[1] The addition of ribavirin is also recommended for patients with either cirrhosis or prior treatment experience, as well as the baseline Y93H mutation. Ribavirin-free treatment regimens administered for the shortest possible duration are needed for these patient populations, which are the most difficult to treat. Glecaprevir (ABT-493) is a pangenotypic NS3/4A protease inhibitor that is being investigated in combination with pibrentasvir (ABT-530) for HCV treatment. The combination has demonstrated strong activity against HCV genotypes 1 to 6, including common NS3 and NS5A variants.[2] The DAAs have been coformulated and are dosed once daily in 3 pills of glecaprevir (100 mg)/pibrentasvir (40 mg). The 2-drug combination has shown minimal metabolism and less than 1% renal excretion.

In a phase 2 study from 2015, glecaprevir (300 mg)/pibrentasvir (100 mg) administered for 12 weeks without ribavirin elicited an SVR12 rate of 100% in treatment-naive patients with HCV genotype 3 infection and compensated cirrhosis.[3] In treatment-experienced patients with HCV genotype 3 infection and no cirrhosis, the SVR12 rate was 92%.

Part 3 of the phase 2 SURVEYOR-II trial (A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-Administration of ABT-493 and ABT-530 With and Without RBV in Subjects With Chronic Hepatitis C Virus [HCV] Genotypes 2, 3, 4, 5 or 6 Infection) evaluated the efficacy and safety of glecaprevir (300 mg)/pibrentasvir (120 mg) administered for 12 or 16 weeks in patients with HCV genotype 3 infection.[4] Eligible patients in part 3 of the study were adults with chronic HCV genotype 3 infection and an HCV RNA level of greater than 1000 IU/mL, without cirrhosis or with compensated cirrhosis. The study enrolled treatment-naive patients as well as patients whose prior treatment included interferon or pegylated interferon, with or without ribavirin, or sofosbuvir plus ribavirin with or without pegylated interferon. Key exclusion criteria included coinfection with hepatitis B virus or human immunodeficiency virus (HIV), previous DAA therapy (excepting sofosbuvir), or a history of hepatic decompensation. Patients with a level of alanine aminotransferase greater than 10 times the upper limit of normal and patients with inadequate levels of albumin (<2.9 g/dL) or platelets (<60 × 10^9/L) were excluded. The primary endpoint was SVR12 based on HCV RNA below the lower limit of quantification (25 IU/mL), with additional safety endpoints.

Forty-four treatment-experienced patients without cirrhosis were randomly assigned to receive glecaprevir/pibrentasvir for 12 or 16 weeks. The 2-drug combination was administered for 12 weeks in 40 treatment-naive patients with cirrhosis, and for 16 weeks in 47 treatment-experienced patients with cirrhosis. The median age in the 4 arms was 56 to 59 years (range, 29-70 years), and approximately two-thirds of patients were male. The median HCV RNA level across the 4 arms was 6.1 to 6.6 $\log_{10}$ IU/mL (range, 4.2-7.5 $\log_{10}$ IU/mL), and the proportion of patients with an HCV RNA level of at least 6 million IU/mL was 10% to 41%. The majority of patients did not have baseline NS3 or NS5A polymorphisms, and no patients exhibited concomitant NS3 and NS5A mutations. Two patients had NS3 polymorphisms, and 24 had NS5A polymorphisms. Of note, while these mutations are associated with resistance to earlier-generation NS3 or NS5A inhibitors, pibrentasvir has demonstrated activity against HCV mutants with established RASs.[2]

Among the treatment-experienced patients without cirrhosis, 12 or 16 weeks of treatment with glecaprevir/pibrentasvir yielded SVR12 rates of 91% and 96%, respectively (Figure 3). In treatment-naive patients with cirrhosis, 12 weeks of treatment yielded an SVR12 rate of 98%, including 1

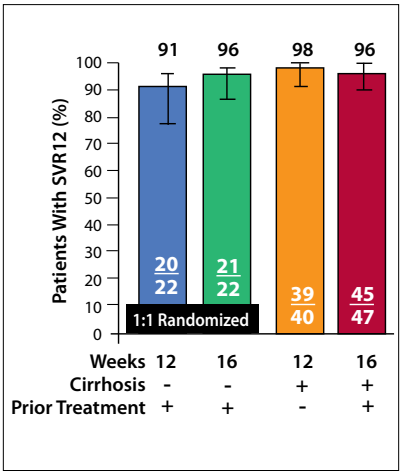

Figure 3. SVR12 among patients treated with glecaprevir/pibrentasvir in the phase 2 SURVEYOR-II trial. SURVEYOR-II, A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-Administration of ABT-493 and ABT-530 With and Without RBV in Subjects With Chronic Hepatitis C Virus [HCV] Genotypes 2, 3, 4, 5 or 6 Infection; SVR12, sustained virologic response at 12 weeks posttreatment. Adapted from Wyles DL et al. AASLD abstract 113. *Hepatology*. 2016;64(suppl 1):62A.[4]

Table 1. Polymorphisms Observed Before and After Treatment With Glecaprevir/Pibrentasvir in Patients Who Experienced Virologic Failure in the SURVEYOR-II Trial

	Type of Failure	NS3		NS5A	
		Baseline	Failure	Baseline	Failure
Patient 1	Relapse	–	–	Y93H	Y93H
Patient 2	Relapse	–	–	A30K	A30K + Y93H
Patient 3	Relapse	–	Y56H + Q168R	A30K	A30K + Y93H
Patient 4	Relapse	–	–	–	L31F + Y93H
Patient 5	Breakthrough	A166S	A156G + A166S	–	A30K + Y93H

SURVEYOR-II, A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-Administration of ABT-493 and ABT-530 With and Without RBV in Subjects With Chronic Hepatitis C Virus [HCV] Genotypes 2, 3, 4, 5 or 6 Infection. Adapted from Wyles DL et al. AASLD abstract 113. *Hepatology.* 2016;64(suppl 1):62A.[4]

patient who was lost to follow-up, and in treatment-experienced patients with cirrhosis, 16 weeks of treatment yielded an SVR12 rate of 96%. Across the 4 arms, 4 patients experienced relapse and 1 patient experienced breakthrough; all 5 patients were treatment-experienced, and all 5 had high baseline viral loads, ranging from 2.84×10^6 IU/mL to 18.9×10^6 IU/mL. The 1 patient who experienced virologic breakthrough had a body-mass index of approximately 42 and had previously failed sofosbuvir plus ribavirin. The patient had the NS3 variant A166S at baseline, and developed the additional A156G variant after breakthrough. This patient had no baseline NS5 variants, and had A30K plus Y93H after breakthrough. One patient who experienced relapse had no baseline NS3 RASs and had the combination of Y56H and Q168R after relapse. The 3 other patients who experienced relapse had no NS3 RASs at baseline or after virologic failure (Table 1). NS5A baseline variants were observed in 3 of the 4 patients who relapsed, including 1 patient with Y93H and 2 patients with A30K. At failure, both patients with baseline A30K had acquired a second mutation of Y93H. The patient with no baseline RASs had the combination of L31F plus Y93H after relapse.

