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Presentation summaries in:

Comprehensive Reports on the Latest Advances in Gastroenterology and Hepatology From:

The 51st Annual Meeting of the European Association for the Study of the Liver

April 13-17, 2016
Barcelona, Spain

Digestive Disease Week 2016

May 21-24, 2016
San Diego, California

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GASTROENTEROLOGY & HEPATOLOGY

THE GASTRO & HEP REPORT

Comprehensive Reports on the Latest Advances in Gastroenterology and Hepatology From:

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A CURE FOR **EVERY TYPE**

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

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

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

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

INDICATIONS

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

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

Study Designs[1,2]

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

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

See full study information on following pages.

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

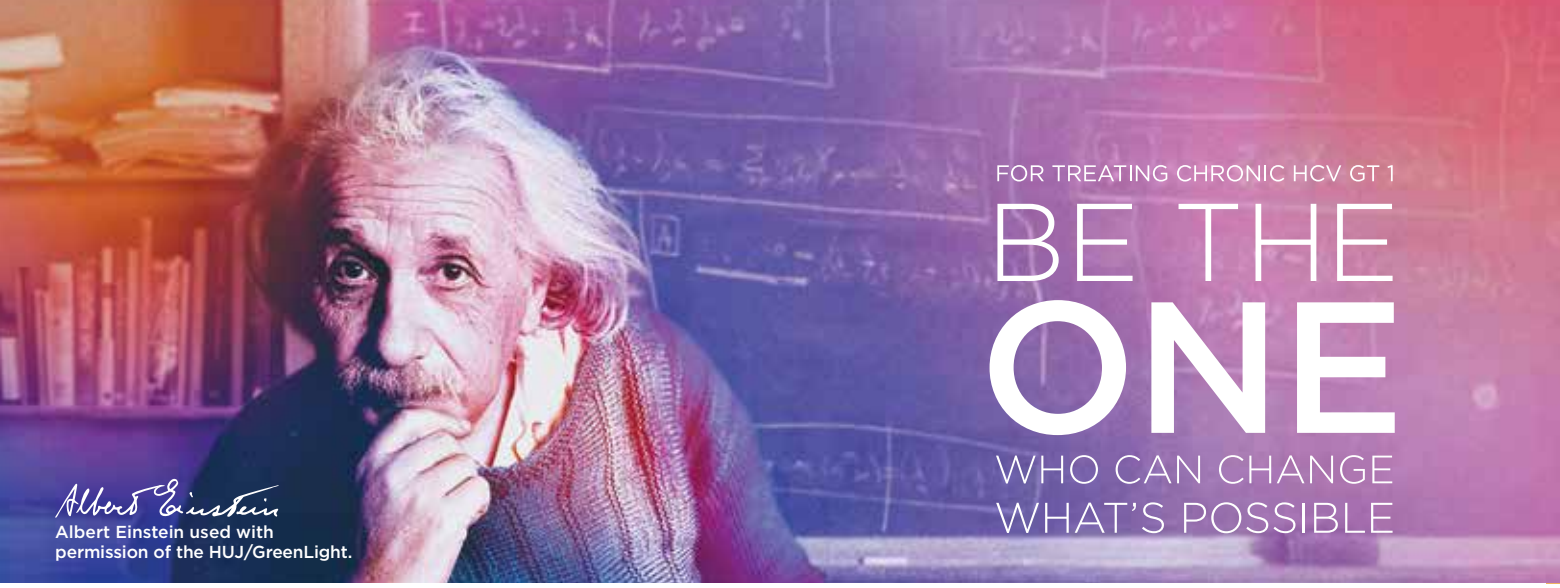
Cirrhosis = compensated cirrhosis (Child-Pugh A), RBV = ribavirin, TE = treatment-experienced (patients who have failed a peginterferon alfa + RBV–based regimen ± an HCV protease inhibitor), TN = treatment-naïve

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

HARVONI®
ledipasvir/sofosbuvir
90 mg/400 mg tablets

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

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



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

97%

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

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

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

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

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

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

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

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

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

IMPORTANT SAFETY INFORMATION FOR HARVONI AND EPCLUSA

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

HARVONI®
ledipasvir/sofosbuvir
90 mg/400 mg tablets

See what's possible at hcp.harvoni.com

NOW APPROVED

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

EXPAND WHAT'S POSSIBLE

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

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

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

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

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

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

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

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

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

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

IMPORTANT SAFETY INFORMATION FOR HARVONI AND EPCLUSA

ADVERSE REACTIONS

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

DRUG INTERACTIONS

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

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

NOW APPROVED

EPCLUSA®
sofosbuvir/velpatasvir
400 mg/100 mg tablets

See what's possible at hcp.epclusainfo.com

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

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS:

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

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

Risks Associated with RBV Combination Treatment

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

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

ADVERSE REACTIONS:

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

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

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

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

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

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

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

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

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

Brief Summary (cont.)

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

DRUG INTERACTIONS:

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

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

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

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

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

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

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

HIV Antiretrovirals:

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

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

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

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS:

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

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

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

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

Geriatric Use: Clinical trials of HARVONI included 225 subjects aged 65 and over (9% of total number of subjects in the clinical studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of HARVONI is warranted in geriatric patients.

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

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

References:

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

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

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

INDICATIONS AND USAGE: EPCLUSA is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection:

- Without cirrhosis or with compensated cirrhosis
- With decompensated cirrhosis for use in combination with ribavirin

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS:

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

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

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

ADVERSE REACTIONS:

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

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

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

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

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

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

Brief Summary (cont.)

DRUG INTERACTIONS:

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

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

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

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

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

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

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

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS:

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

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

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

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

Geriatric Use: Clinical trials of EPCLUSA included 156 subjects aged 65 and over (12% of total number of subjects in the Phase 3 clinical studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of EPCLUSA is warranted in geriatric patients.

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

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

GILEAD

Presentations in Hepatology

Six Weeks of Sofosbuvir/Ledipasvir Results in Undetectable Virus in Patients With Hepatitis C Virus Genotype 1 Infection

For the treatment of patients with hepatitis C virus (HCV) infection, regimens containing direct-acting antiviral (DAA) agents have largely replaced interferon-containing regimens and now represent the standard of care. Efforts to optimize treatment regimens are exploring shorter regimen duration and new combinations of DAA agents. At the 2016 European Association for the Study of the Liver (EASL) meeting, Katja Deterding, MD, of the Hannover Medical School in Hannover, Germany presented results from the HepNet Acute HCV IV Study Group trial, a single-arm trial that investigated the fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) given for 6 weeks to adults with acute HCV genotype 1 infection. The primary endpoint was sustained virologic response at 12 weeks after completion of treatment (SVR12).

