GASTROENTEROLOGY & HEPATOLOGY
The Independent Peer-Reviewed Journal

June 2016 Volume 12, Issue 6, Supplement 2

***A SPECIAL MEETING REVIEW EDITION***

# Advances in the Treatment of Hepatitis C Virus Infection From the 2016 EASL Meeting

## The Annual Meeting of the European Association for the Study of the Liver • April 13–17, 2016 • Barcelona, Spain

**Special Reporting on:**

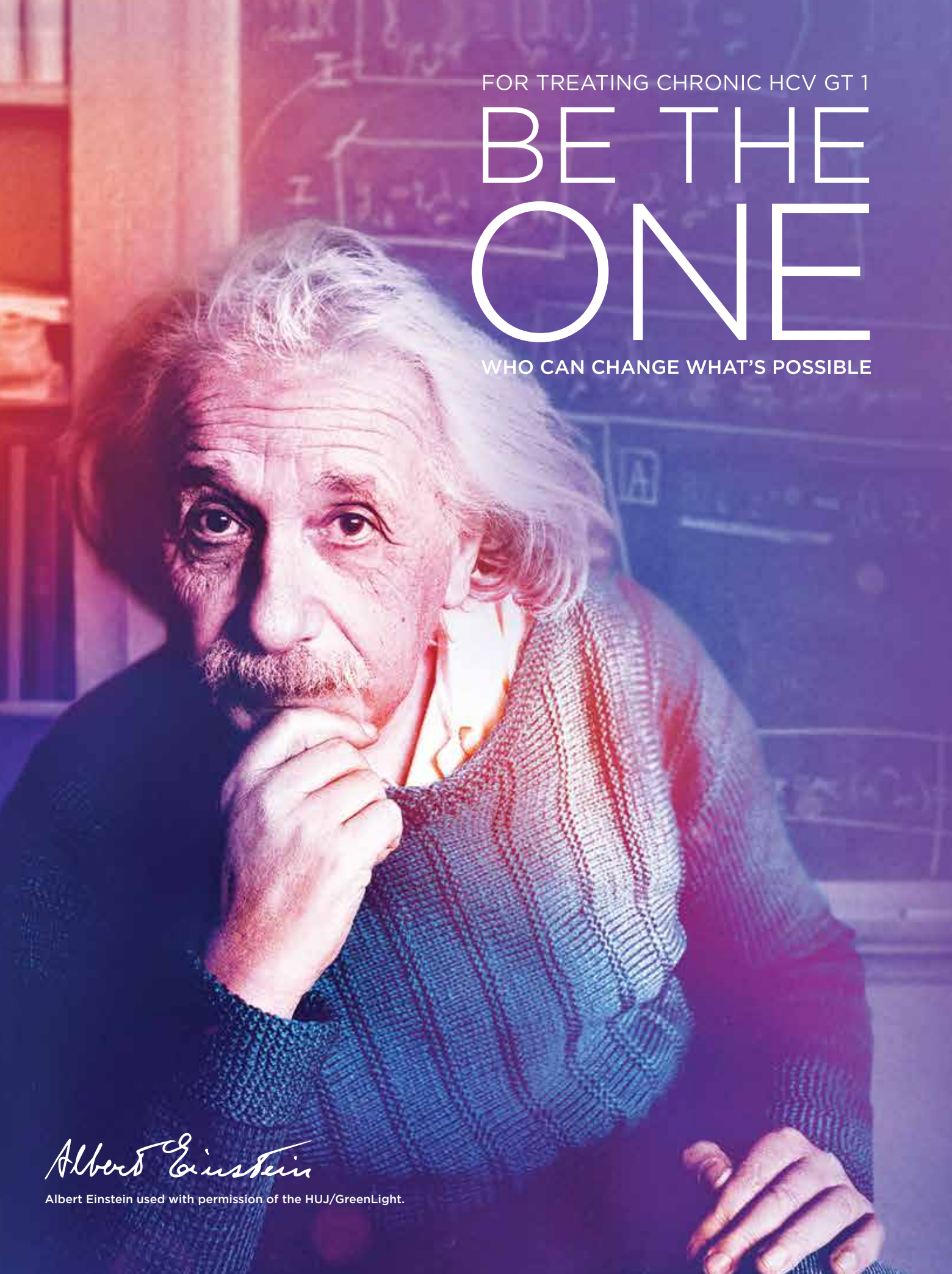
- Six Weeks of Sofosbuvir/Ledipasvir (SOF/LDV) Are Sufficient to Treat Acute Hepatitis C Virus Genotype 1 Monoinfection: The HepNet Acute HCV IV Study
- Treatment of Hepatitis C Virus in Patients With Advanced Cirrhosis: Always Justified? Analysis of the HEPA-C Registry
- High Efficacy of Sofosbuvir/Velpatasvir Plus GS-9857 in Previously Treated Patients With HCV Genotypes 1 Through 6
- Prevalence and Impact of Baseline Resistance-Associated Variants (RAVs) on the Efficacy of Ledipasvir/Sofosbuvir or Simeprevir/Sofosbuvir Against GT1 HCV Infection: HCV-TARGET Interim Analysis
- Sofosbuvir/Velpatasvir for 12 Weeks in Patients Coinfected With HCV and HIV-1: The ASTRAL-5 Study
- 100% SVR12 With ABT-493 and ABT-530 With or Without Ribavirin in Treatment-Naive HCV Genotype 3–Infected Patients With Cirrhosis

**PLUS Meeting Abstract Summaries**

**With Expert Commentary by:**
**Steven L. Flamm, MD**
Chief, Liver Transplantation Program
Professor of Medicine and Surgery
Northwestern University Feinberg School of Medicine
Chicago, Illinois

**ON THE WEB:**
**gastroenterologyandhepatology.net**

Indexed through the National Library of Medicine (PubMed/Medline), PubMed Central (PMC), and EMBASE




Albert Einstein used with permission of the HUJ/GreenLight.

## HARVONI DELIVERED HIGH CURE (SVR) RATES IN SUBJECTS WITH HCV/HIV-1 CO-INFECTION[1,a]


### OVERALL CURE RATE IN GT 1 OR 4 HCV/HIV-1 CO-INFECTED SUBJECTS[1,a]

**ION-4** (n=321/335)

- HARVONI delivered consistently high cure rates regardless of prior HCV treatment experience or cirrhosis status (94% in subjects with cirrhosis and 98% in treatment-experienced subjects with cirrhosis)[1]
- The safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects. See the Drug Interactions section of the HARVONI Prescribing Information for potentially significant drug interactions with HIV antiretrovirals[1]
- For patients with HCV/HIV-1 co-infection, follow the dosage recommendations listed on the next page[1]

[a]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.[2]

**Study Design[1]**

**ION-4:** an open-label trial that included GT 1 and 4 treatment-naïve and treatment-experienced subjects (N=335) with HCV/HIV-1 co-infection with or without cirrhosis. Subjects received HARVONI for 12 weeks. Treatment-experienced subjects had failed prior treatment with Peg-IFN + RBV, Peg-IFN + RBV + an HCV protease inhibitor, or sofosbuvir + RBV. None of the 8 GT 4 subjects had cirrhosis. Subjects were on a stable HIV-1 antiretroviral therapy that included emtricitabine + tenofovir disoproxil fumarate, administered with efavirenz, rilpivirine, or raltegravir.

## INDICATION

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.

## IMPORTANT SAFETY INFORMATION

### CONTRAINDICATIONS

- If HARVONI 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 Coadministered with Amiodarone:** Amiodarone is not recommended for use with HARVONI 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.

**Please see Brief Summary of full Prescribing Information on the following pages.**

HARVONI®
ledipasvir/sofosbuvir
90 mg/400 mg tablets

## HARVONI IS THE ONLY SINGLE-TABLET REGIMEN FOR HCV GT 1 PATIENTS BUILT ON A SOFOSBUVIR BACKBONE[1]

**1**

**1 TABLET ONCE A DAY**
**WITHOUT IFN OR RBV**

**1**

**Recommended treatment duration for HARVONI[1]**

| | | |
|---|---|---|
| **GT 1** | **8 weeks** | Can be considered in TN patients without cirrhosis who have pre-treatment HCV RNA <6 million IU/mL |
| | **12 weeks** | TN patients with or without cirrhosis |
| | | TE patients without cirrhosis |
| | **24 weeks** | TE patients with cirrhosis[a] |
| **GT 4, 5, 6** | **12 weeks** | TN and TE patients with or without cirrhosis |

- The dosing information listed here does not include patients with decompensated cirrhosis (Child-Pugh B or C) or liver transplant recipients
- For patients with HCV/HIV-1 co-infection, follow the dosage recommendations listed above. Refer to the Drug Interactions section of the HARVONI Prescribing Information for dosage recommendations for concomitant HIV-1 antiviral drugs[1]
- Each HARVONI tablet contains 90 mg of ledipasvir and 400 mg of sofosbuvir[1]

[a]HARVONI + RBV for 12 weeks can be considered in TE GT 1 patients with cirrhosis who are eligible for RBV. The daily dosage of RBV is weight-based (1000 mg for patients <75 kg and 1200 mg for those ≥75 kg) administered orally in 2 divided doses with food. Refer to the RBV prescribing information.

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

## HARVONI DELIVERED HIGH CURE (SVR) RATES IN A BROAD RANGE OF GT 1 SUBJECTS[1,b]

**97%**

**OVERALL CURE RATE ACROSS THREE HARVONI PHASE 3 TRIALS[1,3-5,b]**
(n=1042/1079)

- Overall cure rates were 94%-99% across three HARVONI Phase 3 trials[1]
- The HARVONI clinical trial program enrolled the most challenging subjects, regardless of GT 1a or 1b subtype, prior experience with HCV therapy, or presence of cirrhosis[1]

[b]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.[2]

**Study Designs[1]**
**ION-3:** a randomized, open-label trial in GT 1 treatment-naïve subjects (N=647) without cirrhosis. Subjects were randomized in a 1:1:1 ratio to receive HARVONI for 8 weeks, HARVONI + RBV for 8 weeks, or HARVONI for 12 weeks. **ION-1:** a randomized, open-label trial in GT 1 treatment-naïve subjects (N=865) with or without cirrhosis. Subjects were randomized in a 1:1:1:1 ratio to receive HARVONI for 12 weeks, HARVONI + RBV for 12 weeks, HARVONI for 24 weeks, or HARVONI + RBV for 24 weeks. **ION-2:** a randomized, open-label trial in GT 1 treatment-experienced subjects (N=440) with or without cirrhosis. Subjects were randomized in a 1:1:1:1 ratio to receive HARVONI for 12 weeks, HARVONI + RBV for 12 weeks, HARVONI for 24 weeks, or HARVONI + RBV for 24 weeks.

## IMPORTANT SAFETY INFORMATION

### WARNINGS AND PRECAUTIONS (continued)

- **Risk of Reduced Therapeutic Effect of HARVONI Due to P-gp Inducers:** Rifampin and St. John's wort are not recommended for use with HARVONI as they may significantly decrease ledipasvir and sofosbuvir plasma concentrations.
- **Related Products Not Recommended:** HARVONI is not recommended for use with other products containing sofosbuvir.

FOR TREATING CHRONIC HCV GT 1

BE THE ONE WHO CAN CHANGE WHAT'S POSSIBLE.
GO TO **HCP.HARVONI.COM/J2**

## HARVONI WAS SAFE WITH LOW RATES OF DISCONTINUATIONS AND ADVERSE EVENTS (AEs) ACROSS CLINICAL TRIALS[1,3-5]

**≤1%** **DISCONTINUATIONS DUE TO AEs[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]
- No hematologic monitoring or dose adjustments are required with HARVONI[1]

## MORE THAN 200,000 PATIENTS HAVE BEEN PRESCRIBED HARVONI IN THE US[6,c]

**#1** **HARVONI IS THE #1 PRESCRIBED TREATMENT FOR HCV GT 1 IN THE US[7,8,d]**

[c]This information is derived from IMS NPA™, IMS NSP™, and IntegriChain® data; data reflect estimated patient starts for HARVONI from October 2014–November 2015.

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

## HELP YOUR PATIENTS GET STARTED ON HARVONI WITH SUPPORT PATH®

Support Path is a suite of resources that assists with benefits investigations and prior authorizations, and identifies potential financial assistance for patients, such as the HARVONI co-pay coupon program

## IMPORTANT SAFETY INFORMATION

### ADVERSE REACTIONS

Most common (≥10%, all grades) adverse reactions were fatigue, headache and asthenia.