AEs of any grade were observed in at least half of patients in each of the 4 arms. Serious AEs occurred in 3% to 7% of patients in the 4 arms, but no serious AEs were considered related to study drug, and no patients discontinued treatment owing to an AE. AEs occurring in at least 10% of patients included fatigue and headache.

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Sofosbuvir/Velpatasvir/Voxilaprevir for 12 Weeks as a Salvage Regimen in NS5A Inhibitor-Experienced Patients With Genotype 1-6 Infection: The Phase 3 POLARIS-1 Study

In phase 2 studies, sofosbuvir, velpatasvir, and voxilaprevir yielded high rates of SVR12 in patients who had received prior treatment with DAA-containing regimens, including patients with cirrhosis.[1,2] The double-blind, randomized, placebo-controlled phase 3 POLARIS-1 study (Safety and Efficacy of Sofosbuvir/Velpatasvir/Voxilaprevir in Adults With Chronic HCV Infection Who Have Previously Received Treatment With Direct-Acting Antiviral Therapy) evaluated sofosbuvir/velpatasvir/voxilaprevir in patients with HCV genotype 1 to 6 infection who failed prior treatment with an NS5A inhibitor.[3] Patients with HCV genotype 1 infection were stratified based on cirrhosis and randomly assigned to receive 12 weeks of treatment with the once-daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) or placebo. Patients with all other HCV genotypes were enrolled into the active treatment arm. HCV RNA levels were measured by quantitative

ABSTRACT SUMMARY EXPEDITION-IV: Safety and Efficacy of GLE/PIB in Adults With Renal Impairment and Chronic Hepatitis C Virus Genotype 1 – 6 Infection

The ongoing phase 3 EXPEDITION-4 trial (A Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Renally Impaired Adults With Chronic Hepatitis C Virus Genotype 1 - 6 Infection) is evaluating glecaprevir (300 mg)/pibrentasvir (120 mg) in patients infected with HCV genotypes 1 to 6, with severe renal impairment and no cirrhosis (Abstract LB-11). The multicenter, open-label, single-arm trial includes treatment-naive patients and those previously treated with interferon or pegylated interferon, with or without ribavirin, or sofosbuvir plus ribavirin, with or without pegylated interferon. The 104 enrolled patients had a median age of 57 years (range, 28-83 years), and 76% were male. HCV genotypes 1, 2, 3, or 4 were detected in 52%, 16%, 11%, and 19% of patients. Genotype 5 or 6 were each observed in 1% of patients. Fifty-eight percent of patients were treatment-naive, 19% had compensated cirrhosis, and 88% had stage 5 chronic kidney disease. By intent-to-treat analysis, the SVR12 rate was 98%, with no virologic failures. One patient discontinued treatment, and 1 was lost to follow-up. Twenty-four percent of patients experienced a serious AE, with none considered related to DAA therapy, and 4% of patients discontinued owing to an AE. AEs occurring in at least 10% of patients included pruritus (20%), fatigue (14%), and nausea (12%).

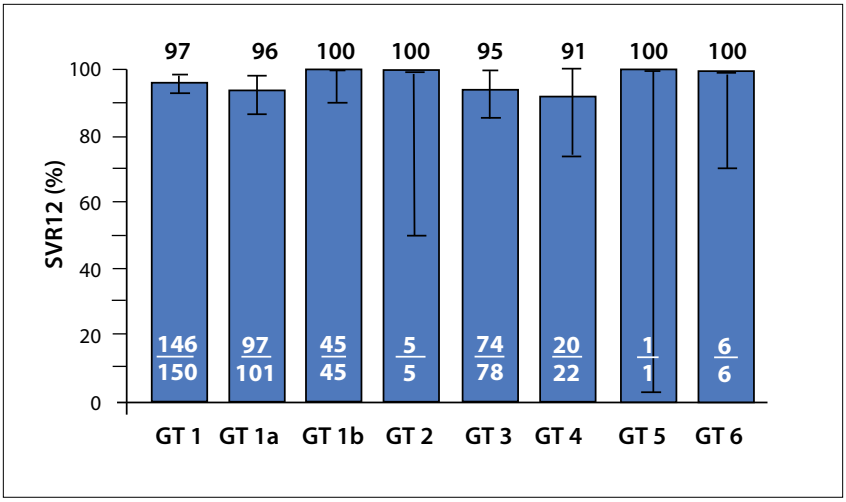

Figure 4. SVR12 according to genotype among patients treated with sofosbuvir/velpatasvir/voxilaprevir in the phase 3 POLARIS-1 study. GT, genotype; POLARIS-1, Safety and Efficacy of Sofosbuvir/Velpatasvir/Voxilaprevir in Adults With Chronic HCV Infection Who Have Previously Received Treatment With Direct-Acting Antiviral Therapy; SVR12, sustained virologic response at 12 weeks posttreatment. Adapted from Bourlière M et al. AASLD abstract 194. *Hepatology*. 2016;64(suppl 1):102A.[3]

polymerase chain reaction with a lower limit of quantification of 15 IU/mL. Deep sequencing was performed using a 15% cutoff, and cirrhosis was determined by liver biopsy, blood biomarker testing, or transient elastography. The primary endpoint was SVR12. Other endpoints included AEs, discontinuations, and laboratory abnormalities.

There were 263 patients in the sofosbuvir/velpatasvir/voxilaprevir arm and 152 patients in the placebo arm. The mean age was 58 years (range, 27-84 years), and more than three-fourths of patients were male. Patients had a mean HCV RNA level of 6.3 $\log_{10}$ IU/mL (range, 1.6-7.7 $\log_{10}$ IU/mL). In the active treatment arm, 57% of patients had HCV genotype 1, 2% had genotype 2, 30% had genotype 3, 8% had genotype 4, and the remainder had genotype 5, 6, or an unknown genotype. In the active treatment arm, 46% of patients had cirrhosis vs 34% in the placebo arm. Previous use of NS5A inhibitors included ledipasvir in 51%, daclatasvir in 27%, and ombitasvir in 11%. In the active treatment arm, 2 patients discontinued treatment: one experienced an AE on day 12, and one was lost to follow-up after week 8 of treatment. In the placebo arm, 3 patients discontinued treatment owing to an AE.

The combination of sofosbuvir/velpatasvir/voxilaprevir administered for 12 weeks yielded an SVR12 rate of 96% (253/263). Six patients relapsed, and 2 withdrew consent. One patient experienced on-treatment failure and had drug exposure levels consistent with nonadherence. One patient was lost to follow-up. No patients in the placebo arm achieved SVR12 (P<.001 for superiority compared with the prespecified performance goal of 85% for the triple-combination therapy). The 3-drug combination yielded an SVR12 rate of 99% (140/142) in the group of patients without cirrhosis. Among the 2 patients who did not achieve SVR12, 1 withdrew consent and 1 was lost to follow-up. The SVR12 rate was 93% (113/121) in the patients with cirrhosis, and included 6 patients who relapsed, 1 with on-treatment failure, and 1 who withdrew consent. SVR12 rates were high across all genotypes, with SVR12 rates of 100% observed for genotype 1b (n=45), 2 (n=5), 5 (n=1), and 6 (n=6; Figure 4). In genotypes 1, 1a, 3, and 4, SVR12 rates were 97%, 96%, 95%, and 91%, respectively. Eighty-three percent of patients had baseline RASs, with the majority in NS5A.