Twenty patients were enrolled at 10 treatment centers in Germany from November 2014 through October 2015. All patients had detectable plasma HCV RNA and compensated liver disease. Patients had a mean age of 46 years (range, 23-63 years), and 55% had genotype 1a infection. All of the patients completed 6 weeks of antiviral treatment. At weeks 6 and 12, HCV RNA was undetectable in all of the patients, yielding a SVR12 of 100% (Figure 1). Rapid viral response did not correlate with baseline viral load, although patients who still had detectable HCV RNA at treatment week 4 were among those with a higher baseline viral load. Levels of alanine transaminase fell rapidly overall during the first 2 weeks of treatment, and 90% of patients had a normal alanine transaminase level at follow-up week 12. Six patients had elevated bilirubin levels at baseline, and in all 6 patients, bilirubin levels returned to normal by week 6 of treatment. By week 12 of treatment, bilirubin levels were above normal in 2 of the 20 study patients. Twenty-two adverse events (AEs) were considered possibly or probably related to study treatment, including gastrointestinal symptoms (n=4), fatigue (n=3), hair loss (n=3), and 2 events each of headache, skin reaction, abdominal pain, and psychiatric disorders.

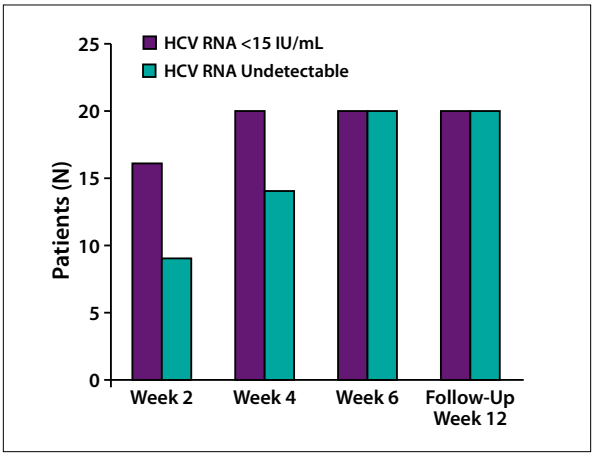


Figure 1. One hundred percent SVR12 at week 6 in a study evaluating sofosbuvir/ledipasvir in 20 patients with acute hepatitis C virus (HCV) genotype 1 monoinfection.

SVR12, sustained virologic response at week 12.

Adapted from Deterding K 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).

Sofosbuvir/Velpatasvir Plus GS-9857 Yields High Efficacy in Previously Treated Patients With Hepatitis C Virus Genotypes 1 Through 6

At the 2016 EASL meeting, Eric Lawitz, MD, of the University of Texas Health Science Center in San Antonio, Texas presented results from three phase 2 trials that investigated the combination of sofosbuvir, velpatasvir, and GS-9857 in previously treated HCV patients. The open-label TRILOGY-3 trial enrolled patients with HCV genotype 1 infection previously treated for at least 6 weeks with a DAA agent. A single daily tablet of sofosbuvir (400 mg)/velpatasvir (100 mg) plus daily GS-9857 (100 mg) was administered to 24 patients for 12 weeks, and 25 patients received the same regimen plus weight-based ribavirin. Patients had a mean age of 54 years (range, 18-75 years). Approximately half had compensated cirrhosis, and 88% had HCV genotype 1a infection. The overall SVR12 rate was 98%, with 1 patient in the ribavirin-containing arm relapsing at follow-up week 4. All 12 of the patients without baseline resistance-associated variants (RAVs) achieved SVR12. Of the 36 patients with any baseline RAV, 35 (97%) achieved SVR12. Most AEs were of mild-to-moderate severity. AEs of any grade occurred in 46% of patients in the ribavirin-free arm and in 60% of patients in the ribavirin-containing arm. One patient in the ribavirin-free arm experienced a serious AE of pneumonia but completed the DAA regimen and achieved SVR12.

Two other phase 2 studies investigated the same DAA combination in patients with HCV genotype 1 infection (GS-US-367-1168) or HCV genotype 2 to 6 infection (GS-US-367-1169). The 2 studies enrolled a total of 128 treatment-experienced patients with or without cirrhosis and included those with prior exposure to DAA agents. The 128 patients received treatment with 12 weeks of daily sofosbuvir (400 mg)/velpatasvir (100 mg) plus daily GS-9857 (100 mg). Patients had a median age of 58 years (range, 37-77 years), approximately three-fourths had the interleukin-28B non-CC genotype, and 48% had cirrhosis. HCV genotypes included 1 (49%), 2 (16%), 3 (27%), and 4 or 6 (7%). All of the 51 patients without baseline RAVs achieved SVR12. RAVs were present in 77 patients (60%) at baseline, and 76 (99%) of these patients achieved SVR12. The single viral failure occurred at follow-up week 8 in a patient with HCV genotype 3 infection. In the entire cohort of previously treated patients, a SVR12 rate of 100% was achieved in patients with HCV genotype 1, 2, 4, or 6, with a SVR12 rate of 97% observed in patients with HCV genotype 3 infection. The ability to achieve SVR12 was not impacted by the presence or absence of cirrhosis. Sixty-five percent of patients experienced an AE of any grade, with the most common being headache (22%), diarrhea (19%), fatigue (20%), and nausea (14%).

ASTRAL-5: 12 Weeks of Sofosbuvir/Velpatasvir in Patients With Hepatitis C Virus and HIV-1 Coinfection

At the 2016 EASL meeting, David Wyles, MD of the University of California in San Diego, California presented findings from the single-arm, open-label, phase 3 ASTRAL-5 study, which investigated the safety and efficacy of the fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) administered daily in a single tablet for 12 weeks in patients with HCV and HIV-1 coinfection. Enrolled patients had HCV genotypes 1 through 6, with or without compensated cirrhosis and with or without prior treatment. All patients were on stable antiretroviral therapy, had a CD4 cell count of at least 100 cell/µL, and had a maximum HIV RNA level of 50 copies/mL.

The 106 patients had a mean age of 54 years (range, 25-72 years) and included 29% treatment-experienced and 18% cirrhotic patients. Patients had a mean HCV RNA level of 6.3 $\log_{10}$ IU/mL (range, 5.0-7.4 $\log_{10}$ IU/mL). The SVR4 and SVR12 rates were both 95%, with 2 patients still in follow-up omitted from the SVR12 results (Figure 2). Two patients relapsed, 2 were lost to follow-up, and 1 withdrew consent, accounting for the 5 patients who failed to achieve SVR12. All HCV genotypes showed high SVR12 rates, including 1a (95%), 1b (92%), 2 (100%), 3 (92%), and 4 (100%). Patients with cirrhosis (n=19) and those without (n=85) achieved high SVR12 rates of 100% and 94%, respectively. Previously treated (n=29) and treatment-naive patients (n=75) had SVR12 rates of 97% and 93%, respectively. SVR12 rates were 100% for patients with RAVs and 98% for those without.