### DRUG INTERACTIONS

- In addition to rifampin and St. John's wort, coadministration of HARVONI is also not recommended with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, and tipranavir/ritonavir. Such coadministration is expected to decrease the concentration of ledipasvir and sofosbuvir, reducing the therapeutic effect of HARVONI.
- Coadministration of HARVONI is not recommended with simeprevir due to increased concentrations of ledipasvir and simeprevir. Coadministration is also not recommended with rosuvastatin or co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate due to increased concentrations of rosuvastatin and tenofovir, respectively.

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

**Please see Brief Summary of full Prescribing Information on the following pages.**

HARVONI®
ledipasvir/sofosbuvir
90 mg/400 mg tablets

## 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 ribavirin (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 ribavirin. 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. Ribavirin 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 ribavirin or pegylated interferon/ribavirin 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 + ribavirin 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 + ribavirin 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 ribavirin or peginterferon/ribavirin 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:** There are no adequate and well-controlled studies in pregnant women. Consider the benefits and risks of HARVONI when prescribing to a pregnant woman. 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.

**Lactation:** It is not known if HARVONI and its metabolites are secreted in human breast milk. 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.

**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.

**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).

**References: 1.** HARVONI US full Prescribing Information. Gilead Sciences, Inc. Foster City, CA. February 2016. **2.** 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. October 2013. **3.** Afdhal N, Zeuzem S, Kwo P, et al; for the ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med.* 2014;370(20):1889-1898. **4.** Kowdley KV, Gordon SC, Reddy KR, et al; for the ION-3 Investigators. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med.* 2014;370(20):1879-1888. **5.** Afdhal N, Reddy KR, Nelson DR, et al; for the ION-2 Investigators. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med.* 2014;370(16): 1483-1493. **6.** Data on file. HARVONI Patient Starts from October 2014–November 2015. Gilead Sciences, Inc. **7.** Data on file. IMS Weekly National Prescription Audit (NPA) Market Dynamics, 11/14/14–1/1/16. Gilead Sciences, Inc. **8.** Data on file. HCV Weekly Sales Reports, 11/14/14–1/1/16. Gilead Sciences, Inc.

GILEAD

# Six Weeks of Sofosbuvir/Ledipasvir (SOF/LDV) Are Sufficient to Treat Acute Hepatitis C Virus Genotype 1 Monoinfection: The HepNet Acute HCV IV Study

Regimens incorporating direct-acting antiviral (DAA) agents are the standard of care in the treatment of patients with chronic hepatitis C virus (HCV) infection. DAA regimens have rapidly supplanted interferon-based regimens for most HCV patients, thereby avoiding the majority of toxicities associated with interferon while yielding high rates of sustained virologic response (SVR). In the first study by the HepNet Acute HCV Study Group, from 2001, early treatment with 6 months of interferon α-2b resulted in undetectable levels of HCV in 98% of patients with acute infection.[1] Subsequent studies demonstrated high SVR rates with pegylated interferon and highlighted the importance of early treatment of all infections, despite the spontaneous viral clearance seen in some patients.[2,3] To further increase response rates achieved with DAAs, regimens are being optimized for specific patient populations, and second-generation DAAs are under development. New combinations and shorter-duration regimens are actively being explored to reduce costs and maximize patient compliance.

The HepNet Acute HCV IV Study Group trial evaluated the fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) given for 6 weeks to adults with acute HCV genotype 1 infection.[4] Sofosbuvir is a nucleotide analogue that inhibits activity of the NS5B polymerase, resulting in chain termination.[5] Ledipasvir inhibits the nonstructural protein 5A (NS5A) and is approved in combination with sofosbuvir.[6] Acute HCV infection was identified based on known or suspected exposure to HCV within the preceding 4 months, documented seroconversion to HCV positivity, and/or an alanine transaminase (ALT) level of more than 10 times the upper limit of normal. All patients had detectable plasma HCV RNA and compensated liver disease. Patients with coinfection or ongoing drug use were excluded. The single-arm trial included 20 patients enrolled at 10 treatment centers in Germany from November 2014 through October 2015. Patients had a mean age of 46 years (range, 23-63 years), and 60% were male. Fifty-five percent had genotype 1a infection. The mean ALT level was 463 U/L (range, 32-2716 U/L), and the mean bilirubin level was 24 mg/dL.

All of the study patients completed 6 weeks of antiviral treatment. At week 6 of treatment, 100% of patients had undetectable HCV RNA, and this result was reiterated at week 12 of follow-up, yielding an SVR12 of 100% (Figure 1). No correlation was observed between baseline viral load and rapid viral response, and patients with the highest baseline viral load experienced a complete viral response with 6 weeks of treatment (Figure 2). However, patients who still had detectable HCV RNA at treatment week 4 were among those with a higher baseline viral load. Treatment elicited a rapid biochemical response, with ALT levels falling noticeably during the first 2 weeks of treatment, and 90% of patients demonstrating a normal ALT level at follow-up week 12. Of the 6 patients with elevated bilirubin at baseline, 100% showed normalized bilirubin levels at week 6 of treatment, with bilirubin levels rising


### ABSTRACT SUMMARY Retreatment of Patients Who Failed DAA-Combination Therapies: Real-World Experience From a Large Hepatitis C Resistance Database

In phase 3 clinical trials of DAAs, as many as 7% of HCV patients have experienced virologic failure. These numbers are expected to increase outside of the clinical trial setting, and effective retreatment regimens have yet to be defined. A clinical study was conducted to examine the role of RAVs on retreatment outcomes in patients who have failed initial DAA treatment (Abstract PS103). Patients who failed guideline-recommended, interferon-free DAA combination therapies were identified from a German HCV resistance database of 3549 patients. Postfailure serum samples were analyzed for the presence of NS3, NS5A, and NS4B RAVs by direct sequencing, and patients were re-treated based on RAV findings. Among the 310 patients who failed DAA therapy, drug class–specific RAVs were detected in 90% of patients with HCV genotype 1 and 39% of patients with genotype 3. Retreatment with an NS5A-directed DAA regimen was initiated in 22 patients who had failed treatment with sofosbuvir plus simeprevir and who did not have NS5A RAVs at baseline. Interim analysis showed an SVR12 rate of 91% in these patients after retreatment. Among 7 patients who had failed NS5A-directed therapy and had no NS3-associated RAVs, retreatment with a protease inhibitor–containing regimen yielded an interim SVR12 rate of 86%. In 7 patients with HCV genotype 3 who had failed treatment with sofosbuvir plus ribavirin, retreatment with a regimen containing an NS5A-directed DAA yielded an SVR12 rate of 100%.

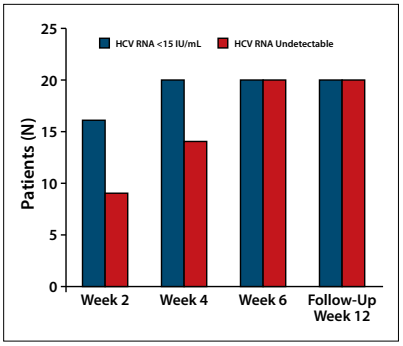



**Figure 1.** Virologic response in a study evaluating sofosbuvir/ledipasvir in 20 patients with acute HCV genotype 1 monoinfection.

HCV, hepatitis C virus. Adapted from Deterding K et al. EASL abstract LB08. *J Hepatol*. 2016;64(suppl 2).[4]

above normal by follow-up week 12 in 2 patients in the entire study population. Through follow-up week 12, there were 22 reports of adverse events (AEs) considered possibly or probably related to study treatment, including gastrointestinal symptoms in 4 patients; fatigue in 3; hair loss in 3; and headache, skin reaction, abdominal pain, and psychiatric disorders, each occurring in 2 patients. One serious AE was reported but was considered unrelated to study treatment. Future studies examining 6 weeks of treatment with the ledipasvir/sofosbuvir combination in other HCV genotypes will be of interest.

## References

1. Jaeckel E, Cornberg M, Wedemeyer H, et al; German Acute Hepatitis C Therapy Group. Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med*. 2001;345(20):1452-1457.
2. Wiegand J, Buggisch P, Boecher W, et al; German HEP-NET Acute HCV Study Group. Early monotherapy with pegylated interferon alpha-2b for acute hepatitis C infection: the HEP-NET acute-HCV-II study. *Hepatology*. 2006;43(2):250-256.
3. Deterding K, Grüner N, Buggisch P, et al; HepNet Acute HCV-III Study Group. Delayed versus immediate treatment for patients with acute hepatitis C: a randomised controlled non-inferiority trial. *Lancet Infect Dis*. 2013;13(6):497-506.
4. Deterding K, Spinner C, Schott E, et al. Six weeks of sofosbuvir/ledipasvir (SOF/LDV) are sufficient to treat acute hepatitis C virus genotype 1 monoinfection: the HepNet Acute HCV IV study [EASL abstract LB08]. *J Hepatol*. 2016;64(suppl 2).
5. Sovaldi [package insert]. Foster City, CA: Gilead Sciences, Inc; 2015.
6. Harvoni [package insert]. Foster City, CA: Gilead Sciences, Inc; 2016.

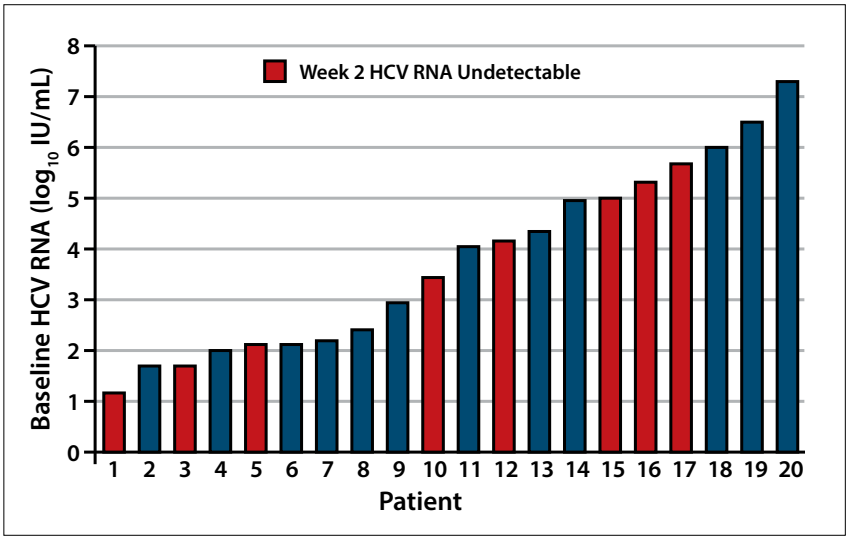



**Figure 2.** Baseline HCV RNA and early virologic response in a study evaluating sofosbuvir/ledipasvir in 20 patients with acute HCV genotype 1 monoinfection.

HCV, hepatitis C virus. Adapted from Deterding K et al. EASL abstract LB08. *J Hepatol*. 2016;64(suppl 2).[4]

### ABSTRACT SUMMARY High Efficacy of ABT-493 and ABT-530 in HCV Genotype 1 Infected Patients Who Have Failed Direct-Acting Antiviral-Containing Regimens: The MAGELLAN-1 Study

The open-label, randomized, phase 2 MAGELLAN-1 (A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of ABT-493 and ABT-530 With and Without Ribavirin in Adults With HCV Who Failed a Prior DAA Containing Therapy) trial evaluated 12 weeks of treatment with ABT-493 plus ABT-530 with or without ribavirin in noncirrhotic patients with HCV genotype 1 infection who had failed prior treatment with DAA therapy (Abstract GS11). A regimen of ABT-493 at 300 mg plus ABT-530 at 120 mg was administered without ribavirin to 22 patients and with ribavirin to another 22 patients. Recruitment to an arm examining ABT-493 at 200 mg plus ABT-530 at 80 mg (without ribavirin) was halted after enrollment of 6 patients based on data from dose-finding trials, but results were still presented. Prior treatment regimens included protease inhibitors in 84% and NS5A inhibitors in 50%. Using a 1% detection threshold, 82% of patients had NS3 and/or NS5A RAVs at baseline. Three patients were lost to follow-up: 1 receiving ABT-493 at 300 mg and ABT-530 at 120 mg, with ribavirin; and 2 receiving that regimen without ribavirin. These 3 patients had achieved an SVR at week 6 or 8. Excluding these patients from the analysis yielded SVR12 rates of 100% in the low-dose treatment arm and 95% in the higher-dose treatment arms, with or without ribavirin. One patient in the higher-dose, nonribavirin arm experienced virologic breakthrough. This patient had Crohn's disease and baseline NS3 and NS5A RAVs. One patient in the ribavirin-containing arm relapsed, and this patient had previously received 2 treatment courses with DAAs. The 6 patients without baseline RAVs achieved an SVR12 rate of 100%. In patients with baseline RAVs, SVR12 rates were 100% in the 15 patients with NS3 RAVs alone, 90% in the 10 patients with NS5A RAVs alone, and 94% in the 16 patients harboring both NS3 and NS5A RAVs. The most common AEs of any grade were headache, fatigue, and nausea, most of which were mild in severity. There were no reports of treatment-related serious AEs, discontinuations due to an AE, or grade 3/4 laboratory abnormalities.