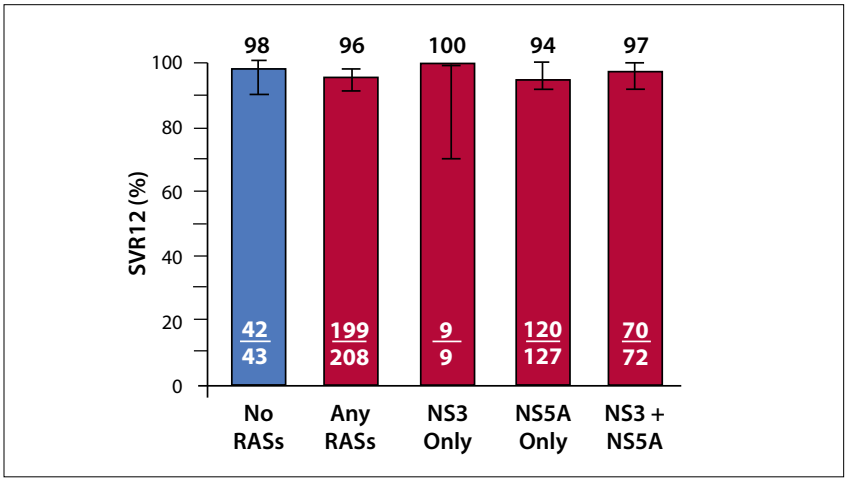

Figure 5. SVR12 according to baseline RASs among patients treated with sofosbuvir/velpatasvir/voxilaprevir in the phase 3 POLARIS-1 study. POLARIS-1, Safety and Efficacy of Sofosbuvir/Velpatasvir/Voxilaprevir in Adults With Chronic HCV Infection Who Have Previously Received Treatment With Direct-Acting Antiviral Therapy; RASs, resistance-associated substitutions; SVR12, sustained virologic response at 12 weeks posttreatment. Adapted from Bourlière M et al. AASLD abstract 194. *Hepatology*. 2016;64(suppl 1):102A.[3]

SVR12 rates in the patients without vs with baselines RASs were 98% and 96%, respectively. Among the patients with baseline RASs, SVR12 rates were 100% (9/9) in those with variants in NS3 only, 94% (120/127) in those with NS5A only, and 97% (70/72) in those with both (Figure 5). None of the patients who relapsed had treatment-emergent mutations.

The fixed-dose combination of sofosbuvir/velpatasvir/voxilaprevir was generally well-tolerated. The proportion of patients with an AE of any grade was 78% in the active treatment arm, vs 70% in the placebo arm. Grade 3/4 AEs occurred in 2% vs 3% of patients, and serious AEs occurred in 2% vs 5%, respectively. No serious AEs were considered related to treatment.

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The Fixed-Dose Combination Regimen of MK-3682/Grazoprevir/MK-8408 With or Without Ribavirin: Results From Parts B and C of C-CREST 1 & 2

The fixed-dose combination of MK-3682 (225 mg)/grazoprevir (50 mg)/ruzasvir (30 mg) is dosed in 2 tablets administered once daily.[1-3] These 3 pangenotypic DAAs have nonoverlapping resistance profiles and are inhibitors of NS5B, NS3/4A, and NS5A, respectively. The regimen is known as MK-3682B or MK3. The parallel-group, multicenter, open-label, randomized phase 2 CREST 1 and 2 trials investigated this regimen with or without ribavirin for 8, 12, or 16 weeks in patients with HCV genotypes 1, 2, and 3. The trials enrolled a total of 664 patients and included 3 arms with ribavirin and 3 arms without ribavirin.

Dr Eric Lawitz presented findings from C-CREST 1 and 2, part B.[4] All enrolled patients had documented chronic HCV genotype 1, 2, or 3 infection. Patients with genotype 1 or 2 infection were required to be treatment-naive, whereas patients with genotype 3 infection could be treatment-naive or could have received prior treatment with pegylated interferon and ribavirin. An HCV RNA level of at least 10,000 IU/mL was required, and coinfection with HIV was allowed. Cirrhotic and noncirrhotic patients were enrolled. Key exclusion criteria were decompensated liver disease, coinfection with hepatitis B virus, evidence or suspicion of hepatocellular carcinoma, elevated transaminase levels, and low levels of hemoglobin or platelets. Patients with HCV genotype 1 were randomized to receive MK3 without ribavirin for 8 or 12 weeks. Patients with genotype 2 or 3 were randomized to receive MK3 with or without ribavirin for 8 or 12 weeks. The primary endpoint was SVR12.

Patient characteristics were well-

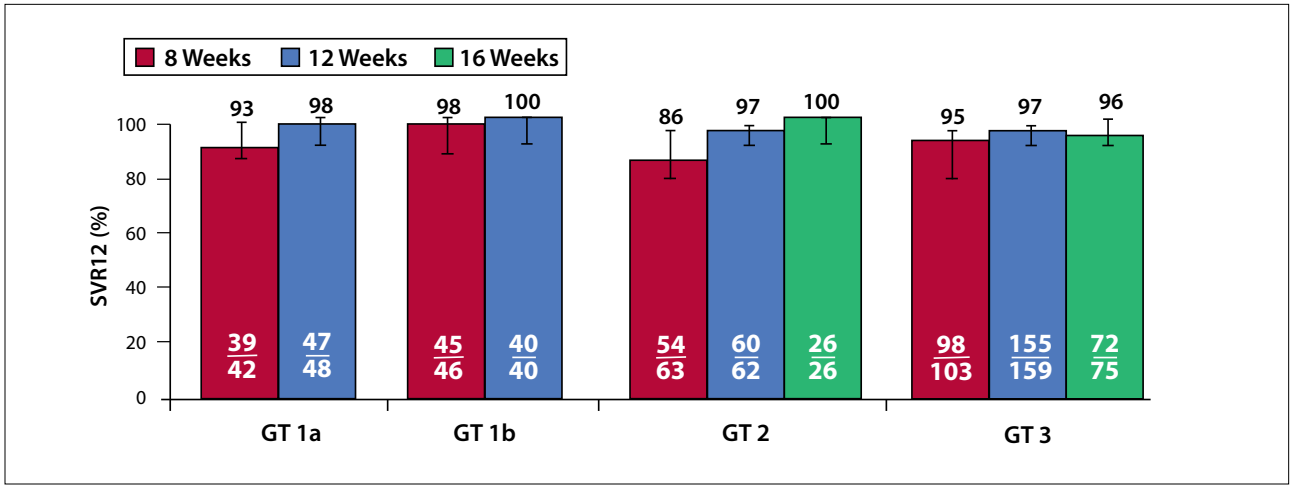

Figure 6. SVR12 according to genotype among patients treated with MK-3682/grazoprevir/ruzasvir in part B of the C-CREST 1 and 2 trials. GT, genotype; SVR12, sustained virologic response at 12 weeks posttreatment. Adapted from Lawitz E et al. AASLD abstract 110. *Hepatology*. 2016;64(suppl 1):60A.[4]