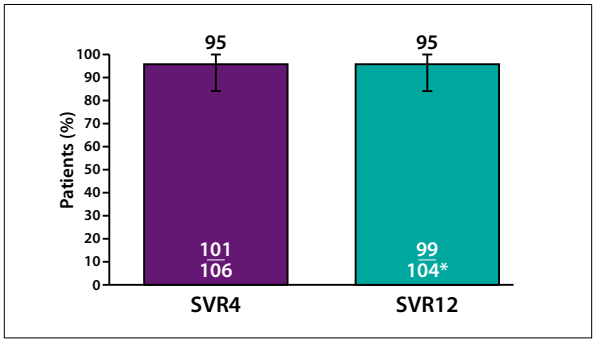


Figure 2. SVR4 and SVR12 rates in the ASTRAL-5 study of patients coinfected with HIV-1 and hepatitis C virus.

*Two patients were pending assessment of SVR12; both achieved SVR4.
SVR4, sustained virologic response at week 4; SVR12, sustained virologic response at week 12.

Adapted from Wyles D 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).

Seventy-one percent of patients experienced an AE of any grade, the majority of which were grade 1 or 2. The most common AEs of any grade were fatigue (25%), headache (13%), arthralgia (8%), upper respiratory tract infection (8%), and diarrhea (8%). Eight percent of patients experienced grade 3/4 AEs. Two patients (2%) experienced serious AEs, neither of which was considered related to study treatment. Study treatment was discontinued in 2% of patients due to an AE.

Cirrhotic Hepatitis C Virus Genotype 3 Patients Successfully Treated With ABT-493 and ABT-530 With or Without Ribavirin

HCV genotype 3 accounts for nearly one-third of HCV infections worldwide and is associated with an increased risk of hepatic steatosis and other complications. The genotype has proven resistant to many DAA regimens. Regimens containing sofosbuvir have achieved SVR12 rates as high as 88% in patients with HCV genotype 3 infection. The next-generation, pangenotypic DAA agents ABT-493 and ABT-530 inhibit NS3/4A and NS5A, respectively; they act synergistically against HCV and have demonstrated efficacy against common NS3 and NS5A RAVs. At the 2016 EASL meeting, Paul Kwo, MD, of the Department of Medicine at Indiana University in Indianapolis, Indiana presented results

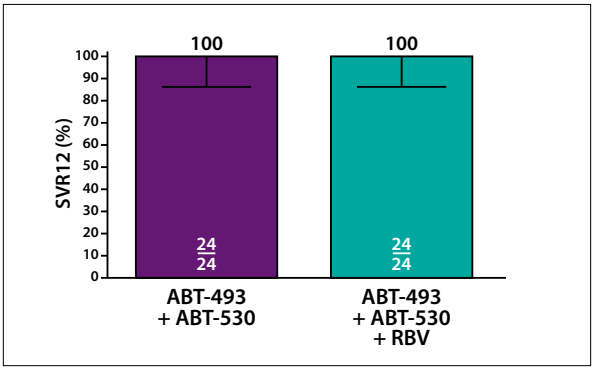


Figure 3. SVR12 rates in an intent-to-treat analysis of the SURVEYOR-II trial.

RBV, ribavirin; SVR12, sustained virologic response at week 12.

Adapted from Kwo PY et al. 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).

of the 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) trial, an open-label, multicenter, phase 2 trial investigating daily ABT-493 (300 mg) plus ABT-530 (120 mg) administered for 12 weeks, with or without ribavirin, in patients with HCV genotype 3 infection and cirrhosis. The study includes several other arms evaluating the same drug combination with varying treatment durations in patients infected with different HCV genotypes, with or without cirrhosis.

Forty-eight patients were evenly randomized to receive study treatment with or without ribavirin (800 mg daily). All patients had HCV genotype 3a infection, an HCV RNA level of greater than 10,000 IU/mL, and compensated cirrhosis. Patients had a median age of 55 years (range, 30-68 years) and a median HCV RNA level of 6.4 $\log_{10}$ IU/mL (range, 4.2-7.3 $\log_{10}$ IU/mL). NS3 or NS5A RAVs were identified in 10 patients (42%) in the ribavirin-free arm and 8 (33%) in the ribavirin-containing arm. After 12 weeks of treatment, both arms yielded SVR12 rates of 100% (Figure 3). The DAA combination was generally well tolerated. The majority of AEs were mild, and no patient discontinued treatment due to an AE. In the ribavirin-free vs the ribavirin-containing arms, AEs of any grade occurred in 88% and 83% of patients, respectively, with serious AEs observed in 4% and 8% of patients, respectively. More frequent AEs in the ribavirin-free arm included urinary tract infections (17% vs 8%) and diarrhea (21% vs 0%).

Exercise Reduces Steatosis in Patients With Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are the most common causes of liver disease in Western populations. In addition to having excessive fat in the liver, some patients with NAFLD also have liver cell injury and inflammation. NAFLD can progress to NASH, greatly increasing the risk of cirrhosis, liver failure, and hepatocellular carcinoma. At Digestive Disease Week (DDW) 2016, Pegah Golabi, MD, of the Inova Health System in Falls Church, Virginia presented findings from a systematic review of pooled data from controlled trials that reported the efficacy of exercise intervention on reducing steatosis associated with NAFLD.

The Ovid Medline and PubMed databases were searched for randomized controlled trials and prospective cohort studies that investigated the effects of exercise alone or a combination of exercise and diet in adult patients with NAFLD. The following keywords, including every possible keyword combination, were used for searching: NASH, NAFLD, nonalcoholic steatohepatitis, nonalcoholic fatty liver disease, fat, steatosis, diet, exercise, MRI, MR spectroscopy, liver biopsy, RCT, and observational study. Included studies were published between January 2010 and August 2015. A clear description of exercise, including type, duration, intensity, and frequency, was required. Confirmation of NAFLD diagnosis and measurement of outcomes by computed tomography, hydrogen magnetic resonance spectroscopy, or liver biopsy was required, as was documentation of adherence to the prescribed exercise regimen.