# Treatment of Hepatitis C Virus in Patients With Advanced Cirrhosis: Always Justified? Analysis of the HEPA-C Registry

Many trials of DAAs have demonstrated efficacy in patients with compensated cirrhosis. However, optimal DAA regimens have yet to be defined for patients with HCV and decompensated cirrhosis.[1] Ribavirin tolerability and renal insufficiency remain problematic in patients with decompensation, and the long-term effects of DAA treatments in these patients are unknown. Several recent trials of various DAA combinations have demonstrated high rates of SVR12 in patients with HCV infection and decompensated cirrhosis.[2-4] A key area of interest is identifying baseline patient characteristics that predict response to DAA treatment.

An analysis of the Spanish Hepa-C registry evaluated the risks and benefits of DAA treatment in 843 patients with advanced liver disease.[5] Patients had clinical symptoms resulting from advanced cirrhosis. They were not permitted to undergo liver transplant while receiving study treatment or during the 12 weeks afterward. The study included 564 patients with a Child-Turcotte-Pugh (CTP) score of A and 175 patients with a CTP score of B or C. Two-thirds of patients were male, and the median age was approximately 57 years (range, 24-82 years). In the CTP A vs CTP B/C cohorts, baseline characteristics included albumin levels of 4 g/dL vs 3.2 g/dL (*P*<.001); bilirubin levels of 1 mg/dL vs 2.1 mg/dL (*P*<.001); platelet levels of 104 × $10^3$/µL vs 62 × $10^3$/µL (*P*<.001); and model for end-stage liver disease (MELD) scores of 8 vs 13 (*P*<.001). Among patients with HCV genotype 3, 7% had CTP A and 13% had CTP B/C. Among the HCV genotype 1 patients, 63% had CTP A and 62% had CTP B/C.

All patients were treated with interferon-free regimens. The most common treatments were sofosbuvir/simeprevir (45%), sofosbuvir/daclatasvir (22%), and sofosbuvir/ledipasvir (16%). The majority of patients also received ribavirin.

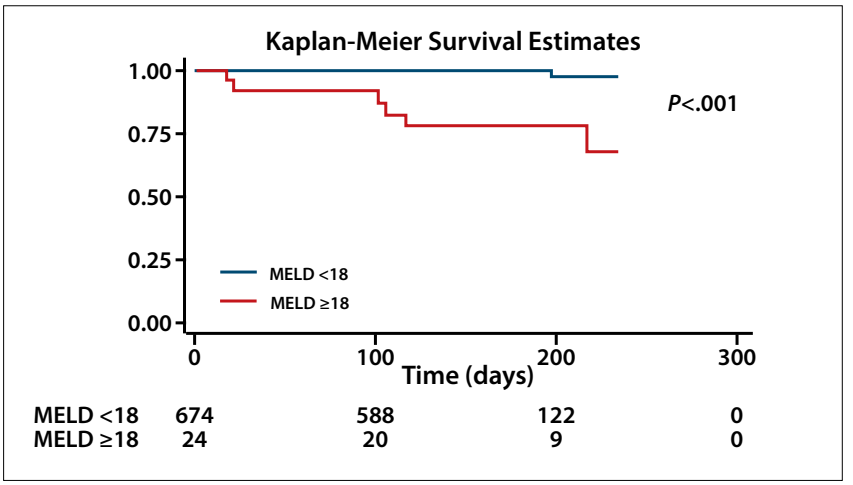



**Figure 3.** Predicted deaths within the study period according to MELD score.

MELD, Model for End-Stage Liver Disease. Adapted from Fernández-Carrillo C et al. EASL abstract GS01. *J Hepatol.* 2016;64(suppl 2).[5]

Overall, patients with a CTP score of B or C experienced lower SVR12 rates, more relapses, and more AEs compared with CTP A patients. In the intent-to-treat population of patients with HCV genotype 1, the SVR12 rate was 94% for patients with a CTP score of A and 78% for patients with a CTP score of B or C (*P*<.001). Rates of relapse were higher in the cohort of patients with CTP B or C (13% vs 4%; *P*=.001). The probability of experiencing a severe AE was higher in patients with advanced cirrhosis based on CTP score (*P*<.001), as well as in those with a MELD score of 18 or higher (*P*<.001) and those with platelet levels below 100,000/µL (*P*<.01). At 36 weeks after starting treatment, a higher MELD score (≥18) was associated with increased mortality (32% vs 3%; *P*<.001; Figure 3). In most patients, changes in MELD score after treatment were not clinically meaningful. After DAA treatment, MELD scores remained unchanged in 12%, worsened in 33%, and improved in 36%. DAA treatment was generally well-tolerated. However, the results show that patients with very advanced liver disease may not benefit from DAA treatment. The study presenter, Dr Carlos Fernández-Carrillo, emphasized the importance of discussing the risks of DAA treatment with patients who have severe cirrhosis.

## References

1. Bunchorntavakul C, Reddy KR. Treat chronic hepatitis C virus infection in decompensated cirrhosis – pre- or post-liver transplantation? The ironic conundrum in the era of effective and well-tolerated therapy. *J Viral Hepat.* 2016;23(6):408-418.
2. Curry MP, O'Leary JG, Bzowej N, et al; ASTRAL-4 Investigators. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. *N Engl J Med.* 2015;373(27):2618-2628.
3. Foster GR, Irving WL, Cheung MC, et al; HCV Research, UK. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol.* 2016;64(6):1224-1231.
4. Poordad F, Schiff ER, Vierling JM, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. *Hepatology.* 2016;63(5):1493-1505.
5. Fernández-Carrillo C, Lens S, Llop E, et al. Treatment of hepatitis C virus in patients with advanced cirrhosis: always justified? Analysis of the HEPA-C registry [EASL abstract GS01]. *J Hepatol.* 2016;64(suppl 2).

# High Efficacy of Sofosbuvir/Velpatasvir Plus GS-9857 in Previously Treated Patients With HCV Genotypes 1 Through 6

Dr Eric Lawitz presented results from 3 phase 2 trials that evaluated the combination of sofosbuvir, velpatasvir, and GS-9857 in patients with previously treated HCV.[1-8] Velpatasvir is an NS5A inhibitor, and GS-9857 is an NS3/4A inhibitor with a superior resistance profile compared with other NS3 protease inhibitors. All 3 DAAs have demonstrated efficacy against HCV genotypes 1 through 6. The single-center, open-label, phase 2 TRILOGY-3 trial enrolled patients with HCV genotype 1 infection previously treated for at least 6 weeks with a DAA.[9] The study design designated enrollment of approximately 50% of patients with compensated cirrhosis. Patients were stratified based on cirrhosis status and prior treatment with NS5A inhibitors. Twenty-four patients received a single daily tablet of sofosbuvir (400 mg)/velpatasvir (100 mg), plus daily GS-9857 (100 mg) for 12 weeks. In 25 patients, this regimen was administered with the addition of weight-based ribavirin. The primary endpoint was SVR12.

Patients had a mean age of 54 years (range, 18-75 years), and approximately two-thirds were male. Approximately 86% of patients had the IL28B non-CC genotype. As planned, half of patients had cirrhosis. The mean level of HCV RNA was 6.3 $\log_{10}$ IU/mL (range, 5.2-7.1 $\log_{10}$ IU/mL). Eighty-eight percent of patients had HCV genotype 1a infection. Previous treatment included an NS5A inhibitor in 41%. Among these patients, 6% had received only the NS5A inhibitor, 14% had also received an NS3 inhibitor, and 20% had received prior treatment with an NS5A inhibitor, an NS5B inhibitor, and an NS3 inhibitor. Among patients who had not received an NS5A inhibitor, prior treatments included an NS3 inhibitor (31%), an NS5B inhibitor (16%), and both (12%).

The overall SVR12 rate was 98%. One patient in the ribavirin-containing arm experienced virologic failure at follow-up week 4. The patient who relapsed was a 61-year-old black man with cirrhosis, who had previously received treatment with ledipasvir/sofosbuvir for 24 weeks. He relapsed after discontinuation of therapy. Baseline analysis for the TRILOGY-3 study showed that this patient had NS5A resistance-associated variants (RAVs), but no NS3 or NS5B RAVs. After relapsing during the follow-up period, the patient was found to have 1 additional NS5A RAV and 4 new NS3 RAVs. In the entire study population, 36 patients (75%) had baseline RAVs. Fifteen percent had NS5A RAVs only, 29% had NS3 RAVs only, and 31% had multiple-class RAVs. Among the 36 patients with any baseline RAVs, 35 (97%) achieved SVR12 (Figure 4). All 12 of the patients who lacked baseline RAVs achieved SVR12.

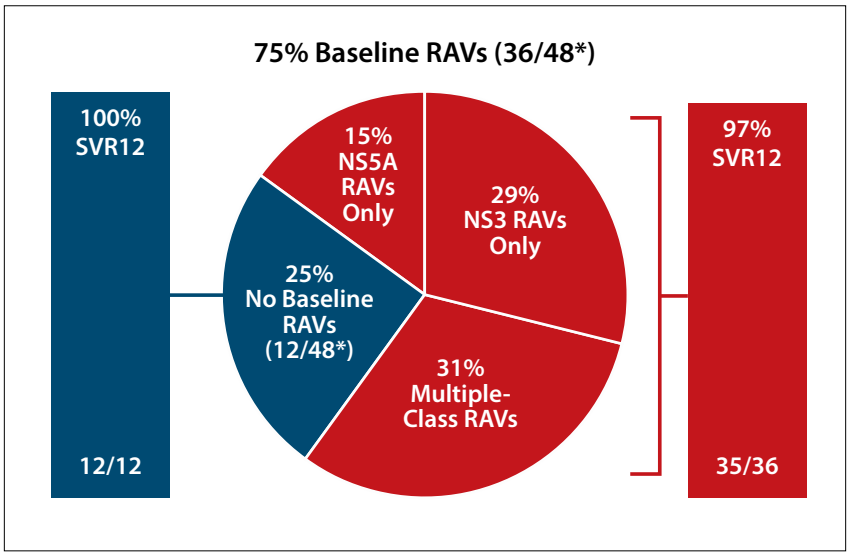



**Figure 4.** Results according to RAVs in a study evaluating sofosbuvir/velpatasvir plus GS-9857 in patients with HCV genotype 1 who had received previous treatment.

*Baseline sequencing was not obtainable for 1 patient. HCV, hepatitis C virus; RAVs, resistance-associated variants; SVR12, sustained virologic response at week 12. Adapted from Lawitz E et al. EASL abstract PS021. *J Hepatol.* 2016;64(suppl 2).[9]

AEs were common but generally mild-to-moderate in severity. AEs of any grade were reported in 11 patients (46%) in the ribavirin-free arm and in 15 patients (60%) in the ribavirin-containing arm. In the ribavirin-containing arm, there was a single grade 3 AE, consisting of rash that resolved upon discontinuation of ribavirin. There were no permanent treatment discontinuations or deaths during the study. One serious AE of pneumonia occurred in the ribavirin-free arm; however, this patient completed the 12 weeks of DAA treatment and achieved SVR12. Grade 3/4 laboratory abnormalities were more common in patients who received ribavirin (24% vs 4%). Hemoglobin levels of less than 10 g/dL were observed in 6 patients (24%) in the ribavirin arm vs none in the ribavirin-free arm. The most common AEs of any grade in the ribavirin arm were fatigue (36%), anemia (16%), and diarrhea (13%). These AEs did not occur in the ribavirin-free arm.