balanced among the 3 arms. The 664 patients had a median age of 54 years (range, 19-85 years), and 59% were male. Thirty-eight percent of patients had cirrhosis, and 4% of patients were coinfected with HIV. Among the 176 patients with genotype 1 infection, SVR12 rates after 8 or 12 weeks of MK3 treatment were 93% and 98%, respectively, for patients with genotype 1a infection, and 98% and 100% for patients with genotype 1b infection (Figure 6). After 8, 12, or 16 weeks of MK3 treatment with or without ribavirin, patients with genotype 2 infection showed SVR12 rates of 86%, 97%, and 100%, respectively, and patients with genotype 3 infection had SVR12 rates of 95%, 97%, and 96%. The MK3 regimen was effective in patients with HCV genotype 1 infection with or without cirrhosis. After 8 weeks of MK3, SVR rates were 97% for genotype 1a patients without cirrhosis and 92% for those with cirrhosis. Among patients with genotype 1b infection, SVR12 was 96% for those without cirrhosis vs 100% for those with cirrhosis. After 12 weeks of MK3, all patients with HCV genotype 1a or 1b infection, with or without cirrhosis, achieved SVR12. In patients with HCV genotype 2 or 3 infection, the addition of ribavirin did not significantly or consistently improve outcomes compared with MK3 alone.

Baseline NS5A RASs did not reduce SVR12 rates in patients with HCV genotype 1 infection. In contrast, in patients with genotype 2 or 3 infection, the presence of baseline NS5A RASs generally reduced the SVR12 rate. In genotype 2 patients without vs with the NS5A L31M RAS at baseline, SVR12 rates were 94% vs 80% after 8 weeks of treatment. However, 12 weeks of treatment yielded SVR12 rates of 100% in all patients with or without the L31M baseline RAS. In genotype 3 patients without vs with Y93H at baseline, SVR12 rates were 98% vs 50% after 8 weeks of treatment and 99% vs 71% after 12 weeks of treatment.

AEs and treatment-related AEs were more common in patients who received treatment containing ribavirin. The most common AEs of any grade in patients receiving MK3 alone were headache (19%), fatigue (15%), and nausea (11.3%).

Dr Edward Gane presented results from C-CREST part C, which evaluated retreatment of patients who relapsed in part A of the same trial.[5] In part A, patients received a 3-DAA combination for 8 weeks. In part C, 24 patients with HCV genotype 1 (n=2), 2 (n=14), or 3 (n=8) who had relapsed in part A received MK3 plus ribavirin for 16 weeks. SVR12 rates for the patients with genotype 1, 2, or 3 were 100%, 93%, and 100%, respectively. The common AEs were headache (25%), fatigue (25%), nausea (25%), rash (21%), and insomnia (21%).

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A Randomized, Controlled, Phase 3 Trial of Sofosbuvir/Velpatasvir/Voxilaprevir or Sofosbuvir/Velpatasvir for 12 Weeks in Direct Acting Antiviral Experienced Patients With Genotype 1-6 HCV Infection: The POLARIS-4 Study

Sofosbuvir (400 mg)/velpatasvir (100 mg) administered for 12 weeks is approved for treatment of HCV patients without prior exposure to DAAs. However, treatments for DAA-experienced patients are needed. Dr Stefan Zeuzem presented results of the open-label, randomized, phase 3 POLARIS-4 trial (Safety and Efficacy of SOF/VEL/VOX FDC for 12 Weeks and SOF/VEL for 12 Weeks in DAA-Experienced Adults With Chronic HCV Infection Who Have Not Received an NS5A Inhibitor), which investigated the fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) in DAA-experienced patients with HCV genotypes 1 to 6 who had not received an NS5A inhibitor.[1-3] Patients with HCV genotypes 1 to 3 were randomly assigned to receive 12 weeks of treatment with sofosbuvir/velpatasvir/voxilaprevir or sofosbuvir/velpatasvir, after stratification for cirrhosis. Patients with genotypes 4 to 6 were assigned to 12 weeks of treatment with sofosbuvir/velpatasvir/voxilaprevir.

The study enrolled 182 patients in the sofosbuvir/velpatasvir/voxilaprevir arm and 151 patients in the sofosbuvir/velpatasvir arm. Patients had a median age of 57 years (range, 24-85 years), more than three-fourths were male, and 46% had cirrhosis. The voxilaprevir-containing arm included 19 patients (10%) with HCV genotype 4. Across the entire study cohort, SVR12 rates were 69% for patients with prior exposure to sofosbuvir and 4% for patients with exposure to an NS5B inhibitor other than sofosbuvir. Patients with prior exposure to sofosbuvir plus simeprevir achieved an SVR12 rate of 11%, whereas those with prior exposure to a different NS5B and NS3 inhibitor combination achieved an SVR12 rate of 14%. In patients with prior DAA exposure to other unspecified DAA regimens, the SVR12 rate was 2%. All patients treated with sofosbuvir/velpatasvir/voxilaprevir completed study treatment. In the comparator arm, 1 patient discontinued treatment owing to an AE and 1 patient discontinued owing to lack of efficacy. Treatment with sofosbuvir/velpatasvir/voxilaprevir yielded an SVR12 rate of 97% and a *P* value of <.001 for superiority compared with a prespecified 85% performance goal. One patient relapsed, 1 patient died, and 3 patients were lost to follow-up. Treatment with sofosbuvir/velpatasvir yielded an SVR12 rate of 90%, and a *P* value of .092 for superiority. One patient exhibited viral breakthrough, and 14 patients relapsed.

After 12 weeks of treatment, in patients without cirrhosis, SVR12 rates were 98% with sofosbuvir/velpatasvir/voxilaprevir vs 94% with sofosbuvir/velpatasvir. In patients with cirrhosis, SVR12 rates were 96% vs 86%, respectively (Figure 7). After treatment with the 3-drug vs the 2-drug regimen, SVR12 rates were 98% vs 89% in genotype 1a–infected patients, 96% vs 95% in genotype 1b–infected patients, 100% vs 97% in genotype 2–infected patients, and 94% vs 85% in genotype 3–infected patients. In the 19 patients with genotype 4 infection, the 3-drug combination yielded an SVR12 rate of 100%.