Seven studies encompassing 390 patients met the selection criteria. Of the 7 included studies, 5 used exercise alone and 2 used exercise and diet as intervention. Five of the studies were randomized controlled trials. Hydrogen magnetic resonance spectroscopy was the most commonly used modality for assessing steatosis after intervention. In the exercise-only group, fat mobilization ranged from 5.7% to 35.8%. In the cohort with exercise and diet intervention, fat mobilization was 6.7% and the NAFLD activity score decreased by 0.9 ± 1.3 (P<.001). The single study that compared the efficacy of aerobic vs resistance exercise found no difference in outcomes.

Epidemiologic Trends in Hepatitis B Virus Infection in Hospitalized Patients

The prevalence of hepatitis B virus (HBV) infection has been estimated at 3.61% worldwide, but prevalence varies widely across different regions. In the United States, a country with low endemicity, implementation of vaccination

programs and general improvements in health care have resulted in a current prevalence estimate of approximately 0.3% to 0.4%. Limited data are available describing the prevalence of acute, carrier, and chronic HBV infection in the United States among hospitalized patients. At DDW 2016, Albert Do, MD, of the Yale-New Haven Hospital in New Haven, Connecticut presented findings from an analysis of HBV infection rates in patients hospitalized in the United States from 2000 to 2012.

Patient data were extracted from the Nationwide Inpatient Sample, the largest database with inpatient care data from all payers. The database contains reports of approximately 7 to 8 million annual hospital stays from approximately 1000 hospitals in the United States. Data were extracted for all patients with International Classification of Disease, 9th edition primary or secondary diagnosis of acute HBV infection with (070.20) or without (070.30) hepatic coma; chronic HBV infection with (070.22) or without (070.33) hepatic coma; and HBV carrier (V02.61). Trends testing was performed with univariate linear regression and determination of coefficient estimation interpreted as a per-year rate change.

The incidence of acute HBV infection increased from 69.7 cases per 100,000 people in 2000 to 106.5 cases in 2012, reflecting an annual increase of 3.2 cases per 100,000 people (P<.001). From 2000 to 2012, the prevalence of chronic HBV infection increased from 69.0 cases per 100,000 people to 89.8 cases, an annual increase of 1.5 cases per 100,000 people (P=.012). During the same 12-year period, the prevalence of HBV carriers decreased from 29.5 cases per 100,000 people to 21.8 cases, or −1.1 cases per 100,000 people per year (P=.016). Identification of key mechanisms responsible for the increase in acute and chronic HBV infection rates is necessary for the development of effective interventions.

Hepatic Encephalopathy as an Organ Allocation Factor in Patients Awaiting Liver Transplantation

Patients requiring a liver transplantation undergo extensive evaluation to determine the extent of disease and level of urgency. Because the demand for donor livers far exceeds the supply, patients with the perceived highest need are given priority. As wait times for donor livers have increased, more patients are being removed from waitlists due to morbidity and mortality. The Model for End-Stage Liver Disease (MELD) score was developed to provide an objective measure of disease severity and give transplant priority to patients with the most urgent medical need. The score incorporates measurement of serum creatinine, total bilirubin, and the international normalized ratio of prothrombin time. Hepatic encephalopathy has been identified as an independent predictor of mortality and has been associated with increased short-term mortality in patients with MELD scores ranging from 6 to the maximum of 40.

At DDW 2016, Avin Aggarwal, MD, of the Stanford University School of Medicine in Stanford, California presented results of a study that determined the 90-day survival time among liver transplant waitlist registrants with no hepatic encephalopathy vs those with grade 3/4 hepatic encephalopathy based on West Haven criteria. All patients had a MELD score of 21 or greater. Survival data were further analyzed based on MELD scores of 21 to 25, 26 to 30, 31 to 35, and 36 to 40.

Based on analysis by MELD score, 90-day survival was reduced in patients with grade 3/4 hepatic encephalopathy vs those without. Differences in 90-day mortality for patients with grade 3/4 vs no hepatic encephalopathy increased dramatically in patients with MELD scores of 31 or higher. For the cohort of patients with MELD scores of 31 to 35, mean 90-day survival was 73.04% vs 47.86% in patients with grade 3/4 vs no hepatic encephalopathy, respectively (P=.0003). For the cohort of patients with MELD scores of 36 to 40, mean 90-day survival was 60.26% vs 36.64% in patients with grade 3/4 vs no hepatic encephalopathy, respectively (P=.012). Patients with grade 3/4 hepatic encephalopathy and MELD scores of 30 to 34 had a mean 90-day survival of 52.24%; in contrast, patients with a MELD score of 35 or greater had a mean 90-day survival of 62.97% (P=.01). The data demonstrate that patients with grade 3/4 hepatic encephalopathy are at increased risk of death that is not captured by the MELD score.

Presentations in IBD

Reduced-Dose Azathioprine Plus Infliximab in Patients With Inflammatory Bowel Disease

The combination of infliximab plus azathioprine is the most effective treatment approved for patients with Crohn's disease (CD) or ulcerative colitis (UC), but the combination of azathioprine with agents that inhibit the activity of tumor necrosis factor α (TNFα) appears to increase the risk of infection and hepatosplenic lymphoma. At DDW 2016, Emilie Del Tedesco, MD, of the Centre Hospitalier Universitaire de Saint-Étienne in Saint-Priest en Jarez, France presented results of a prospective study that investigated combinations of infliximab with reduced doses of azathioprine in patients with inflammatory bowel disease (IBD). The study included 3 cohorts of patients who had received at least 1 year of treatment with infliximab plus azathioprine. All patients were in deep remission for at least 6 months based on clinical, endoscopic, and/or biomarker analysis. All patients had a trough level of infliximab of greater than 2 µg/mL and were on stable doses of azathioprine, ranging from 2.0 mg/kg to 2.5 mg/kg daily, plus infliximab (5 mg/kg every 8 weeks). Patients in cohort A continued on pre-enrollment doses of both drugs. Patients in cohort B received one-half of the pre-enrollment dose of azathioprine, with a minimum dose of 50 g daily. Patients in cohort C discontinued azathioprine and continued receiving infliximab monotherapy. The primary endpoint was failure, defined as clinical relapse and/or the need to change the original regimen due to AEs.