Dr Lawitz also presented results for treatment-experienced patients enrolled in 2 phase 2 trials that investigated treatment with sofosbuvir, velpatasvir, and GS-9857.[10] Study GS-US-367-1168 included 197 patients with HCV genotype 1 infection; study GS-US-367-1169 included 128 patients with HCV

genotype 2 to 6. Both trials included patients with or without cirrhosis, as well as patients who had received prior HCV treatment, including DAAs. Patients with HCV genotype 1 had received prior treatment with an NS5A inhibitor or at least 2 DAAs from different classes. Patients with genotypes 2 through 6 had received prior treatment with pegylated interferon plus ribavirin or any DAA. The 2 studies enrolled a total of 128 treatment-experienced patients, all of whom received 12 weeks of treatment with daily sofosbuvir (400 mg)/velpatasvir (100 mg) plus daily GS-9857 (100 mg).

The 128 patients had a mean age of 58 years (range, 37-77 years), 75% were male, and 82% were white. Approximately three-fourths of patients had the IL28B non-CC genotype, and 48% had cirrhosis. The mean HCV RNA level was 6.3 $\log_{10}$ IU/mL (range, 3.8-8.1 $\log_{10}$ IU/mL). Patients had HCV genotypes 1 (49%), 2 (16%), 3 (27%), and 4 or 6 (7%). Prior DAA treatments included 1 DAA class in 28% and 2 or more DAA classes in 51%, and 27% of patients had received prior treatment with an NS5A inhibitor. Twenty-one percent of patients had received prior treatment with pegylated interferon plus ribavirin but no prior DAA treatment. Among the 66 patients (52%) with prior non-NS5A DAA treatment, 24% had received prior treatment with an NS5B inhibitor alone. Another 24% had received treatment with an NS5B inhibitor and an NS3 inhibitor. The remaining 4% of patients had received treatment with an NS3 inhibitor, an NS5B nucleotide polymerase inhibitor, and/or an NS5B nonnucleotide polymerase inhibitor. Among the 35 patients (27%) who had received prior treatment with an NS5A inhibitor, 11% had received prior treatment with an NS3 inhibitor and an NS5A inhibitor, with other combinations accounting for the remaining patients, including 1 patient who had failed all 4 classes of DAAs.

At baseline, 77 patients (60%) had RAVs, and 76 of these patients (99%) achieved SVR12. The 1 patient who failed to achieve SVR12 was infected with HCV genotype 3 and relapsed at follow-up week 8. Among the 51 patients (40%) without baseline RAVs, 51 (100%) achieved SVR12. Among the 77 patients with baseline RAVs, 76 achieved SVR12 (99%; Figure 5). In the entire study group, SVR12 was reported in 100% of patients with HCV genotype 1, 2, 4, or 6 and in 97% of patients with HCV genotype 3. Subgroup analysis showed that the presence or absence of cirrhosis did not affect the likelihood of achieving SVR12. Similarly, prior treatment had no apparent impact on the likelihood of achieving SVR12. The single patient who experienced virologic failure had HCV genotype 3, was cir-


## ABSTRACT SUMMARY Ledipasvir/Sofosbuvir +/- Ribavirin in HCV Post-Transplant Patients: Real-World Heterogeneous Population From the TRIO Network

A study was conducted to determine SVR12 rates in a real-world heterogeneous population of HCV patients who had undergone liver transplant and received treatment with sofosbuvir plus ledipasvir with or without ribavirin for 8, 12, or 24 weeks (Abstract 269). Data were collected from several providers and specialty pharmacies. All post-transplant HCV genotype 1 patients who had initiated treatment between October 2014 and March 2015 were included in the analysis. Among the 67 patients, 21% were treated at a community site, and 79% were treated at an academic site. Ribavirin had been a component of treatment in 54%. Two-thirds of patients had HCV genotype 1a, 55% were treatment-experienced, and 31% had cirrhosis. The SVR12 rate was 97%. SVR12 rates did not significantly differ when patients were stratified according to whether or not they had received previous treatment, treatment duration (8, 12, or 24 weeks), the presence of cirrhosis, high or low viral load, and ethnicity (African American or not). No differences in response rates were detected based on patient age, sex, HCV genotype 1a vs 1b, platelet levels, or cirrhotic status. The only significant difference that emerged from the analysis was an improved likelihood of achieving SVR12 among patients treated at an academic center compared with a community setting (*P*=.044).

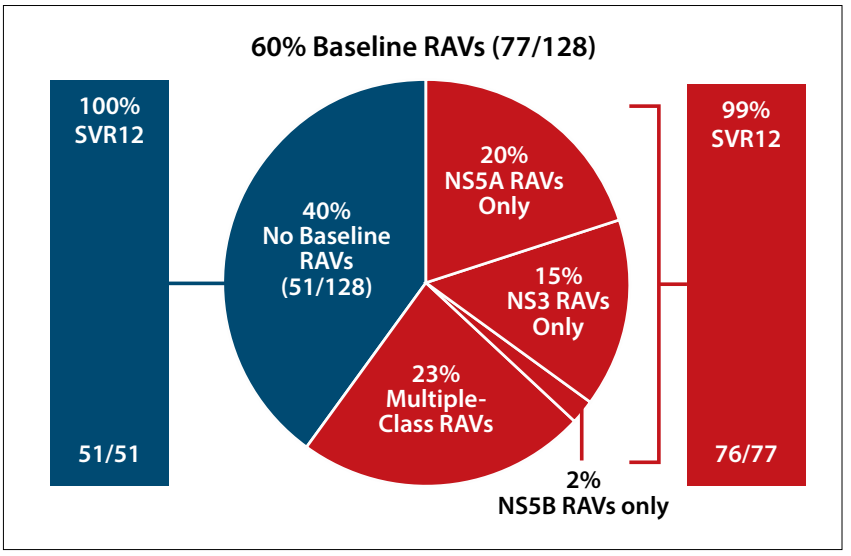




**Figure 5.** Results according to RAVs in a study evaluating sofosbuvir/velpatasvir plus GS-9857 in patients with HCV genotypes 1 through 6 who had received previous treatment.

HCV, hepatitis C virus; RAVs, resistance-associated variants; SVR12, sustained virologic response at week 12. Adapted from Lawitz E et al. EASL abstract PS008. *J Hepatol.* 2016;64(suppl 2).[10]

### ABSTRACT SUMMARY High Rate of SVR in Adolescents Treated With the Combination of Ledipasvir/Sofosbuvir

The prevalence of HCV infection is estimated to be 0.4% among children in the United States and Europe, and up to 6% among children in countries with more limited resources. Despite the advances seen with DAA therapy, the standard of care for children ages 3 years or older is pegylated interferon plus ribavirin administered for 24 to 48 weeks (Serranti D et al. *World J Gastroenterol.* 2014;20[43]:15965-15974). An international study was conducted to evaluate the efficacy and safety of daily ledipasvir (90 mg)/sofosbuvir (400 mg) administered for 12 weeks in adolescents (Abstract GS17). Eligible patients were ages 12 to 17 years, with or without prior treatment. The study enrolled 100 patients, with a mean age of 15 years (range, 12-17 years). Eighty-one percent of patients had HCV genotype 1a infection, 20% were treatment-experienced, and 1% had cirrhosis. Pharmacokinetic exposure to the DAA combination was similar to that observed in adults. The study yielded an overall SVR12 rate of 97%, with rates of 96% in treatment-naive patients and 100% in those who had received previous treatment. The single patient with cirrhosis was treatment-naive and achieved SVR12. Three patients were lost to follow-up. No virologic failures occurred. Grade 1/2 AEs occurred in 72% of patients, with no grade 3/4 AEs, no serious AEs, and no treatment discontinuations due to an AE. Nine patients experienced grade 3/4 laboratory abnormalities, and 1 patient experienced a reduction in hemoglobin level below 10 g/dL. The most common AEs were headache (27%), diarrhea (14%), and fatigue (13%).

rhotic, had no prior NS5A exposure, and had been exposed to 1 class of DAA therapy prior to study enrollment.

Sixty-five percent of patients experienced an AE of any grade. Two patients (2%) experienced a grade 3 AE, and 2 patients (2%) experienced a serious AE. One patient (<1%) discontinued treatment due to an AE considered unrelated to study treatment, and 1 patient (<1%) died from a presumed sudden cardiac arrest 14 weeks after completing the study. Eleven patients (9%) had grade 3/4 laboratory abnormalities without clinical consequences. The most common AEs were headache (22%), diarrhea (19%), fatigue (20%), and nausea (14%).

Dr Edward Gane presented results from treatment-naive patients enrolled in studies GS-US-367-1168 and GS-US-367-1169.[11] Patients received a single daily tablet of sofosbuvir (400 mg)/velpatasvir (100 mg) plus daily GS-9857 (100 mg) for either 6 weeks (n=67) or 8 weeks (n=99). A larger proportion of patients achieved SVR12 after 8 weeks of treatment (96% vs 79%). Thirty-one patients with HCV genotype 1 infection and cirrhosis received triple-DAA therapy plus ribavirin, and these patients achieved an SVR12 rate of 81%. The relapse rate was higher in patients who received only 6 weeks of treatment, and the addition of ribavirin did not provide an additional efficacy benefit over the combination of sofosbuvir/velpatasvir and GS-9857. Two patients in the 8-week ribavirin-free arm experienced serious AEs. Grade 3/4 AEs were reported in 3 patients, none of whom received ribavirin. The most common AEs across all 3 treatment arms were headache, nausea, fatigue, and diarrhea. Anemia was frequently observed in patients treated with ribavirin. In a separate trial, patients who had failed treatment with sofosbuvir/velpatasvir were treated with the same 2 drugs plus weight-based ribavirin for 24 weeks.[12] Twenty-six percent of patients had cirrhosis, and 99% had previously relapsed. Although SVR12 rates were high for patients with HCV genotype 1 or 2 infection, patients with HCV genotype 3 and baseline NS5A RAVs had a response rate of 77%.

## References


1. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013;368(20):1878-1887.
2. Rodriguez-Torres M, Glass S, Hill J, et al. GS-9857 in patients with chronic hepatitis C virus genotype 1-4 infection: a randomized, double-blind, dose-ranging phase 1 study [published online March 9, 2016]. *J Viral Hepat*. doi:10.1111/jvh.12527.
3. Lawitz E, Freilich B, Link J, et al. A phase 1, randomized, dose-ranging study of GS-5816, a once-daily NS5A inhibitor, in patients with genotype 1-4 hepatitis C virus. *J Viral Hepat*. 2015;22(12):1011-1019.
4. Jacobson IM, Gordon SC, Kowdley KV, et al; POSITRON Study; FUSION Study. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med*. 2013;368(20):1867-1877.
5. Cheng G, Tian Y, Yu M, et al. GS-5816, a second-generation HCV NS5A inhibitor with potent antiviral activity, broad genotypic coverage, and a high resistance barrier [EASL abstract 1191]. *J Hepatol*. 2013;58(suppl 1):S484-S485.
6. German P, Pang P, Yang C, et al. Healthy volunteer first-in-human evaluation of GS-5816, a novel second generation broad-genotypic NS5A inhibitor with potential for once-daily dosing [EASL abstract 1195]. *J Hepatol*. 2013;58(suppl 1):S486.
7. Taylor JG, Appleby T, Barauskas O, et al. Preclinical profile of the pan-genotypic HCV NS3/4A protease inhibitor GS-9857 [EASL abstract P0899]. *J Hepatol*. 2015;62(suppl 2).
8. Kirby B, Yang J, Yang C, et al. Evaluation of the pan-genotypic HCV NS3/4A protease inhibitor GS-9857 in healthy volunteers [EASL abstract P0861]. *J Hepatol*. 2015;62(suppl 2).
9. Lawitz E, Poordad F, Wells J, et al. High efficacy of sofosbuvir/velpatasvir/GS-9857 with or without ribavirin for 12 weeks in direct acting antiviral-experienced patients with genotype 1 HCV infection [EASL abstract PS021]. *J Hepatol*. 2016;64(suppl 2).
10. Lawitz E, Kowdley K, Curry M, et al. High efficacy of sofosbuvir/velpatasvir plus GS-9857 for 12 weeks in treatment-experienced genotype 1–6 HCV-infected patients, including those previously treated with direct-acting antivirals [EASL abstract PS008]. *J Hepatol*. 2016;64(suppl 2).
11. Gane EJ, Nguyen M, Kwo P, et al. Short duration treatment with sofosbuvir/velpatasvir plus GS-9857 in treatment-naive genotype 1-6–infected patients with or without cirrhosis [EASL abstract SAT-138]. *J Hepatol*. 2016;64(suppl 2).
12. Gane EJ, Shiffman ML, Etzkorn K. Sofosbuvir/velpatasvir in combination with ribavirin for 24 weeks is effective retreatment of patients who failed prior NS5A containing DAA regimens: results of the GS-US-342-1553 study [EASL abstract PS024]. *J Hepatol*. 2016;64(suppl 2).