In patients without baseline RASs, SVR12 was 94% with voxilaprevir vs 89% without. In patients with baseline RASs, SVR12 was 100% with voxilaprevir vs 90% without. The addition of voxilaprevir yielded SVR12 rates of 100% in patients with baseline RASs

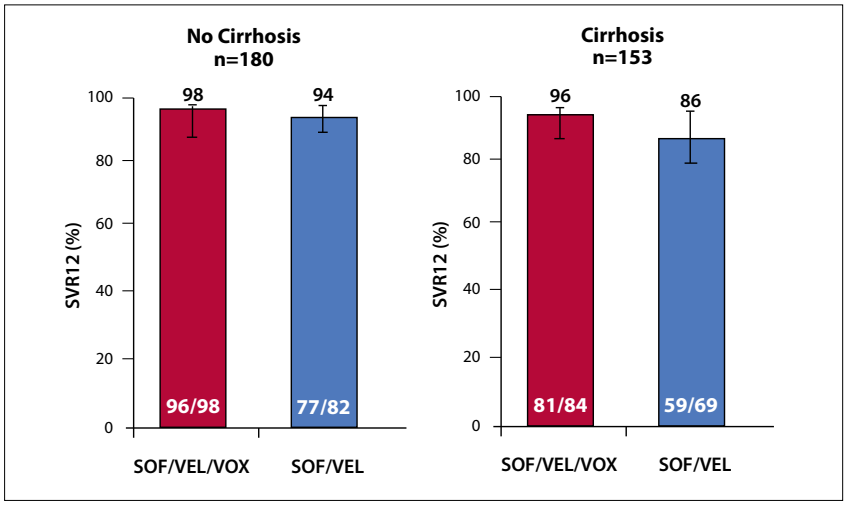

Figure 7. SVR12 according to the presence of cirrhosis in the phase 3 POLARIS-4 trial. POLARIS-4, Safety and Efficacy of SOF/VEL/VOX FDC for 12 Weeks and SOF/VEL for 12 Weeks in DAA-Experienced Adults With Chronic HCV Infection Who Have Not Received an NS5A Inhibitor; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SOF/VEL, sofosbuvir/velpatasvir; SVR12, sustained virologic response at 12 weeks posttreatment. Adapted from Zeuzem S et al. AASLD abstract 109. *Hepatology.* 2016;64(suppl 1):59A.[3]

in NS3 only, NS5A only, or both NS3 and NS5A. Without voxilaprevir, these rates were 91%, 94%, and 50%, respectively. Twenty-two patients had baseline NS5B RASs, and all achieved SVR12. No treatment-emergent RASs were reported in the patient who relapsed after 3-drug treatment. In the cohort of patients treated with sofosbuvir/velpatasvir, 10 of the 15 patients who experienced virologic failure exhibited treatment-emergent Y93H or Y93C.

The triple-therapy treatment was generally well-tolerated. AEs of any grade were reported in approximately three-fourths of patients in either treatment cohort. Grade 3/4 AEs occurred in 2 patients (1%) in each cohort, and serious AEs occurred in 4 patients (2%-3%) in each cohort. No serious AEs were considered treatment-related. The most common AEs of any grade occurring in more than 10% of patients in the 3-drug vs the 2-drug cohort were headache (27% vs 28%), fatigue (24% vs 28%), diarrhea (20% vs 5%), and nausea (12% vs 8%).

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C-ISLE: Grazoprevir/Elbasvir Plus Sofosbuvir in Treatment-Naive and Treatment-Experienced HCV GT3 Cirrhotic Patients Treated for 8, 12 or 16 Weeks

Patients with HCV genotype 3 infection and cirrhosis remain a challenging population.[1] Within this group, treatment-experienced patients and those with baseline NS5A RASs present an even greater treatment challenge. Dr Graham Foster presented findings from the C-ISLE trial (Elbasvir/Grazoprevir [EBR/GZR] and Sofosbuvir [SOF] With and Without Ribavirin [RBV] in Cirrhotic Subjects With Chronic HCV GT3 Infection), which evaluated the combination of daily sofosbuvir (400 mg) plus the fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg), with or without weight-based ribavirin, in patients with HCV genotype 3 infection and cirrhosis.[2] The 3 drugs are already approved for HCV treatment and thus could be implemented immediately for this population. The study design included 5 treatment arms, with a planned enrollment of 25 patients per arm. Patients with or without prior treatment experience were eligible. Treatment-naive patients received 8 weeks of sofosbuvir plus elbasvir/grazoprevir with ribavirin or 12 weeks of this treatment without ribavirin. Treatment-experienced patients received 12 weeks of 3-drug therapy with or without ribavirin or 16 weeks of treatment without ribavirin. The primary endpoint was SVR12. Adult patients with chronic HCV genotype 3 infection were enrolled. Compensated cirrhosis was defined by biopsy or noninvasive testing. Patients could be treatment-naive or could have received treatment with pegylated interferon plus ribavirin. HIV coinfection was permitted. Next-generation sequencing of RASs was performed using a 15% threshold.

ABSTRACT SUMMARY Safety and Efficacy of the Fixed-Dose Combination Regimen of MK-3682/Grazoprevir/MK-8408 in Cirrhotic or Non-Cirrhotic Patients With Chronic HCV GT1 Infection Who Previously Failed a Direct-Acting Antiviral Regimen (C-SURGE)

The multicenter, open-label, randomized, phase 2 C-SURGE trial (Efficacy and Safety of MK-3682B [MK-5172 + MK-3682 + MK-8408] Fixed Dose Combination in Chronic HCV Participants Failing Prior Antiviral Treatment [MK-3682-021]) is evaluating the coformulation of MK-3682 (450 mg)/grazoprevir (100 mg)/ruzasvir (60 mg), known as MK3 (Abstract 193). The ongoing trial enrolled patients with HCV genotype 1 who had previously experienced treatment failure on sofosbuvir/ledipasvir or grazoprevir/elbasvir. Patients were randomly assigned to receive MK3 plus weight-based ribavirin for 16 weeks or MK3 alone for 24 weeks. Preliminary efficacy data were reported. At 8 weeks posttreatment, the SVR rates were 98% for MK3 plus ribavirin for 16 weeks vs 100% for MK3 alone for 24 weeks. One patient in the 16-week treatment arm discontinued treatment after 3 doses of medication, and there were no virologic failures. The presence of baseline RASs had no impact on SVR outcomes. Treatment was generally well-tolerated. There were no discontinuations owing to an AE, and no deaths occurred during the study.

The 100 enrolled patients had a median age of 53 ± 8.7 years, and 68% were male. Cirrhosis was evaluated by transient elastography in 84% of patients, yielding a mean score of 25.4 ± 12.1 kPa. The mean HCV RNA level was 6.2 ± 0.7 $\log_{10}$ IU/mL. The mean platelet count was 148 × 103 cells/μL (range, 46-396 cells/μL), and 24 patients had a platelet count of less than 100 × 10^3 cells/μL.

In treatment-naive patients, 8 weeks of sofosbuvir plus elbasvir/grazoprevir with ribavirin yielded an SVR12 rate of 91%, including 2 relapses, and 12 weeks of 3-DAA therapy without ribavirin yielded an SVR12 rate of 96%, with 1 failure in a patient who did not complete the treatment course. In treatment-experienced patients, 12 weeks of 3-DAA therapy without ribavirin achieved an SVR12 rate of 100%, and the same treatment with ribavirin achieved an SVR12 rate of 94%, with 1 failure in a patient who did not complete treatment. The 16-week regimen of 3-DAAs without ribavirin also yielded an SVR12 rate of 94%, with 1 failure in a patient who did not complete treatment. Approximately half of the study patients had baseline NS5A RASs, and the SVR12 rate was 98% in patients with or without these mutations. One patient with a Y93 RAS in the 8-week treatment arm experienced virologic failure, and 3 patients harboring a Y93 RAS achieved SVR12 with a 12- or 16-week regimen.