Cohorts A, B, and C included 28, 27, and 26 patients, respectively. In cohorts A, B, and C, 5 (17.8%), 3 (11.5%), and 8 (30.7%) patients experienced failure at 1 year (P=.1 across groups). In cohort A, 3 patients had to discontinue azathioprine or reduce the dose due to myelotoxicity or digestive intolerance. In cohort A, trough levels of infliximab remained similar at baseline and at 1 year (3.95 µg/mL vs 3.6 µg/mL, respectively). In cohort B, the mean trough level also remained stable at baseline and at 1 year after reduction of the azathioprine dose (3.95 µg/mL vs 2.60 µg/mL, respectively); however, mean 6-thioguanine nucleotide levels decreased significantly (310 pmol/8 × 10^8 red blood cells vs 128 pmol/8 × 10^8 red blood cells, respectively; P=.03). In cohort C, mean trough levels of infliximab decreased significantly at 1 year (4.2 µg/mL vs 2.1 µg/mL; P=.02). An unfavorable pharmacokinetic profile, defined as a decrease in trough infliximab level below 1 µg/mL or undetectable serum infliximab with positive antibodies to infliximab at 1 year, was observed in 4 (14.2%) patients in cohort A, 5 (18.5%) patients in cohort B, and 14 (53.8%) patients in cohort C (P=.01 for A vs C and for B vs C). Based on receiver-operator characteristic analysis, a 6-thioguanine nucleotide level of less than 105 pmol/8 × 10^8 red blood cells was associated with this unfavorable pharmacokinetic outcome.

Insufficient Exposure to Infliximab Is Linked to Immunogenicity and Increased Infliximab Clearance in Inflammatory Bowel Disease

Patient development of antibodies to infliximab has been associated with reduced serum levels of infliximab and reduced clinical response, presenting a serious challenge to effective IBD treatment. However, the majority of information on infliximab pharmacokinetics has been derived from clinical trials. At DDW 2016, Johannan Brandse, MD, of the Academic Medical Center in Amsterdam, The Netherlands presented results of study of a real-world IBD patient cohort from a single IBD center to identify parameters that influence infliximab pharmacokinetics. Serum levels of infliximab and antibodies to infliximab were measured using an enzyme-linked immunosorbent assay and antigen-binding test. Pharmacokinetics and antibodies to infliximab were measured simultaneously using nonlinear mixed-effects modeling.

The study included 253 CD and 79 UC patients, with 997 measurements of infliximab levels and 756 measurements of antibodies to infliximab. Infliximab was the first anti-TNFα agent in 80% of patients, and 43% received concomitant immunomodulation. The mean infliximab dose was 5.47 ± 1.33 mg/kg. Antibodies to infliximab were detected in 75 (23%) patients. Anti-infliximab antibody titers of greater than 30 AU/mL were consistently associated with undetectable serum infliximab concentrations. Increased rates of infliximab clearance were associated with several factors, including increased body mass, reduced levels of serum albumin, and higher titers of anti-infliximab antibodies (Table 1). Increasing cumulative time spent with infliximab exposure below a trough level of 3 µg/mL was associated with up to a 4-fold increase in risk of developing antibodies

Table 1. Factors Associated With the Development of Antibodies to Infliximab in Inflammatory Bowel Disease Patients

Factor	Range	Clearance (L/day)
Body mass (kg)	40-149	0.27-0.53
Serum albumin (g/dL)	2.0-5.4	0.93-0.24
Titers of antibodies to infliximab (AU/mL)	0-53,000	0.36-15.93

Adapted from Brandse JF et al. Insufficient infliximab exposure predisposes to immunogenicity and enhanced clearance of infliximab in IBD [DDW abstract 695]. *Gastroenterology.* 2016;150(4)(suppl).

to infliximab. The development of a model that predicts serum infliximab concentrations and the presence of anti-infliximab antibodies may facilitate individualized dosing and cost reduction.

IM-UNITI: A Phase 3 Trial of Ustekinumab Maintenance Therapy in Patients With Moderate-to-Severe Crohn's Disease

Ustekinumab is a humanized monoclonal antibody that binds to the p40 subunit of interleukin-12 and interleukin-23, both of which are involved in regulating immune system activity. In two phase 3 trials, a single intravenous infusion of the antibody induced clinical responses and remissions in patients with CD who are refractory to TNFα antagonists or have failed conventional therapies. At DDW 2016, William Sandborn, MD, of the University of California at San Diego in La Jolla, California presented results from the double-blind, placebo-controlled phase 3 IM-UNITI (A Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Patients With Moderately to Severely Active Crohn's Disease) trial of ustekinumab maintenance therapy in patients with moderate-to-severe CD. The study included patients who achieved a clinical response at week 8 in 1 of the ustekinumab induction trials. Three hundred thirty-eight patients were randomized to receive subcutaneous injections of placebo or ustekinumab (90 mg) every 8 or 12 weeks. The primary endpoint was clinical remission at week 44.

At week 44, ustekinumab demonstrated superiority in patients dosed every 8 weeks (53.1%; *P*=.005) or every 12 weeks (48.8%; *P*=.040) vs placebo (35.9%). The treatment effect difference between ustekinumab and placebo was numerically higher for treatment every 8 weeks vs every 12 weeks (17.2% vs 13.0%). The proportion of patients who maintained a clinical response at week 44 was higher in the patients who received ustekinumab every 8 weeks (59.4%) or every 12 weeks (58.1%) vs placebo (44.3%; *P*<.05 for both). In patients not receiving concomitant corticosteroids, the proportion of patients in clinical remission at week 44 was 46.9% and 42.6% in the cohorts receiving ustekinumab every 8 or 12 weeks, respectively, and was superior to placebo (29.8%; *P*=.004 and *P*=.035, respectively). In the 3 arms, rates of AEs ranged from 80.3% to 83.5%. In the patients receiving ustekinumab every 8 weeks or every 12 weeks or placebo, rates of serious AEs were 9.9%, 12.2%, and 15.0% and rates of serious infections were 2.3%, 5.3%, and 2.3%, respectively. No deaths or major cardiovascular events were reported.

A Study of Drug Dose Adjustment Based on Symptoms Vs Serum Levels in Patients With Crohn's Disease

The combination of infliximab and azathioprine can eradicate colonic ulcers in approximately half of CD patients. To obtain the optimal therapeutic window, infliximab dosing can be adjusted to achieve serum levels of approximately 6 µg/mL to 10 µg/mL. At DDW 2016, Geert D'Haens, MD, PhD, of the Academic Medical Center in Amsterdam, The Netherlands presented results of a double-blind, multicenter, randomized, controlled study that compared outcomes in CD patients treated with infliximab and azathioprine with patients randomized to receive infliximab dose adjustments based on either serum drug levels or symptom severity. Included patients had active CD, based on a CD activity index (CDAI) score of greater than 220, a serum C-reactive protein level of greater than 5 mg/L and/or a fecal calprotectin level of greater than 250 µg/g with endoscopic ulcerations, and no prior exposure to biologic treatments for their CD. Patients received induction treatment comprising 3 infusions of infliximab (5 mg/kg) in combination with azathioprine (2-2.5 mg/kg daily). At week 14, patients were randomized to receive 1 of 3 maintenance regimens: dose intensification of infliximab in steps of up to 2.5 mg/kg based on clinical symptoms, biomarker analysis, and serum drug concentrations; infliximab dose intensification from 5 mg/kg to 10 mg/kg based on the same criteria as for group 1; and infliximab dose increase to 10 mg/kg based on clinical symptoms alone. The primary endpoint was sustained corticosteroid-free clinical remission from weeks 22 to 54 and the absence of ulceration at 1 year based on centrally evaluated endoscopy. The target serum level of infliximab was a trough concentration greater than 3 µg/mL.