# Prevalence and Impact of Baseline Resistance-Associated Variants (RAVs) on the Efficacy of Ledipasvir/Sofosbuvir or Simeprevir/Sofosbuvir Against GT1 HCV Infection: HCV-TARGET Interim Analysis

In real-world practice, the impact of baseline RAVs on patient outcomes is unclear. There is particular interest in identifying any differences in levels of RAVs among patients with vs without cirrhosis, those who have undergone liver transplant, and treatment-naive vs treatment-experienced patients. Dr Gary Wang presented interim results of HCV-TARGET (Hepatitis C Therapeutic Registry and Research Network), a multicenter, prospective, observational cohort study examining outcomes after 8, 12, and 24 weeks of treatment with sofosbuvir-containing regimens in patients with HCV infection.[1] The study has 2 aims: to evaluate the prevalence of NS3, NS5A, and NS5B RAVs (aim 1) and to assess their impact on the efficacy of DAA treatment in patients with HCV genotype 1 infection undergoing routine clinical care (aim 2). The study included patients with HCV genotype 1 infection who consented to serum collection before initiation of treatment. All patients received treatment with the fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) or simeprevir (150 mg) plus sofosbuvir (400 mg), each with or without ribavirin. Next-generation sequencing was performed to identify RAVs using a 10% variant reporting threshold. For aim 1, known RAVs with defined amino acid substitutions were identified to determine the prevalence of baseline NS3, NS5A, and NS5B RAVs. For aim 2, RAVs considered clinically relevant for the respective treatment regimen were analyzed to determine their impact on DAA treatment efficacy. Susceptibility to sofosbuvir, ledipasvir, and simeprevir was interpreted using a proprietary algorithm.

The study included 492 patients for RAV prevalence analysis and 472 for the efficacy analysis. Among the 472 patients included in the aim 2 analysis, 194 (41.4%) had received treatment with ledipasvir/sofosbuvir, 33 (7.0%) had received the same treatment with ribavirin, 187 (39.6%) had received treatment with sofosbuvir plus simeprevir, and 58 (12.3%) had received the same treatment with ribavirin. For the entire study population of 492 patients, the median age was 60 years (range, 56-65 years), 62.6% were male, and 70.7% were white. More than half of patients (53.7%) were treatment-experienced, including 8.1% who had received prior DAA treatment. Ribavirin-containing regimens were more commonly prescribed for previously treated patients, cirrhotic patients, and those who had undergone liver transplant. Fifty-two percent of patients had cirrhosis, and 17.7% had received a liver transplant. Three-fourths of patients had HCV genotype 1a, and the mean HCV RNA level was 6.6 $\log_{10}$ IU/mL.

Baseline RAV data for NS3, NS5A, and NS5B were available for 482 patients (98%). The overall presence of baseline RAVs was 45% for NS3, 13% for NS5A, and 8% for NS5B. Ten percent of patients had 2 or more classes of RAVs at baseline. RAV prevalence varied for HCV genotype 1a vs 1b, with frequencies of 54% vs 16%, respectively, for NS3, 12% vs 17% for NS5A, and 4% vs 22% for NS5B. The most common NS3 RAV was Q80K/R, which was present in 45% of patients with HCV genotype 1a infection vs 3% of patients with 1b infection. NS5A RAVs were more common in patients with HCV genotype 1b infection, and the most common mutation was Y93C/H/N, which was present in 11% of patients with HCV genotype 1b vs 3% of patients with genotype 1a. NS5B RAVs were more common in patients with HCV genotype 1b infec-

**ABSTRACT SUMMARY Antiviral Treatment in Patients With Advanced HCV Cirrhosis Using Sofosbuvir and Ledipasvir/Daclatasvir, With or Without Ribavirin—Outcomes Compared to Untreated Patients and Long-Term Outcomes**

The English Expanded Access Program enables patients with advanced liver disease to receive treatment with DAAs. A study was conducted in HCV patients with advanced cirrhosis to evaluate outcomes up to 12 months after termination of DAA therapy (Abstract PS097). The study included 467 patients, of whom 88% had current or past decompensation. Among the 409 patients with decompensated cirrhosis who received treatment, the SVR12 rate was 80.4%. These patients fared better than a comparator population of 261 patients with cirrhosis who did not receive treatment, based on the rate of decompensation, worsening MELD score, and total adverse outcomes during the first 6 months after treatment ($P$<.05 for each). At 12 months after the cessation of treatment, among patients who had achieved SVR12, a greater rate of AE-free survival was observed in patients with a MELD score of less than 15 ($P$<.05) and in patients with CTP class B vs class C ($P$<.05). Among patients who achieved SVR12, 20% of patients with CTP class C disease remained free of AEs by 15 months after treatment cessation vs 60% of CTP class B patients.

### ABSTRACT SUMMARY High SVR Rates With ABT-493 + ABT-530 Co-Administered for 8 Weeks in Noncirrhotic Patients With HCV Genotype 3 Infection

As reported at the 2015 meeting of the American Association for the Study of Liver Diseases (AASLD), the dose-ranging portion of the SURVEYOR-II study showed that 12 weeks of treatment with daily ABT-493 (300 mg) plus ABT-530 (120 mg) was associated with an SVR12 rate of 97% in 29 noncirrhotic patients with genotype 3 infection and no cirrhosis [AASLD Abstract 248]. In part 2 of the study, the same treatment given for 8 weeks was evaluated in 29 treatment-naive, noncirrhotic patients with HCV genotype 3 infection (Abstract PS098). Baseline NS3 and/or NS5A RAVs were detected in 13 of the 28 patients (46%) with available data. An SVR12 rate of 97% was achieved in the overall study population, with no virologic failures. One patient who withdrew consent after treatment week 6 had undetectable HCV RNA at the time of discontinuation. An AE of any grade occurred in 76% of patients, but there were no serious AEs or AEs leading to study drug discontinuation. The most common AE of any grade was headache (17%), followed by fatigue, diarrhea, insomnia, oropharyngeal pain, and toothache (each occurring in 10% of patients). The only laboratory abnormality observed was a single incident of grade 2 bilirubin elevation.

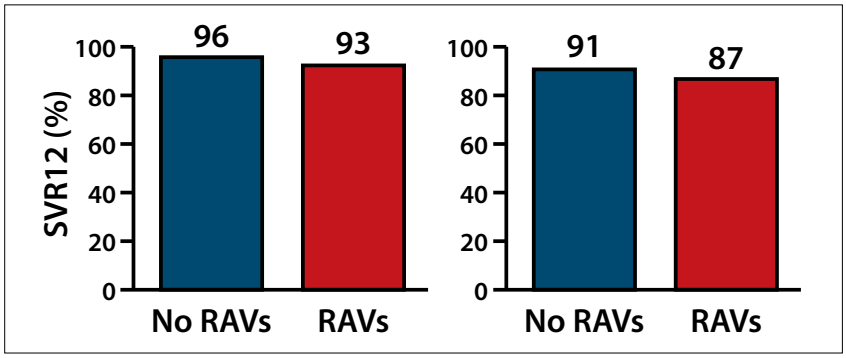



**Figure 6.** Efficacy according to RAVs in an interim analysis of the HCV-TARGET study. The chart on the left shows treatment with ledipasvir/sofosbuvir. The chart on the right shows treatment with simeprevir/sofosbuvir.

RAVs, resistance-associated variants; SVR12, sustained virologic response. Adapted from Wang GP et al. EASL abstract PS102. *J Hepatol.* 2016;64(suppl 2).[1]

tion, and the most common variant was S556G, which was present in 2% of 1a patients and 14% of 1b patients. Variant C316N was observed in 8% of genotype 1b patients, and was not observed in any patients with HCV genotype 1a infection. Overall RAV prevalence was similar in subgroups based on cirrhosis status, liver transplant status, and prior treatment experience.

In general, the presence of baseline RAVs did not significantly impact SVR12 rates, although numerical differences in SVR12 rates were observed. SVR12 rates in patients treated with ledipasvir/sofosbuvir were 96% in patients without baseline RAVs vs 93% in those with baseline RAVs (Figure 6). In patients who also received ribavirin, SVR12 rates were 97% vs 100%, respectively. Treatment with simeprevir plus sofosbuvir yielded SVR12 rates of 91% in patients without baseline RAVs vs 87% in patients with baseline RAVs. The addition of ribavirin to this regimen yielded SVR12 rates of 89% vs 87%, respectively.

RAVs at NS5A amino acids 28, 30, 31, 58, and 93 are associated with resistance to ledipasvir. In patients who received ledipasvir and had genotype 1a HCV, SVR12 rates were 96% for those without baseline ledipasvir-associated RAVs and 94% in those with baseline ledipasvir-associated RAVs. In patients with HCV genotype 1b, these SVR12 rates were 95% vs 88%, respectively. Also in the subgroup of patients who received ledipasvir, no significant differences in SVR12 emerged in those without vs with baseline ledipasvir-associated RAVs in patients without cirrhosis (97% vs 92%) or with cirrhosis (94% vs 91%) or in patients who were treatment-naive (95% vs 94%) or treatment-experienced (96% vs 92%). The amino acid variant Y93C/H/N was present in 8 of the 194 patients (4.1%) who received sofosbuvir plus ledipasvir with or without ribavirin. The presence of this RAV was associated with a significant reduction in SVR12 (96% vs 75%; *P*=.046). Analysis of a larger cohort of patients with the Y93C/H/N variant may be of interest.

RAVs at NS3 amino acids 80, 122, 155, 168, and 170 are associated with resistance to treatment with simeprevir. SVR12 rates in the overall population of 187 patients treated with simeprevir plus sofosbuvir without ribavirin were 91% in patients without simeprevir-associated RAVs vs 87% in those with simeprevir-associated RAVs. These rates were 91% vs 85% in patients with HCV genotype 1a infection and 91% vs 100% in those with genotype 1b infection. (Only 4 patients had HCV 1b infection with simeprevir-associated RAVs.) For the cohort of 58 patients who received simeprevir plus sofosbuvir with ribavirin, SVR12 rates were similar for patients without vs with simeprevir-associated RAVs (90% vs 86%) and in the subsets of patients with HCV genotype 1a infection (95% vs 86%). The subset of patients with HCV genotype 1b infection showed SVR12 rates of 78% without baseline simeprevir-associated RAVs vs 100% with baseline simeprevir-associated RAVs. (This subset contained only 9 patients without relevant baseline RAVs and 1 patient with them, and the difference in outcomes was not signifi-

cant.) SVR12 rates in patients without or with baseline RAVs associated with simeprevir resistance were similar when analyzed according to cirrhosis status and prior treatment status. The presence of baseline simeprevir-associated RAVs was associated with a reduction in SVR12 by 15% in one subgroup: previously treated HCV 1a patients with baseline simeprevir-associated RAVs who had infection and cirrhosis. The effect of RAVs on response to treatment with ribavirin was also examined, and no obvious correlation emerged.

## Reference

1. Wang GP, Reeves J, Terrault N, et al. Prevalence and impact of baseline resistance-associated variants (RAVs) on the efficacy of ledipasvir/sofosbuvir or simeprevir/sofosbuvir against GT1 HCV infection: HCV-TARGET interim analysis [EASL abstract PS102]. *J Hepatol*. 2016;64(suppl 2).

# Sofosbuvir/Velpatasvir for 12 Weeks in Patients Coinfected With HCV and HIV-1: The ASTRAL-5 Study

Patients who are coinfected with HCV and HIV are at increased risk of cirrhosis, end-stage liver disease, hepatocellular cancer, and accelerated liver disease progression.[1] Effective HCV therapies showing limited or manageable interactions with antiretroviral therapy are needed for this patient population. Velpatasvir is an NS5A inhibitor that has demonstrated activity in combination with sofosbuvir in patients infected with HCV genotypes 1 through 6, as well as in cirrhotic patients and those who have received previous treatment.[2-4] The once-daily, fixed-dose combination tablet has been given breakthrough therapy designation by the US Food and Drug Administration. ASTRAL-5 was an open-label, single-arm, phase 3 trial that investigated the safety and efficacy of daily sofosbuvir (400 mg)/velpatasvir (100 mg) administered in a fixed-dose combination tablet for 12 weeks in patients with HCV and HIV coinfection.[5] The study included patients with HCV genotypes 1 through 6, with or without prior treatment, and with or without compensated cirrhosis. Patients were required to have been on stable antiretroviral therapy for at least 8 weeks, and to have a CD4 cell count of at least 100 cells/μL and an HIV RNA level of no more than 50 copies/mL. Permitted antiretroviral therapies included nonnucleoside reverse transcriptase inhibitors, integrase inhibitors, and protease inhibitor regimens with tenofovir disoproxil fumarate/emtricitabine or with abacavir/lamivudine. The primary endpoint was SVR12. Additional monitoring was performed for safety, maintenance of HIV suppression, laboratory abnormalities, and changes in renal function.