No safety signals were raised in this population of cirrhotic patients with HCV genotype 3 infection. In the entire study population, 5 patients experienced a serious AE.

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Eight Weeks Treatment Duration With Ledipasvir/Sofosbuvir (LDV/SOF) Is Effective for Appropriately Selected Patients With Genotype 1 Hepatitis C Virus (HCV) Infection: An Analysis of Multiple Real World Cohorts Totaling >6,500 Patients

Two studies investigated real-world treatment with ledipasvir/sofosbuvir, one in patients with HCV genotype 1 infection[1] and the other in patients coinfected with HIV-1.[2] Based on a post-hoc analysis of data from the ION-3 trial (Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed-Dose Combination ± Ribavirin for the Treatment of HCV), ledipasvir/sofosbuvir for 8 weeks can be considered in treatment-naive patients with HCV genotype 1 infection, no cirrhosis, and a pretreatment HCV RNA level of less than 6,000,000 IU/mL.[3] A study was conducted to evaluate the real-world effectiveness of 8 weeks vs 12 weeks of ledipasvir (90 mg)/sofosbuvir (400 mg) and to evaluate predictors of relapse.[1] The primary analysis included pooled data from treatment-naive adults without cirrhosis identified in the HCV TRIO Health network. A secondary analysis consisted of a systematic review and a random effects meta-analysis of additional real-world cohorts from observational studies to identify any differences between 8 and 12 weeks of treatment. Among the 868 patients in the pooled analysis, virologic outcomes were available for 857, and 798 were considered eligible for 8 weeks of treatment with ledipasvir/sofosbuvir per the indication from the US Food and Drug Administration. Among the 798 patients eligible for 8 weeks of ledipasvir/sofosbuvir, the SVR12 rate was 98.5%. In white, African American, or Hispanic patients, SVR12 rates were 99.1%, 96.5%, and 98.8%, respectively. In patients with genotype 1a or 1b infection, SVR12 rates were 98.3% and 99.2%, respectively. Patients with fibrosis of stage 0, 1, 2, or 3 had SVR12 rates of 100%, 98.3%, 99.6%, and 95.2%, respectively. The SVR12 rate in 18 patients with HIV coinfection was 100%. Sixty-one patients with a viral load of greater than 6,000,000 IU/mL yielded an SVR12 rate of 100%. No variables were associated with relapse, including age, sex, and genotype. Based on the systematic review and meta-analysis of 6 studies, per-protocol SVR12 rates were 95.8% and 97.2% for 8 vs 12 weeks of treatment, respectively. The risk of relapse was similar for both cohorts.

A separate study evaluated the efficacy of ledipasvir/sofosbuvir in patients coinfected with HCV genotype 1 and HIV-1 based on a pooled analysis of patients from clinical trials vs the real world.[2] For the clinical trial population, the pooled analysis included 353 patients from the phase 3 ION-4 study (Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed-Dose Combination for 12 Weeks in Subjects With Chronic Genotype 1 or 4 HCV and HIV-1 Co-Infection), 50 patients from the phase 2b ERADICATE trial (Study of a Combination Pill With GS-7977 and GS-5885 for Hepatitis C

in People With HIV), and 68 patients from the phase 2 Pilot Study to Assess Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination in Treatment Experienced Subjects With Hepatitis C Virus (HCV) Genotype 1 - HIV Co-Infection, conducted in France.[4-6] For the real-world population, the pooled analysis included 150 patients from the TRIO network, 600 from the phase 4 ASCEND study (Study to Assess Community-Based Treatment of Chronic Hepatitis C Monoinfection and Coinfection With HIV in the District of Columbia), 270 from the US Veterans Health Administration, and 211 from the Portuguese Universal Coverage Program to Eradicate Hepatitis C.[7-10] Approximately 20% to 30% of patients in each pooled population had cirrhosis. The pooled analysis yielded SVR12 rates of 97% (428/442) for patients in clinical trials and 94% (688/731) for real-world patients. Patients with negative predictive factors demonstrated high rates of SVR12 in the clinical trial and real-world cohorts. SVR12 rates were 98% vs 97% in treatment-experienced patients, 96% vs 94% in cirrhotic patients, and 93% vs 92% in black patients, respectively.

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Highlights in the Treatment of Hepatitis C Virus From the 2016 AASLD Liver Meeting: Commentary

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Presentations at the 2016 American Association for the Study of Liver Diseases (AASLD) Liver Meeting provided data representing important advances in the treatment of hepatitis C virus (HCV). This may seem surprising since there are now very effective therapies for HCV. It is still possible, however, to improve in certain areas. Many of the studies presented at the meeting attempted to refine the current therapeutic regimens. Other studies evaluated new therapies, with several goals in mind. One goal is to shorten the treatment course to 8 weeks. Most current regimens are administered for 12 weeks, and some patients require 24 weeks. Only a specific group of patients can be cured with 8 weeks of direct-acting antiviral (DAA) therapy with sofosbuvir and ledipasvir.

Another goal of the new therapies is to limit or avoid the use of ribavirin. Ribavirin remains a component of several current therapeutic regimens. Although the use of ribavirin is not onerous for most patients, there are several disadvantages. Ribavirin can cause anemia, so the patient's red blood cell count must be monitored during use. It has teratogenic effects, so pregnancy must be avoided. It is associated with several other side effects leading to poor tolerability in some patients. Regimens that do not require ribavirin are highly sought.

Some of the novel regimens aim to improve response rates in patients who respond poorly to the current DAA therapies. The available regimens have been effective in most patients; the exceptions, depending upon the regimen, include those with renal failure, those with genotype 3, and those who have failed previous treatment with a DAA regimen. For unclear reasons, the worst outcomes with the current regimens are seen in patients with genotype 3 who have cirrhosis or who have already failed interferon α–based regimens. New therapies are being sought to better achieve sustained virologic response (SVR) in these populations.

Lastly, other presentations at the meeting addressed the question of whether the positive results achieved in clinical trials for HCV will extend to real-life scenarios. Several abstracts at The Liver Meeting presented real-

world data, with a focus on identifying factors that predict failure.

Special Populations

Genotype 3

Most of the regimens under evaluation in special populations have not yet been approved in the United States, but they should be within the next year or so. A study by Wyles and colleagues evaluated the combination of 2 new medications: glecaprevir, a protease inhibitor, and pibrentasvir, an NS5A inhibitor.[1] Ribavirin was not a component of this regimen. The study population consisted of approximately 130 patients with genotype 3. For enrollment, treatment-naive patients were required to have cirrhosis. The presence of cirrhosis was not required for treatment-experienced patients. The study had 4 arms. Treatment-naive patients with cirrhosis received 12 weeks of glecaprevir/pibrentasvir. Treatment-experienced patients with cirrhosis received a longer course of 16 weeks. Patients without cirrhosis were randomly assigned to receive 12 or 16 weeks of this combination.