One hundred twenty-two patients were randomized to treatment. Patients had a median age of 29.8 years, and 58% were female. Central evaluation of endoscopies

had not been completed at the time of the presentation. Based on local evaluation, the proportion of patients who met the primary endpoint criteria was 47% (21/45) in group 1, 38% (14/37) in group 2, and 40% (16/40) in group 3. The proportion of patients without ulceration at week 54 in groups 1, 2, and 3 was 49%, 51%, and 45%, respectively, and dose intensification was performed in 51%, 65%, and 40% of patients in the same groups, respectively. Results based on central evaluation of endoscopy results, as well as detailed pharmacokinetic, immunogenic, and biomarker analysis, will be forthcoming.

6-Mercaptopurine for Preventing Recurrence of Crohn's Disease After Surgical Resection

As many as 65% of CD patients require an operation to control the disease within the first 10 years after acquiring the condition. At DDW 2016, Ian Arnott, MD, of the Edinburgh Clinical Trials Unit at the University of Edinburgh in Edinburgh, United Kingdom presented results of TOPPIC (Randomised Controlled Trial of 6-Mercaptopurine [6MP] Versus Placebo to Prevent Recurrence of Crohn's Disease Following Surgical Resection), a prospective trial that evaluated 6-mercaptopurine vs placebo for the delay or prevention of postoperative recurrence of CD. The double-blind, parallel-group, randomized trial included patients with a confirmed diagnosis of CD from 29 hospitals in the United Kingdom. Each patient received a daily oral dose of 6-mercaptopurine or placebo for a maximum 36 months. The 6-mercaptopurine dose was adjusted by weight and thiopurine methyltransferase levels. Safety monitoring was blinded. The primary endpoint was defined by clinical recurrence of CD, defined as a CDAI score of greater than 150 plus a 100-point score increase, and the need for anti-inflammatory rescue therapy or primary surgical intervention. The secondary endpoint was endoscopic recurrence.

One hundred twenty-eight (53%) patients were randomized to 6-mercaptopurine and 112 (47%) to placebo. A greater proportion of patients in the placebo group achieved the primary endpoint (23.2% vs 12.5%; adjusted *P*=.073; hazard ratio [HR], 0.535; 95% CI, 0.27-1.06). Smokers were more likely to achieve the primary endpoint compared with nonsmokers *(P*=.018; HR, 0.127; 95% CI, 0.04-0.46). Smoking was a predictive factor for the primary outcome (HR, 2.06; 95% CI, 1.09-3.90), but age at diagnosis, disease duration, sex, previous surgery, prior thiopurine treatment, and prior treatment with anti-TNFα agents were not. Based on post hoc analysis, a greater proportion of patients maintained complete endoscopic remission in the 6-mercaptopurine group compared with the placebo group at week 49 (29.7% vs 14.4%; *P*=.006) and week 157 (22.5% vs 12.5%; *P*=.041). The median duration of treatment was similar in the 6-mercaptopurine and placebo groups.

Oral Tofacitinib Induction Therapy Achieves Phase 3 Endpoints in Patients With Moderate-to-Severe Ulcerative Colitis

Tofacitinib is an orally available small molecule inhibitor of Janus kinase 3, a key mediator of inflammation. At DDW 2016, William Sandborn, MD, of the University of California at San Diego in La Jolla, California presented findings from two phase 3 trials of tofacitinib in patients with UC. The OCTAVE (A Study Evaluating the Efficacy and Safety of CP-690,550 in Patients With Moderate to Severe Ulcerative Colitis) Induction 1 and OCTAVE Induction 2 trials enrolled adult patients who had moderately to severely active UC, defined by full Mayo criteria, and had previously failed treatment with corticosteroids, azathioprine, 6-mercaptopurine, and/or inhibitors of TNFα. Patients were randomized 4:1 to receive tofacitinib (10 mg twice daily) or placebo for 8 weeks. The primary endpoint was remission at week 8, defined as a total Mayo score of 2 or lower, no Mayo subscore greater than 1, and a rectal bleeding subscore of 0. Mucosal healing at week 8, defined as a Mayo endoscopic subscore of 1 or lower, was a key secondary endpoint.

At baseline, 53% to 58% of patients in all arms in both studies had prior exposure to a TNFα inhibitor. Both trials met the primary endpoint, with remission rates at week 8 for tofacitinib vs placebo of 18.5% vs 8.2% (*P*<.01; 95% CI, 4.3%-16.3%) in OCTAVE Induction 1 and 16.6% vs 3.6% (*P*<.001; 95% CI, 8.1%-17.9%) in OCTAVE Induction 2. Also at week 8, a significantly greater proportion of patients in the tofacitinib arms had achieved mucosal healing and clinical response vs placebo (Table 2). Efficacy outcomes were similar in patients with vs without prior exposure to anti-TNFα therapy. Improvements in partial Mayo score were significantly greater in patients treated with active drug compared with placebo at weeks 2, 4, and 8. No new safety signals were raised. Rates of AEs and serious AEs were comparable across the 4 treatment arms. One patient receiving tofacitinib (10 mg twice daily) died of a dissecting aortic aneurysm. Increased levels of serum lipids and creatinine kinase were observed in patients treated with tofacitinib.