ASTRAL-5 enrolled 106 HIV-positive patients with a mean age of 54 years (range, 25-72 years), of whom 86% were male and 45% were black. Median body mass index was 27 kg/m$^2$ (range, 19-43 kg/m$^2$). Eighteen percent had cirrhosis, and 29% were treatment-experienced. The mean level of HCV RNA was 6.3 $\log_{10}$ IU/mL (range, 5.0-7.4 $\log_{10}$ IU/mL). HCV genotypes included 1a (62%), 1b (11%), 2 (10%), 3 (11%), and 4 (5%). The mean CD4 cell count was 598 cells/μL (range, 183-1513 cells/μL). At baseline, medication included protease inhibitors in 47%, an integrase inhibitor in 34%, a nonnucleoside reverse transcriptase inhibitor in 12%, and more than 1 of the preceding drug classes in 7%. Nucleoside reverse transcriptase inhibitors in use at baseline included tenofovir in a boosted (53%) or nonboosted (33%) regimen or abacavir/lamivudine (14%). All patients received a single tablet of the fixed-dose combination of sofosbuvir/velpatasvir daily for 12 weeks.

### ABSTRACT SUMMARY Resistance Analyses for Ledipasvir/Sofosbuvir–Containing Regimens in Patients Infected With Chronic HCV Who Have Advanced Liver Disease or Are Post Liver Transplant (SOLAR-1 and -2 Studies)

The SOLAR-1 (Ledipasvir/Sofosbuvir Fixed-Dose Combination + Ribavirin in Subjects With Chronic HCV With Advanced Liver Disease or Post-Liver Transplant) and SOLAR-2 trials investigated ledipasvir/sofosbuvir plus ribavirin in patients with HCV genotype 1 or 4 infection (Charlton M et al. *Gastroenterology*. 2015;149[3]:649-659; Manns M et al. *Lancet Infect Dis*. 2016; Epub ahead of print). To determine the impact of RAVs on response, deep sequencing of NS5A and NS5B was performed at baseline for all patients, and then again after treatment in patients who did not achieve SVR12 (Abstract PS09). In patients with NS5A RAVs, SVR12 rates were 96% in genotype 1 patients and 87% in those with genotype 4. Among patients without baseline NS5A RAVs, SVR12 rates were 97% in patients with HCV genotype 1 and 100% in those with genotype 4. Among patients with HCV genotype 1 or 4 infection, SVR12 rates were similar regardless of the presence of baseline RAVs in the cohorts of patients treated for 12 or 24 weeks. No significant differences in SVR12 rates emerged for patients with vs without baseline RAVs in analyses based on HCV genotype 1a, HCV genotype 1b, decompensated cirrhosis, compensated cirrhosis, or treatment duration of 12 weeks or 24 weeks. Among genotype 1–infected patients with decompensated cirrhosis who received 12 weeks of treatment, patients with vs without baseline NS5A RAVs achieved SVR12 rates of 83% vs 93%. Baseline NS5B RAVs did not have a clinically meaningful impact on SVR12 rates. At the time of relapse, NS5A RAVs were detected in 91% of patients, and NS5B RAVs were detected in 16%.

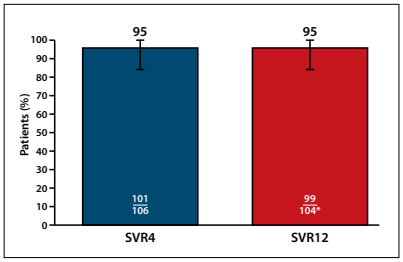



**Figure 7.** SVR4 and SVR12 rates in the ASTRAL-5 study of patients coinfected with HIV and HCV.

*Two patients were pending assessment of SVR12; both achieved SVR4. HCV, hepatitis C virus; HIV, human immunodeficiency virus; SVR4, sustained virologic response at week 4; SVR12, sustained virologic response at week 12. Adapted from Wyles D et al. EASL abstract PS104. *J Hepatol.* 2016;64(suppl 2).[5]

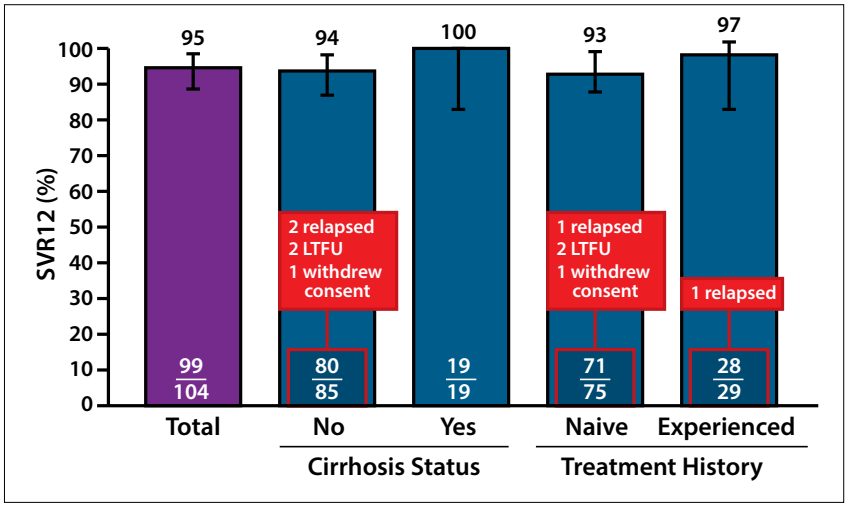



**Figure 8.** SVR12 rates according to cirrhosis status and treatment history in the ASTRAL-5 study of patients coinfected with HIV and HCV.

HCV, hepatitis C virus; HIV, human immunodeficiency virus; LTFU, lost to follow-up; SVR12, sustained virologic response at week 12. Adapted from Wyles D et al. EASL abstract PS104. *J Hepatol.* 2016;64(suppl 2).[5]

The SVR4 rate was 95% (101 of 106 patients), and the SVR12 rate was 95% (99 of 104 patients; Figure 7). Two patients still in follow-up were omitted from the latter result. Of the 5 patients who failed to achieve SVR12, 2 relapsed, 2 were lost to follow-up, and 1 withdrew consent. High SVR12 rates were observed across all HCV genotypes, including 1a (95%), 1b (92%), 2 (100%), 3 (92%), and 4 (100%). Patients without cirrhosis (n=85) achieved an SVR12 rate of 94%, and those with cirrhosis (n=19) achieved an SVR12 rate of 100% (Figure 8). SVR12 was 93% in treatment-naive patients (n=75) vs 97% in treatment-experienced patients (n=29). SVR12 rates were 98% for the cohort of patients without baseline NS5A RAVs vs 100% in those with baseline RAVs.

Most patients (71%) experienced an AE of any grade; however, the majority of AEs were grade 1 or 2. Grade 3/4 AEs were observed in 8% of patients, and serious AEs occurred in 2%. One serious AE was a case of radial nerve palsy that was not considered related to study drug treatment. The palsy resolved, and the patient continued on study treatment. The second serious AE occurred in a patient with a history of gout. This patient experienced inflammation of a toe, which was thought to be a possible infection or gout flair. After initiation of antibiotic treatment, the patient's ALT level increased to 5 times the baseline level. Based on preset criteria, the study drug was discontinued at week 7. This serious AE was not considered related to study drug treatment, and the patient eventually achieved SVR12. Two percent of patients discontinued study treatment due to an AE. No patient experienced HIV virologic breakthrough while receiving study treatment, and no deaths occurred.

The most common AEs of any grade were fatigue (25%), headache (13%), arthralgia (8%), upper respiratory tract infection (8%), and diarrhea (8%). The most common laboratory abnormality was elevated bilirubin in patients taking boosted atazanavir. Creatinine clearance

## ABSTRACT SUMMARY Real-World Safety and Effectiveness of Ombitasvir/Paritaprevir/R ± Dasabuvir ± Ribavirin in the German Hepatitis C Registry

A noninterventional, prospective cohort study of 1017 patients with HCV genotype 1 or 4 infection enrolled in a German registry evaluated the real-world safety and efficacy of treatment with ombitasvir/paritaprevir/ritonavir (Abstract GS07). Ombitasvir inhibits NS5A, paritaprevir inhibits NS3/4A, and ritonavir is an inhibitor of the cytochrome P450 isozyme 3A4 that enhances the pharmacokinetics of paritaprevir. Treatment choice and duration were at the physician's discretion, and some treatment regimens also included dasabuvir and/or ribavirin. Twelve percent of patients had HCV genotype 4 infection. More than half had received prior treatment for their HCV infection. Cirrhosis was reported in 22%, and 59% were receiving at least 1 non-HCV medication. Based on the efficacy population of 558 patients, the SVR12 rate was 96% for patients with HCV genotype 1 infection and 100% for HCV genotype 4 patients. Overall, 6 patients (1.1%) experienced virologic relapse. Analysis of patients based on HCV genotype 1, 1a, 1b, or 4 yielded SVR12 rates that ranged from 96% to 100% in patients without cirrhosis and from 93% to 100% in patients with cirrhosis. SVR12 rates in treatment-naive vs treatment-experienced patients ranged from 96% to 98%. Patients with renal insufficiency also demonstrated high SVR12 rates. Subgroup analysis showed improved results in patients treated according to current guidelines (99% vs 92%). Serious AEs were reported in 2% of patients, and the rate of discontinuation due to an AE was 1.5%. The most common AEs of any grade were fatigue (24%), pruritus (10%), and headache (9%). Two deaths occurred, but they were not considered related to study treatment.

was maintained throughout the study among patients taking a boosted tenofovir regimen, a nonboosted tenofovir regimen, and a regimen that did not contain tenofovir. No patient discontinued or changed antiretroviral therapy due to a renal AE during the study.

## References


1. Weber R, Sabin CA, Friis-Møller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*. 2006;166(15):1632-1641.
2. Curry MP, O'Leary JG, Bzowej N, et al; ASTRAL-4 Investigators. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. *N Engl J Med*. 2015;373(27):2618-2628.
3. Feld JJ, Jacobson IM, Hézode C, et al; ASTRAL-1 Investigators. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med*. 2015;373(27):2599-2607.
4. Foster GR, Afdhal N, Roberts SK, et al; ASTRAL-2 Investigators; ASTRAL-3 Investigators. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. *N Engl J Med*. 2015;373(27):2608-2617.
5. Wyles D, Brau N, Kottilil S, et al. Sofosbuvir/velpatasvir for 12 weeks in patients coinfected with HCV and HIV-1: the ASTRAL-5 study [EASL abstract PS104]. *J Hepatol*. 2016;64(suppl 2).