The cure rate with this regimen was 98% in patients who were treatment-naive with cirrhosis. In the population that had received previous treatment and had cirrhosis—those patients with 2 strikes against them—the 16-week regimen achieved an SVR12 of 96%. In the treatment-experienced patients without cirrhosis, SVR12 was 91% after 12 weeks of treatment. There were only 22 patients in that arm, and 2 patients failed. In the treatment-experienced, noncirrhotic patients who received 16 weeks of treatment, the SVR12 rate was 96%. One of the 21 patients in this group did not achieve an SVR12.

This study showed that a regimen of glecaprevir and pibrentasvir, without ribavirin, worked extremely well. A 12-week course of therapy achieved high rates of SVR12 in treatment-naive patients with cirrhosis and in treatment-experienced patients without cirrhosis. In treatment-experienced patients with cirrhosis, 16 weeks of therapy was effective.

Foster and coworkers presented results of the POLARIS-3 trial, which enrolled patients with genotype 3 and cirrhosis.[2] The regimen consisted of sofosbuvir, a polymerase inhibitor; velpatasvir, the most recently approved NS5A inhibitor; and voxilaprevir, a new protease inhibitor. This triple regimen includes DAA agents from each of the 3 classes currently in use against HCV. The study enrolled both treatment-naive and treatment-experienced patients. Sofosbuvir/velpatasvir/voxilaprevir, administered for 8 weeks, was compared against the recently approved regimen of sofosbuvir/velpatasvir given for 12 weeks. Overall, the cure rate was 96% with both the short, 8-week course of triple therapy and the approved 12-week course of sofosbuvir/velpatasvir. With some regimens, patients with genotype 3 may have lower cure rates when they have baseline resistance-associated substitutions (RASs). In this study, however, the presence of RASs did not impact response rates. Treatment-naive genotype 3 patients with cirrhosis had a cure rate of 96% with sofosbuvir/velpatasvir/voxilaprevir vs 99% with the currently available sofosbuvir/velpatasvir regimen. Among treatment-experienced patients, SVR12 was 99% with the new 8-week regimen of sofosbuvir/velpatasvir/voxilaprevir, vs only 91% for the sofosbuvir/velpatasvir 12-week regimen. This study showed that this new 8-week, triple-therapy regimen is highly effective in genotype 3 patients with cirrhosis, regardless of whether they had received previous treatment.

Patients with HCV genotype 3 and cirrhosis, who were treatment-experienced or treatment-naive, were enrolled in the C-ISLE trial, also presented by Foster and colleagues.[3] This study evaluated sofosbuvir (a polymerase inhibitor), grazoprevir (a protease inhibitor), and elbasvir (an NS5A inhibitor), with or without ribavirin. There were 5 treatment arms enrolling 100 patients. The treatment-naive patients received elbasvir/grazoprevir/sofosbuvir with or without ribavirin for 12 weeks. The cure rates were 96% without ribavirin and 91% with ribavirin. The treatment-experienced population, a more challenging group, was divided among the other 3 treatment arms. Elbasvir/grazoprevir/sofosbuvir administered without ribavirin for 12 weeks achieved an SVR12 rate of 100%. SVR12 was lower (94%) when this new regimen was administered with ribavirin for 12 weeks and without ribavirin for 16 weeks. Therefore, 12 weeks of this triple-therapy regimen, without ribavirin, in treatment-naive or treatment-experienced genotype 3 patients with cirrhosis was effective. However, it would be difficult to administer this regimen at present because it is not currently approved for this indication, and costs would be high.

Renal Impairment

Gane and colleagues evaluated patients with HCV and renal impairment in the EXPEDITION-IV trial.[4] Treatment consisted of 12 weeks of glecaprevir and pibrentasvir, without ribavirin. The study enrolled 104 patients and included genotypes 1 through 6. Most patients had genotypes 1 (n=54), 2 (n=17), 3 (n=11), or 4 (n=20). Genotypes 5 and 6 were represented by 1 patient each. This open-label, single-arm study enrolled patients with severe renal insufficiency or who were on dialysis. Among the 88% of patients with stage 5 chronic kidney disease, most were receiving dialysis. The remaining 12% of patients had stage 4 chronic kidney disease. Cirrhosis was reported in 20% of patients, and 42% were treatment-experienced. In this challenging patient population, 98% achieved an SVR12. Among the 2 patients who did not, 1 patient died from massive intracerebral hemorrhage secondary to uncontrolled hypertension, and 1 patient discontinued treatment for nonvirologic reasons. The per-protocol SVR12 rate was 100%. This important study suggests that glecaprevir and pibrentasvir will be highly effective in patients with renal failure.

Patients Who Did Not Respond to Previous DAA Therapy

The POLARIS-1 trial evaluated the new combination of sofosbuvir/velpatasvir/voxilaprevir in patients who were not cured by previous treatment with a DAA regimen that included an NS5A inhibitor, such as sofosbuvir/ledipasvir, sofosbuvir/daclatasvir, or ombitasvir/paritaprevir/ritonavir with dasabuvir.[5] Patients could have genotypes 1 through 6, with or without cirrhosis. There were 150 patients with genotype 1, 5 with genotype 2, 78 with genotype 3, 22 with genotype 4, 1 with genotype 5, and 6 with genotype 6. In 1 patient, the genotype was unknown. This large trial is one of few with a placebo arm. Patients with genotype 1 were randomly assigned to receive 12 weeks of sofosbuvir/velpatasvir/voxilaprevir (n=150) or 12 weeks of placebo (n=152). The other 113 non–genotype 1 patients were assigned to the open-label treatment arm. Overall, the SVR12 rate was 96% in the treatment group. Among the 10 patients who did not achieve an SVR12, 7 relapsed and 3 had nonvirologic reasons for the failure. SVR12 was 97% in genotype 1 patients and 95% in genotype 3 patients. Among patients without cirrhosis, SVR12 was 99% overall and 100% in the per-protocol analysis. In cirrhotic patients, SVR12 was 93% overall. These data are very encouraging for patients not cured by initial DAA therapy, and the regimen should be available in mid to late 2017.

The POLARIS-4 trial evaluated the same regimen, but in patients who had failed a DAA regimen that did not include an NS5A inhibitor.[6] For example, patients could have received treatment with sofosbuvir and simeprevir (a protease inhibitor). Although patients with genotypes 1 through 6 were eligible, no patients with genotypes 5 or 6 enrolled. The study included 333 patients. They received treatment either with 12 weeks of sofosbuvir/velpatasvir/voxilaprevir or with the currently approved regimen sofosbuvir/velpatasvir. The SVR12 rate was 97% among the patients treated with sofosbuvir/velpatasvir/voxilaprevir (n=182) vs 90% in the patients treated with sofosbuvir/velpatasvir (n=151). Among patients with cirrhosis, SVR12 was 96% in those receiving sofosbuvir/velpatasvir/voxilaprevir (n=84) vs 86% in those receiving sofosbuvir/velpatasvir (n=69). These are promising data in patients who failed a DAA regimen without an NS5A inhibitor.