Response to Vedolizumab Is Recaptured by Escalating the Dose to Every 4 to 6 Weeks

In a single study of patients with CD whose response to vedolizumab has declined, increasing the frequency of the vedolizumab dose from 300 mg every 8 weeks to 300 mg every 4 weeks was shown to recapture patient

Table 2. Outcomes at 8 Weeks in the OCTAVE Induction 1 and 2 Trials

	OCTAVE Induction 1		
	Tofacitinib (n=476)	**Placebo (n=122)**	**95% CI**
Remission, n (%)	88 (18.5)	10 (8.2)	4.3-16.3
Mucosal healing, n (%)	149 (31.3)	19 (15.6)	8.1-23.4
Clinical response, n (%)	285 (59.9)	40 (32.8)	17.7-36.5
	OCTAVE Induction 2		
Remission, n (%)	71 (16.6)	4 (3.6)	8.1-17.9
Mucosal healing, n (%)	122 (28.4)	13 (11.6)	9.5-24.1
Clinical response, n (%)	236 (55.0)	32 (28.6)	16.8-36.0

Adapted from Sandborn W et al. Efficacy and safety of oral tofacitinib as induction therapy in patients with moderate to severe ulcerative colitis: results from two phase 3 randomized controlled trials [DDW abstract 767]. *Gastroenterology*. 2016;150(4)(suppl).

response. However, little information is available on the efficacy of the practice in a real-world setting. At DDW 2016, Antonio Mendoza Ladd, MD, of the University of Pennsylvania in Philadelphia, Pennsylvania presented findings from a retrospective analysis of outcomes in IBD patients with a lost response to vedolizumab and subsequent dose escalation who were treated at a large university referral practice.

A retrospective analysis was performed of all medical records of adult IBD patients who achieved a response with vedolizumab (300 mg) every 8 weeks from June 2014 through August 2015. Patients who lost their response to treatment and were started on vedolizumab (300 mg) every 4 or 6 weeks were identified. Of the 172 patients who received initial treatment with vedolizumab, 108 completed the 3 induction doses and were included in the study. Patients had a mean age of 45 years, and the mean follow-up from initiation of vedolizumab treatment was 23 weeks (range, 6-66 weeks). Responses to vedolizumab (300 mg) every 8 weeks were observed in 42 (50.6%) of 83 patients with CD and 15 (65%) of 23 patients with UC. Of the responding patients, 16 (38%) of the CD patients and 3 (20%) of the UC patients eventually lost their response, based on the opinion of the treating physician. In the patients who lost response, the vedolizumab dosing frequency was increased to 4 or 6 weeks in 10 and 9 patients, respectively. All of the patients exhibited a response to vedolizumab following dose escalation. One patient receiving vedolizumab (300 mg) every 4 weeks experienced pruritus, comprising the only AE.

Presentations in GERD

Risk Factors for Progression in Patients With Barrett Esophagus and Low-Grade Dysplasia

Ablation is recommended in patients with Barrett esophagus with low-grade dysplasia; however, in most patients, low-grade dysplasia does not progress, and the cost-effectiveness of ablation has not been evaluated. At DDW 2016, Anna Tavakkoli, MD, of the University of Michigan in Ann Arbor, Michigan presented results of a study that identified factors that predict progression from low-grade to high-grade dysplasia or esophageal adenocarcinoma and factors that predict regression to nondysplastic Barrett esophagus.

The authors identified 3064 patients diagnosed with Barrett esophagus between 1994 and 2014 in a pathology database of patients at the University of Michigan. From the subset of 1638 patients whose medical records had been abstracted, all patients with low-grade dysplasia who had undergone at least 1 esophagogastroduodenoscopy (EGD) after the diagnosis of low-grade dysplasia were identified. Exclusion criteria included endoscopic therapy and the presence of high-grade dysplasia or esophageal adenocarcinoma prior to the diagnosis of low-grade dysplasia. Prevalent cases were identified by the presence of low-grade dysplasia at the time of first EGD; incident cases were identified by the development of low-grade dysplasia after nondysplastic Barrett esophagus. Progression was defined as the development of high-grade dysplasia or esophageal adenocarcinoma. The extent of low-grade dysplasia was classified as unifocal, multifocal, or not otherwise specified.

Table 3. Adjusted Odds Ratios Associated With Progression and Regression of Low-Grade Dysplasia in Patients With Barrett Esophagus

	Regression to Nondyplastic BE, Odds Ratio (95% CI)	Progression to EAC or HGD, Odds Ratio (95% CI)
Incident LGD	1.0 (reference)	1.0 (reference)
Prevalent LGD	0.58 (0.230-1.47)	7.57 (1.90-30.2)
BMI (per increments of 5 kg/m^2)	1.57 (1.00-2.48)	0.520 (0.285-0.946)
Dysplasia Type		
Low-grade NOS	1.0 (reference)	1.0 (reference)
Unifocal LGD	2.41 (0.600-9.65)	0.168 (0.018-1.58)
Multifocal LGD	1.12 (0.415-3.04)	0.65 (0.198-2.15)

BE, Barrett esophagus; BMI, body mass index; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NOS, not otherwise specified.

Adapted from Tavakkoli A et al. Risk factors for progression of Barrett's esophagus with low-grade dysplasia [DDW abstract 838]. *Gastroenterology*. 2016;150(4)(suppl).

Ninety-seven patients with low-grade dysplasia were included in the analysis. Patients had a mean age of 73.6 years and had undergone a mean number of 4.8 EGD procedures with a mean follow-up of 4.3 years. Fifty-seven point seven percent of patients had long-segment Barrett esophagus. At the time of the first EGD, low-grade dysplasia was prevalent in 55 (56.7%) patients. Fifty-three patients (54.6%) regressed to nondysplastic Barrett esophagus. Twenty-three men and no women progressed to esophageal adenocarcinoma or high-grade dysplasia (23.7% vs 0%, respectively; *P*=.01). Patients with prevalent low-grade dysplasia were more likely to progress to esophageal adenocarcinoma or high-grade dysplasia (adjusted odds ratio [OR], 7.57; 95% CI, 1.90-30.2; Table 3). Increasing body mass index was inversely correlated with progression (adjusted OR based on increments of 5 kg/m^2, 0.520; 95% CI, 0.285-0.946). Patients with unifocal low-grade dysplasia were most likely to regress to nondysplastic Barrett esophagus (OR vs low-grade dysplasia not otherwise specified, 3.67; 95% CI, 1.01-13.3). In the cohort of patients who had undergone 2 or more EGD procedures, patients with low-grade dysplasia or who were indefinite for dysplasia on their second EGD were at increased risk of progression to high-grade dysplasia or esophageal adenocarcinoma (OR, 7.25; 95% CI, 1.28-41.1). The results suggest that patients with low-grade dysplasia may benefit from undergoing at least 1 surveillance EGD prior to considering ablation.

Progression Is Unlikely in Patients With Irregular Z Lines With Barrett Esophagus of Short Length

Patients with irregular esophageal Z lines with a Barrett esophagus length of less than 1 cm and intestinal metaplasia meet the definition of Barrett esophagus and usually undergo surveillance for progression; however, the risk of these patients developing high-grade dysplasia or esophageal adenocarcinoma has not been established. At DDW 2016, Prashanthi Thota, MD, of the Cleveland Clinic in Cleveland, Ohio presented results of a multicenter study of patients with nondysplastic Barrett

esophagus, which was defined by the presence of columnar mucosa on endoscopy and intestinal metaplasia on biopsy. Patients who developed dysplasia and esophageal adenocarcinoma within 1 year of the initial diagnosis were considered prevalent cases.