# 100% SVR12 With ABT-493 and ABT-530 With or Without Ribavirin in Treatment-Naive HCV Genotype 3–Infected Patients With Cirrhosis

HCV genotype 3 accounts for 30% of HCV infections globally.[1] Compared with other genotypes, HCV genotype 3 is associated with increased risk of liver steatosis, hepatocellular carcinoma, and progression of fibrosis. Moreover, patients with genotype 3, particularly those with cirrhosis, are less likely to be cured by DAA therapy.[2] Guidelines from the European Association for the Study of the Liver for patients with HCV genotype 3 infection and concurrent cirrhosis recommend sofosbuvir-containing regimens, which are associated with SVR12 rates as high as 88%.[3-5] In an open-label, phase 3 trial conducted at 80 sites in Europe, North America, Australia, and New Zealand, treatment-experienced patients with HCV genotype 3 infection and cirrhosis achieved SVR12 rates of 84% after 24 weeks of treatment with sofosbuvir and ribavirin and 88% after 12 weeks of treatment with sofosbuvir plus pegylated interferon and ribavirin.[3] The combination of sofosbuvir and daclatasvir with or without ribavirin administered for 12 or 24 weeks yielded SVR12 rates ranging from 81% to 86%.[4,5]

ABT-493 is a next-generation NS3/4A protease inhibitor with pangenotypic activity, and ABT-530 is a pangenotypic NS5A inhibitor. These therapies have shown synergistic antiviral activity, as well as activity against common NS3 and NS5A RAVs.[6,7] ABT-493 and ABT-530 are compatible with oral dosing once daily, with half-maximal effective concentrations ($EC_{50}$) of 1.6 nM and 2 pM, respectively, against a stable GT3a replicon. Both drugs show minimal metabolism and primary biliary excretion, with less than 1% renal excretion. ABT-530 has demonstrated excellent antiviral activity in vitro against HCV genotype 3 variants, including M28T, A30K, and Y93H, as evidenced by alterations in $EC_{50}$ ranging from 0.4-fold to 2.5-fold. The combination of ABT-493 (300 mg) plus ABT-530 (120 mg) given for 8 or 12 weeks demonstrated SVR12 rates of 100% in treatment-naive patients with HCV genotype 3 infection and no cirrhosis.[8,9]

The open-label, multicenter, phase 2 SURVEYOR-II (A Randomized, Open-Label, Multicenter 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) study is evaluating daily ABT-493 (300 mg) plus ABT-530 (120 mg) administered for 12 weeks in 48 patients with cirrhosis.[10] Patients were

### ABSTRACT SUMMARY Real World Effectiveness of Ledipasvir/Sofosbuvir in Treatment-Experienced Cirrhotic Genotype 1 Patients With Chronic HCV: A Comparative Analysis of Gilead Sponsored Trials With 4 Real-World Cohorts

Real-world efficacy and safety were compared to results from clinical trials in treatment-experienced, cirrhotic patients with HCV genotype 1 infection who received treatment with ledipasvir (90 mg)/sofosbuvir (400 mg) with or without ribavirin (Abstract 214). Aggregated data from 507 patients in 4 real-world cohorts were compared with data from 421 patients in 7 clinical trials. Among patients who received on-label treatment, ledipasvir/sofosbuvir with ribavirin for 12 weeks yielded SVR12 rates of 96% in clinical trials vs 100% in the real-world setting. Patients who received ribavirin-free treatment for 24 weeks achieved SVR12 rates of 98% in clinical trials vs 93% in the real-world setting. SVR12 rates of 92% and greater were achieved in all cohorts stratified by sex, HCV genotype, and platelet counts. The real-world cohort yielded a virologic failure rate of 2.4%. Eight patients discontinued treatment in the real-world cohort; however, no patient in either cohort discontinued the study drug due to a treatment-related AE. No deaths occurred in either cohort. Limitations of the study included its retrospective nature, varying inclusion criteria, and the collection of real-world data via chart review.

### ABSTRACT SUMMARY C-EDGE Head to Head: Efficacy and Safety of Elbasvir and Grazoprevir Compared With Sofosbuvir/Pegylated Interferon/Ribavirin: A Phase 3 Randomized Controlled Trial

The open-label, parallel-group, phase 3 C-EDGE Head-to-Head study compared the fixed-dose combination of elbasvir/grazoprevir vs sofosbuvir, pegylated interferon, and ribavirin in patients with chronic HCV genotype 1, 4, or 6 infection (Abstract PS002). Patients were treatment-naive or had received previous treatment with pegylated interferon plus ribavirin. The 255 patients were randomly assigned to receive 12 weeks of daily elbasvir (50 mg)/grazoprevir (100 mg) or sofosbuvir (400 mg once daily) plus pegylated interferon and ribavirin. SVR12 was 99.2% with elbasvir/grazoprevir and 90.5% with sofosbuvir plus pegylated interferon and ribavirin. In patients with HCV genotype 1a infection, both treatments yielded SVR12 rates of 100%. The combination of elbasvir/grazoprevir was superior in patients with HCV genotype 1b (99.0% vs 90.4%) and genotype 4 (100% vs 60.0%). Subgroup analyses showed superior outcomes with the DAA combination among men, patients with the IL28B non-CC genotype, patients with cirrhosis, those with a high viral load, and patients who had previously shown no response to treatment with pegylated interferon and ribavirin. Elbasvir/grazoprevir demonstrated superior safety outcomes based on tier 1 events, which included any serious drug-related AE, discontinuation due to a drug-related AE, neutrophil count below 0.75 × $10^9$/L, and hemoglobin level below 10 g/dL.


randomly assigned to receive treatment with or without ribavirin (800 mg daily). The study includes several other arms evaluating the same drug combination in patients infected with different HCV genotypes, with or without cirrhosis, and with varying treatment durations. The current analysis included patients with HCV genotype 3a infection and compensated cirrhosis, as determined by a CTP score of 6 or less, plus results from a liver biopsy, transient elastography, or serum blood testing for the presence of liver fibrosis. Patients had an HCV RNA level of greater than 10,000 IU/mL. Exclusion criteria included prior HCV treatment, a history of hepatic decompensation, HIV coinfection, an albumin level below the lower limit of normal, a platelet count of less than 90 × $10^9$/L, and the use of herbal supplements or potent P-glycoprotein inducers. The primary endpoint was SVR12.

Patients had a median age of 55 years (range, 30-68 years), and most were male. The median HCV RNA level was 6.4 $\log_{10}$ IU/mL (range, 4.2-7.3 $\log_{10}$ IU/mL). A smaller proportion of patients in the ribavirin-containing arm had a CTP score of 6 (13% vs 21%). NS3 or NS5A RAVs were detected in 10 patients (42%) in the ribavirin-free arm and 8 patients (33%) in the ribavirin-containing arm. Based on an intent-to-treat analysis, the SVR12 rates were 100% after 12 weeks of treatment with or without ribavirin (Figure 9). AEs were primarily mild, with no patients discontinuing treatment due to an AE. AEs of any grade were reported in 88% of patients in the ribavirin-free arm vs 83% of patients in the ribavirin-containing arm, with serious AEs occurring in 4% and 8% of patients, respectively. The only serious AE that was considered related to study treatment was anemia, which occurred in a single patient in the ribavirin-containing arm. The new DAA combination was generally well tolerated. The most common AEs of any grade were headache (13% without ribavirin vs 33% with ribavirin), fatigue (8% vs 25%), and nausea (8% vs 25%). AEs that occurred more frequently in the ribavirin-free arm included urinary tract infections (17% vs 8%) and diarrhea (21% vs 0%). There were no reports of grade 2 or higher increases in levels of ALT, aspartate transaminase, or alkaline phosphatase. One patient in the ribavirin-free arm who had high bilirubin at baseline experienced a grade 3 bilirubin elevation that resolved after treatment ended.

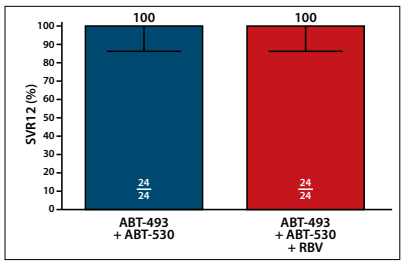



**Figure 9.** SVR12 rates in an intent-to-treat analysis of the SURVEYOR-II trial.

RBV, ribavirin; SVR12, sustained virologic response at week 12. Adapted from Kwo PY et al. EASL abstract LB01. *J Hepatol.* 2016;64(suppl 2).[10]

## References


1. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology*. 2015;61(1):77-87.
2. Ampuero J, Romero-Gómez M, Reddy KR. Review article: HCV genotype 3 – the new treatment challenge. *Aliment Pharmacol Ther*. 2014;39(7):686-698.
3. Foster GR, Pianko S, Brown A, et al; BOSON Study Group. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. *Gastroenterology*. 2015;149(6):1462-1470.
4. Welzel TM, Petersen J, Ferenci P, et al. Safety and efficacy of daclatasvir plus sofosbuvir with or without ribavirin for the treatment of chronic HCV genotype 3 infection: interim results of a multicenter European compassionate use program [AASLD abstract 37]. *Hepatology*. 2015;62(suppl 1):225A.
5. Hezode C, de Lendinghen V, Fontaine H, et al. Daclatasvir plus sofosbuvir with or without ribavirin in genotype 3 patients from a large French multicenter compassionate use program [AASLD abstract 206]. *Hepatology*. 2015;62(suppl 1);314A.
6. Ng T, Reisch T, Middleton T, et al. ABT-493, a potent HCV NS3/4A protease inhibitor with broad genotype coverage. Abstract presented at: the 21st Conference on Retroviruses and Opportunistic Infections; March 3-6, 2014; Boston, Massachusetts. Abstract 636.
7. Ng T, Krishnan P, Kati W, et al. ABT-530, an HCV NS5A inhibitor with potent pangenotypic activity and high genetic barrier to resistance. Abstract presented at: the 21st Conference on Retroviruses and Opportunistic Infections; March 3-6, 2014; Boston, Massachusetts. Abstract 639.
8. Muir AJ, Strasser S, Wang S, et al. High SVR rates with ABT-493 + ABT-530 co-administered for 8 weeks in non-cirrhotic patients with HCV genotype 3 infection [EASL abstract PS098]. *J Hepatol*. 2016;64(suppl 2).
9. Kwo PY, Bennett M, Wang S, et al. High SVR4 rates achieved with the next generation NS3/4A protease inhibitor ABT-493 and NS5A inhibitor ABT-530 in non-cirrhotic treatment-naive and treatment-experienced patients with HCV genotype 3 infection (SURVEYOR-2) [AASLD abstract 248]. *Hepatology*. 2015;62(suppl 1).
10. Kwo PY, Wyles DL, Wang S, et al. 100% SVR12 with ABT-493 and ABT-530 with or without ribavirin in treatment-naive HCV genotype 3-infected patients with cirrhosis [EASL abstract LB01]. *J Hepatol*. 2016;64(suppl 2).

# Advances in the Treatment of Hepatitis C Virus Infection From the 2016 EASL Meeting: Commentary

Steven L. Flamm, MD
Chief, Liver Transplantation Program
Professor of Medicine and Surgery
Northwestern University
Feinberg School of Medicine
Chicago, Illinois

The 2016 International Liver Congress of the European Association for the Study of the Liver (EASL) was held in Barcelona, Spain, in April. There were many important presentations in the field of chronic hepatitis C virus (HCV) infection. With the availability of oral, well-tolerated, highly efficacious regimens for all HCV genotypes, it may seem that numerous presentations on HCV may be unnecessary. However, there are still many aspects of treatment for HCV that can be improved.

The presentations on HCV treatment fell into 3 general categories. First, several abstracts provided data on newer regimens that may further improve efficacy and tolerability. Second, many studies focused on areas of treatment that remain challenging, even with the new available regimens. An example would be how to re-treat the rare patients who are not cured by an initial course of direct-acting antiviral therapy. Management of patients with genotype 3 is another example. The currently available therapies are less successful in patients with genotype 3, particularly those with cirrhosis and/or who have received previous treatment.[1] Therefore, active investigation is evaluating new strategies to improve the response rates in these patient populations. The third general area of EASL abstracts regarding treatment of HCV focused on subpopulations of patients, such as those coinfected with HIV and HCV and those who have undergone renal transplantation.

## RAVs vs RASs

The French virologist Dr Jean-Michel Pawlotsky raised an issue concerning the term "resistance-associated variants," also known as "RAVs."[2] Emergence of RAVs has been used to identify treatment resistance in patients receiving any class of direct-acting antiviral agents, including protease inhibitors, polymerase inhibitors, and NS5A inhibitors. The term "RAVs" is used in the literature to date, as well as in the studies discussed here. "RAVs" is also used in the management guidelines from the American Association for the Study of Liver Diseases/Infectious Diseases Society of America.[3] Dr Pawlotsky, however, said that a more accurate term is "resistance-associated substitution," or "RAS." It would not be surprising to me if in the relatively near future, the terminology is changed from "RAVs" to "RASs." My discussion here will use the term "RAVs."

## Retreatment

A series of significant presentations addressed the best way to re-treat patients who were not cured by an initial course of direct-acting antiviral agents. This issue is especially problematic in patients with resistance to NS5A agents because NS5A RAVs are particularly troublesome. Most current regimens are less efficacious in patients with baseline NS5A RAVs.[4] Furthermore, the small number of patients without RAVs at baseline who fail an approved regimen including an NS5A inhibitor will frequently, if not always, develop NS5A RAVs. Such patients will therefore have baseline NS5A RAVs when beginning their next regimen.