Wyles and coworkers evaluated another novel treatment in patients not cured by DAA therapy.[7] The regimen consisted of grazoprevir plus 2 new therapies: an NS5A inhibitor known as ruzasvir and a polymerase inhibitor called MK-3682. This triple-therapy regimen has agents from each of the 3 classes of DAAs. Patients did or did not have cirrhosis. The 93 patients were assigned to 1 of 2 arms: triple therapy with ribavirin for 16 weeks or triple therapy without ribavirin for 24 weeks.

This preliminary report provided rates of SVR8, which was 98% in the 44 patients who received triple therapy plus ribavirin for 16 weeks vs 100% in the 30 patients who received triple therapy without ribavirin for 24 weeks. Therefore, the addition of ribavirin was not beneficial, and 16 weeks of treatment was no worse than 24 weeks. This study showed that this new triple-therapy regimen for 16 weeks, without ribavirin, was very effective in patients who have failed an initial course of DAA therapy.

New Regimens

Shorter Duration of Therapy

Zeuzem and colleagues presented results from the ENDURANCE-1 trial, which evaluated 8 weeks of glecaprevir and pibrentasvir in genotype 1 patients without cirrhosis.[8] Patients could be treatment-naive or treatment-experienced. Patients with human immunodeficiency virus (HIV) coinfection were eligible. This large trial enrolled 703 patients, including 4% to 5% with HIV. Overall, slightly less than 10% had stage 2 fibrosis, and slightly less than 10% had stage 3 fibrosis. The study compared treatment durations of 8 weeks (n=352) vs 12 weeks (n=351). The cure rate was over 99%. Among the 4 patients who did not achieve an SVR12, 3 were lost to follow-up or discontinued for nonvirologic reasons. Only 1 patient (genotype 1a and treatment-experienced) of 703 was considered to have relapsed. The cure rates were over 99% in the intent-to-treat group and over 99% per protocol. This study, therefore, showed extremely impressive rates of SVR12 with only 8 weeks of therapy in noncirrhotic, genotype 1 patients, regardless of whether they had received previous treatment, had HIV coinfection, or had stage 2 or stage 3 fibrosis.

Jacobson and coworkers presented the POLARIS-2 trial, which compared 8 weeks of sofosbuvir/velpatasvir/voxilaprevir vs 12 weeks of sofosbuvir/velpatasvir in genotype 1 through 6 patients with or without cirrhosis.[9] This study enrolled 941 patients to determine whether the new regimen was noninferior to the existing regimen. SVR12 was 95% with sofosbuvir/velpatasvir/voxilaprevir for 8 weeks vs 98% with sofosbuvir/velpatasvir for 12 weeks. Therefore, the new treatment was not noninferior to the existing treatment. The higher relapse rate in the sofosbuvir/velpatasvir/voxilaprevir arm was largely due to more relapses in genotype 1a patients. Among patients without cirrhosis, SVR12 was 96% for the 8-week arm vs 98% for the 12-week arm. The difference was large among patients with cirrhosis, at 91% in the 8-week arm and 99% in the 12-week arm.

It appears, therefore, that 8 weeks of sofosbuvir/velpatasvir/voxilaprevir cannot replace the current 12-week regimen of sofosbuvir/velpatasvir. In patients without cirrhosis, it may be possible to shorten therapy to 8 weeks. For patients with cirrhosis, however, the current treatment regimen of sofosbuvir/velpatasvir for 12 weeks is superior to the 8-week triple regimen.

A study presented by Lawitz and coworkers evaluated a triple regimen consisting of grazoprevir, the new

NS5A inhibitor ruzasvir, and the new polymerase inhibitor MK-3682, with or without ribavirin.[10] The study enrolled 664 patients with genotypes 1, 2, or 3. Genotype 1 and 2 patients were treatment-naive, and patients with genotype 3 could be treatment-naive or treatment-experienced. HCV genotype 1 patients were randomly assigned to receive triple therapy without ribavirin for 8 or 12 weeks. Patients with genotypes 2 or 3 were randomized to receive triple therapy with or without ribavirin for 8 or 12 weeks. The study found that the SVR rates for 12 weeks were 97% or higher. Ribavirin was unnecessary with this triple regimen. SVR12 for 8 weeks of treatment ranged from 86% to 98%. Among the patients who received 16 weeks of treatment, SVR12 was 100% for those with genotype 2 and 96% for those with genotype 3. The results from this study suggested that it is not possible to reduce treatment to 8 weeks; rather, 12 weeks is the optimal duration for this triple regimen.

Real-Life Analyses

There were several real-world analyses presented at The Liver Meeting, and the one by Sundaram and colleagues was among the most important.[11] A major question for practitioners who care for patients with chronic HCV is whether the 8-week regimen of sofosbuvir/ledipasvir will be as efficacious in real-life as it was in the pivotal ION-3 trial.[12] This clinical trial showed that 8 weeks of sofosbuvir/ledipasvir was effective in genotype 1 patients who were treatment-naive, did not have cirrhosis, and had a baseline viral load of less than 6,000,000 IU/mL. Some practitioners have worried, however, that perhaps 12 weeks is better than 8 weeks in real life. The study by Sundaram included 2 different analyses. The primary analysis was performed in 798 patients from various databases who had received 8 weeks of sofosbuvir and ledipasvir. The study confirmed that these patients were appropriate candidates for the 8-week therapy, and the cure rate was 98%; 786 of the 798 patients achieved an SVR12. These rates are similar to those observed in the ION-3 trial.[12] The study was unable to identify any factors predictive of treatment failure, including characteristics such as genotype 1a or 1b, stage of fibrosis, HIV status, age, and race. The secondary analysis of the study examined a more robust number of databases, which included more than 5600 patients, to identify any differences in outcome for patients treated for 12 weeks vs 8 weeks. The study found no differences; SVR12 was 96% in the 8-week treatment arm and 97% in the 12-week treatment arm. The study suggests that 8 weeks of therapy should suffice in appropriately chosen patients.

Conclusion

The 2016 AASLD Liver Meeting featured HCV presentations confirming that an 8-week regimen of sofosbuvir and ledipasvir is effective in appropriately selected patients—those who are treatment-naive, without cirrhosis, and with a baseline viral load of less than 6,000,000 IU/mL—in a real-life setting. Furthermore, many studies presented data on new DAA regimens that seek to improve features of the current approaches. In particular, additional regimens are forthcoming that will not require ribavirin. Eight-week regimens may be available for an expanded group of patients. Encouraging data were also presented for new regimens administered to HCV patients with renal failure, those with genotype 3, and those who had previously failed DAA regimens. HCV therapy continues to be refined, and populations of patients that represent unmet medical needs are being addressed.

Disclosure

Dr Flamm has performed research for Gilead, AbbVie, and BMS. He is a consultant for Gilead, AbbVie, BMS, and Merck.

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