Dr Eric Lawitz presented results from an important study evaluating treatment with the NS5B polymerase inhibitor sofosbuvir and the new NS5A inhibitor velpatasvir, plus the investigational protease inhibitor GS-9857, in HCV genotype 1–infected patients who had previously failed direct-acting antiviral therapy.[5] This regimen includes therapies from all 3 classes of direct-acting antiviral agents. It is expected that the US Food and Drug Administration will approve the combination of sofosbuvir/velpatasvir (dual therapy) in June 2016, based on phase 3 data showing high efficacy in genotypes 1 through 6.[6] Forty-nine patients were randomly assigned to receive the triple-therapy regimen, with or without ribavirin, for 12 weeks in a single-center study. Among the 49 patients, 48 (98%) achieved a sustained virologic response (SVR). The 1 patient who failed treatment was in the ribavirin arm. Among the 36 patients with baseline RAVs, 35 achieved SVR12 (97%). The regimen was well-tolerated. Dr Lawitz concluded that this triple-therapy regimen, without ribavirin, administered for 12 weeks was highly effective in patients who had previously failed direct-acting antiviral agents. Baseline RAVs were inconsequential for this regimen.

Dr Lawitz also presented results from an open-label, multicenter trial that evaluated the same triple-therapy

regimen of sofosbuvir, velpatasvir, and GS-9857 in 128 patients with HCV genotype 1 through genotype 6 infection who had previously failed regimens including direct-acting antiviral agents.[7] The patients received once-daily treatment, without ribavirin, for 12 weeks. Overall, 127 of 128 patients achieved SVR12 (99%). Among the 51 patients who did not have preexisting RAVs, all achieved SVR12 (100%). There were 77 patients who had at least 1 RAV, and 76 of them achieved SVR12 (99%). As in the single-center study, the regimen was well-tolerated. Sofosbuvir/velpatasvir plus GS-9857 is an exciting potential future option for patients who have failed direct-acting antiviral therapy, as it is a highly efficacious salvage regimen.

Dr Fred Poordad presented results from the MAGELLAN-1 trial of patients who had failed therapy with direct-acting antiviral agents.[8] The treatment regimen consisted of the investigational agents ABT-493, a protease inhibitor, and ABT-530, an NS5A inhibitor. The trial enrolled patients with genotype 1 who did not have cirrhosis. The study had 3 arms: one with a lower dose of ABT-493 and ABT-530, and 2 with a higher dose, with or without ribavirin. Among the 50 patients, 6 were in the low-dose arm, 22 were in the high-dose with ribavirin arm, and 22 were in the high-dose without ribavirin arm. Most of the patients had previously failed a regimen containing a protease inhibitor, and 50% had previously failed a regimen containing an NS5A inhibitor. Most of the patients had preexisting RAVs.

Three of the 50 patients were lost to follow-up. Among the remaining 47, 45 achieved SVR12, providing a rate of 95% in the modified intent-to-treat analysis. The addition of ribavirin was not beneficial. One of the relapsed patients was in the ribavirin-containing arm, and the other was in the nonribavirin-containing arm. The study carefully evaluated NS5A RAVs. Y93 is the NS5A RAV with the most profound effect on treatment response. Among the 10 patients with Y93, all responded to the regimen (100%). Among the 25 patients with multiple variants, 23 achieved SVR12 (92%). This regimen was also well-tolerated. The results showed that a 12-week regimen of ABT-493 and ABT-530, without ribavirin, was highly efficacious in patients who had previously failed a direct-acting antiviral regimen.

## HCV Genotype 3 Infection

There were 2 important presentations regarding treatment of HCV genotype 3 infection. Dr Paul Kwo presented results from SURVEYOR-II, a study of treatment-naive patients with genotype 3 and cirrhosis.[9] As previously mentioned, genotype 3 patients with cirrhosis are among the most difficult patients to treat with the currently available direct-acting antiviral regimens, as they have low rates of SVR. Dr Kwo examined the same regimen as in the study by Dr Poordad: ABT-493 and ABT-530. The study by Dr Kwo evaluated 12 weeks of this combination therapy, with or without ribavirin, in 24 patients. One hundred percent achieved an SVR12. Ribavirin proved to be unnecessary. The regimen was well-tolerated. This study was important because there are no other regimens with this high rate of response among patients with genotype 3 and cirrhosis.

Another study evaluated ABT-493 and ABT-530 in genotype 3 patients without cirrhosis.[10] This open-label study examined an 8-week regimen, which is a shorter duration of therapy than normally used in patients with genotype 3. In this study, 28 of 29 patients achieved SVR12 (97%). The 1 patient who did not achieve an SVR12 withdrew from the trial. Therefore, the modified intent-to-treat analysis showed an SVR12 of 100%. The regimen again had excellent tolerability. The results of this study are very exciting.

## Special Populations

The ASTRAL-5 trial evaluated a 12-week regimen of sofosbuvir and velpatasvir in patients with HCV/HIV coinfection.[11] Results were presented by Dr David Wyles. Patients with HCV genotypes 1 through 4 were enrolled in this open-label study, and they could be treatment-naive or treatment-experienced, and with or without cirrhosis. In regard to the HIV infection, patients had to be relatively well, with a CD4 count of at least 100 cells/mm$^3$ and an HIV viral load of 50 copies/mL or lower. Patients were receiving stable antiretroviral medication regimens. Among the 106 patients enrolled, 2 patients relapsed, and 3 withdrew from the study. The overall SVR12 rate was 95%. In the 12 patients with preexisting RAVs, all achieved SVR12 (100%). The regimen was well-tolerated, and all adverse events were mild. Renal function was stable throughout. Sofosbuvir/velpatasvir therefore works very well for patients with HIV/HCV coinfection. It should be noted that all direct-acting antiviral regimens have a potential for drug-drug interactions, particularly when administered with antiretroviral therapy, and this needs to be considered prior to commencing HCV treatment.

Another special population is patients who have undergone renal transplantation. Previously, patients with severe chronic kidney disease have posed a dilemma for hepatologists. Ribavirin is poorly tolerated in patients receiving dialysis, such as those awaiting kidney transplantation, and therefore these patients were frequently ineligible for treatment with the interferon α–based regimens. After kidney transplantation, interferon is thought to increase the risk of renal rejection, so patients could not receive HCV treatment after renal transplantation, either. This population represents an important unmet medical need in HCV because most of these patients have gone untreated in the past.

Dr Massimo Colombo presented results from a study evaluating direct-acting antiviral agents in the post–kidney transplantation setting.[12] The study evaluated ledipasvir and sofosbuvir in durations of 12 and 24 weeks in patients who had undergone renal transplantation. Patients had genotype

1 or 4, and could be treatment-naive or treatment-experienced, with or without cirrhosis. Approximately 30% of the patients were treatment-experienced, and approximately 15% had cirrhosis. Among the 114 patients enrolled, 1 patient discontinued the study early due to an adverse event, and 2 were lost to follow-up. Excluding the patients lost to follow-up, the SVR12 was 100% with both treatment durations.

This study also looked at baseline RAVs. Among the 21 patients with these variants, all achieved an SVR12. The regimen was well-tolerated. Four patients developed mildly depressed renal function while on therapy, but overall, the glomerular filtration rates were stable. Therefore, ledipasvir/sofosbuvir was well-tolerated and highly efficacious among patients who had undergone renal transplantation.

***Disclosure***

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

## References


1. Ampuero J, Romero-Gómez M, Reddy KR. Review article: HCV genotype 3 – the new treatment challenge. *Aliment Pharmacol Ther*. 2014;39(7):686-698.
2. Pawlotsky J-M. Interferon-free treatment failures and HCV resistance. Paper presented at: the 2016 International Liver Congress of the European Association for the Study of the Liver; April 13-17, 2016; Barcelona, Spain.
3. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology*. 2015;62(3):932-954.
4. Jacobson IM, Asante-Appiah E, Wong P, et al. Prevalence and impact of baseline NS5A resistance associated variants (RAVs) on the efficacy of elbasvir/grazoprevir (EBR/GZR) against GT1a infection [AASLD abstract L22]. *Hepatology*. 2015;62(suppl 1).
5. Lawitz E, Poordad F, Wells J, et al. High efficacy of sofosbuvir/velpatasvir/GS-9857 with or without ribavirin for 12 weeks in direct acting antiviral-experienced patients with genotype 1 HCV infection [EASL abstract PS021]. *J Hepatol*. 2016;64(suppl 2).
6. Feld JJ, Jacobson IM, Hézode C, et al; ASTRAL-1 Investigators. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med*. 2015;373(27):2599-2607.
7. Lawitz E, Kowdley K, Curry M, et al. High efficacy of sofosbuvir/velpatasvir plus GS-9857 for 12 weeks in treatment-experienced genotype 1–6 HCV-infected patients, including those previously treated with direct-acting antivirals [EASL abstract PS008]. *J Hepatol*. 2016;64(suppl 2).
8. Poordad F, Gordon SC, Asatryan A, et al. High efficacy of ABT-493 and ABT-530 in HCV genotype 1 infected patients who have failed direct-acting antiviral-containing regimens: the MAGELLAN-1 study [EASL abstract GS11]. *J Hepatol*. 2016;64(suppl 2).
9. Kwo PY, Wyles DL, Wang S, et al. 100% SVR12 with ABT-493 and ABT-530 with or without ribavirin in treatment-naive HCV genotype 3-infected patients with cirrhosis [EASL abstract LB01]. *J Hepatol*. 2016;64(suppl 2).
10. Muir AJ, Strasser S, Wang S, et al. High SVR rates with ABT-493 + ABT-530 co-administered for 8 weeks in non-cirrhotic patients with HCV genotype 3 infection [EASL abstract PS098]. *J Hepatol*. 2016;64(suppl 2).
11. Wyles D, Brau N, Kottilil S, et al. Sofosbuvir/velpatasvir for 12 weeks in patients coinfected with HCV and HIV-1: the ASTRAL-5 study [EASL abstract PS104]. *J Hepatol*. 2016;64(suppl 2).
12. Colombo M, Aghemo A, Liu H, et al. Ledipasvir/sofosbuvir (LDV/SOF) for 12 or 24 weeks is safe and effective in kidney transplant recipients with chronic genotype 1 or 4 HCV infection [EASL abstract GS13]. *J Hepatol*. 2016;64(suppl 2).

SUPERSONIC imagine

SANDHILL SCIENTIFIC
a medovations company

# Partners in transforming patient outcomes

Renowned ultrasound imaging company **SuperSonic Imagine** has announced a key agreement with **Sandhill Scientific**, a leader in gastrointestinal diagnostic solutions, to distribute the breakthrough Aixplorer system.

The Aixplorer's innovative imaging capability is transforming lives with a fast, non-invasive exam taking just 60 seconds.

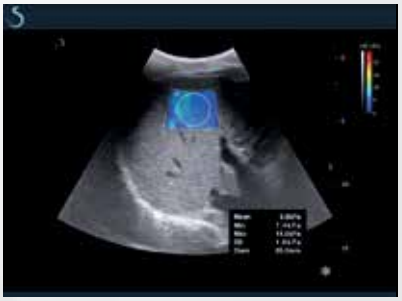
## ShearWave Elastography sees more

ShearWave Elastography easily detects and visualizes tissue stiffness resulting from liver fibrosis as never before. Color-coded mapping brings more clarity and accuracy to diagnosis and ongoing management of the disease in real time.

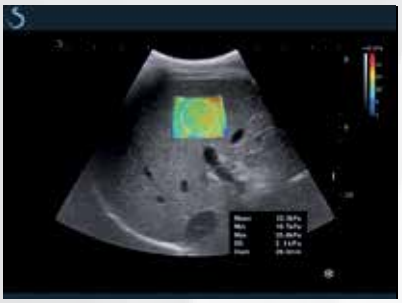
This exciting new agreement promises improved outcomes for those with liver disease, delivered through gastroenterologists and hepatologists across the United States.

F1

F2



F2-F3



F4

SWE images illustrating increased stiffness values as fibrosis severity advances from F1 – F4.

## For more information


**SUPERSONIC IMAGINE**

**Tel:** +1 (954) 660 3528

**www.supersonicimagine.com**

**SANDHILL SCIENTIFIC**

**Tel:** 800 558 6408 or +1 (303) 470 7020

**Fax:** +1 (303) 470 2975

**Email:** sales@sandhillsci.com

**www.sandhillsci.com**


G&H