For the 1791 patients who met the inclusion criteria, the mean follow-up was 5.9 years; 167 patients had a Barrett esophagus length of less than 1 cm based on the presence of irregular Z lines. These 167 patients underwent a median of 3 endoscopies (interquartile range [IQR], 3.1-8.3). Compared with patients with a Barrett esophagus length of greater than 1 cm, patients with a Barrett esophagus length of less than 1 cm were more likely to be female (26.3% vs 14.8%; *P*<.001) and were less likely to have a history of smoking (33.5% vs 52.6%; *P*<.001). None of the 167 patients developed high-grade dysplasia or esophageal adenocarcinoma during the median follow-up of 4.8 years. In the entire cohort of 1791 patients, 71 incidents of high-grade dysplasia or esophageal adenocarcinoma occurred, and all were in patients with a Barrett esophagus length of greater than 1 cm.

Oral Budesonide Suspension as Maintenance Therapy in Adolescents and Adults With Eosinophilic Esophagitis

At DDW 2016, Evan Dellon, MD, of the University of North Carolina in Chapel Hill, North Carolina presented results of an open-label extension of a multicenter, double-blind, randomized, placebo-controlled study that evaluated the safety and efficacy of oral budesonide suspension for inducing and maintaining response in adolescents and adults with eosinophilic esophagitis. Patients were between the ages of 11 to 40 years with a diagnosis of eosinophilic esophagitis based upon 2011 consensus guidelines. Participants had completed the initial study treatment period, comprising 12 weeks of oral budesonide suspension (2 mg twice daily) or placebo, and had posttreatment esophageal biopsies. Patients enrolled in the extension study received an additional 24 weeks of open-label oral budesonide suspension. Outcomes after 24 weeks of treatment included histologic response, defined as 6 or fewer eosinophils per high-power field, and endoscopic severity, based on the Eosinophilic Esophagitis Endoscopic Reference Score (EREFS; range, 0-20).

During the initial 12 weeks of the open-label extension study, all patients received oral budesonide suspension (2 mg once daily). Subsequently, patients received clinically indicated dose increases of 1.5 mg twice daily and 2.0 mg twice daily. Esophageal biopsies were centrally evaluated by a single pathologist who was blinded to treatment allocation. The analysis was performed on 2 patient cohorts, those who received placebo followed by oral budesonide suspension (the placebo-first cohort) and those who received oral budesonide suspension throughout the entire initial and extension studies (the budesonide-only cohort).

The extension study enrolled 37 patients into the placebo-first cohort and 45 into the budesonide-only cohort. Twenty-seven (73%) and 37 (82%) patients, respectively, completed the 24-week extension treatment. For the placebo-first cohort, peak eosinophil count decreased from 119 eosinophils per high-power field at extension study baseline to 29 eosinophils at week 24 (*P*<.001). Forty-nine percent of patients achieved and maintained a histologic response, and the EREFS decreased from 7.6 to 3.6 (*P*<.001). For the budesonide-only cohort, the peak eosinophil count increased from 38 eosinophils per high-power field at extension study baseline to 72 eosinophils at week 24 (*P*=.007). Twenty-three percent had an ongoing histologic response, and the EREFS did not significantly change (3.8 at baseline vs 4.1 after treatment; *P*=.66). However, analysis of the same cohort data based upon histologic response showed that 42% of patients with an initial histologic response maintained that response. In this group, peak eosinophil count was 0.7 at baseline and 1.1 after extension study treatment, and the EREFS was 2.4 at baseline and 1.9 posttreatment. In patients who failed to achieve an initial response, continued treatment on the extension study did not induce a response. In this group, peak eosinophil count at baseline was 66 and increased to 94 after extension study treatment, and the EREFS was 4.8 at baseline and 4.9 after treatment. Accounting for dose changes did not affect the results. AEs were uncommon, and no safety concerns were raised.

Correlation Between Baseline Impedance, Postreflux Swallow-Induced Peristaltic Wave Index, and Gastroesophageal Reflux Disease Symptoms

Esophageal intraluminal baseline impedance and the postreflux swallow-induced peristaltic wave (PSPW) index are 2 impedance parameters that have been developed to evaluate esophageal mucosal integrity and chemical clearance. Incorporation of these 2 measurements has improved the diagnosis of gastroesophageal reflux disease (GERD), but the correlation between these novel impedance parameters and the extent of GERD symptoms has not been established. At DDW 2016, Joon Seong Lee, MD, of the Institute for Digestive Research in Seoul, South Korea presented findings from a retrospective review that evaluated the correlation between baseline impedance, the PSPW index, and GERD symptoms.

Impedance-pH tracings were evaluated from patients with suspected GERD. Quantitative descriptions of GERD symptoms with scores of 0 to 4 for severity and frequency had been obtained prior to impedance-pH monitoring. The overall severity of symptoms was obtained by adding the values of the severity and frequency scores. The PSPW index was defined as the number of reflux events followed within 30 seconds by a swallow-induced peristaltic wave divided by the total number of refluxes. Baseline impedance was measured in 6 impedance-measuring sites, from z1 to z6. Analysis of the relationship between the PSPW index, baseline impedance, and the degree of each symptom was carried out using the Pearson correlation.

Impedance-pH tracings from 143 patients were analyzed. The PSPW index was significantly lower in patients with heartburn (r=−0.186; *P*<.05). In contrast, the PSPW index was not significantly associated with the degree of dysphagia (r=−0.091; *P*=.168). Distal baseline impedance was significantly associated with the degree of dysphagia, as demonstrated by Pearson correlations for z3, z4, z5, and z6 of −0.328, −0.361, −0.316, and −0.273, respectively (*P*<.05). Other symptoms were not associated with distal baseline impedance, including heartburn, acid regurgitation, chest pain, hoarseness, and cough. Symptoms of heartburn were inversely correlated with the PSPW index, suggesting that delayed chemical clearance in the esophagus may induce heartburn, and dysphagia was inversely correlated with distal baseline impedance.

Measurement of the Esophagogastric Junction Contractile Integral in Patients With Gastroesophageal Reflux Disease or Erosive Esophagitis

At DDW 2016, Yu Kyung Cho, MD, of the Catholic University College of Medicine in Seoul, South Korea presented results of a study that assessed the clinical value of measuring the esophagogastric junction contractile integral (EGJ-CI) by high-resolution manometry in patients with suspected GERD. The study enrolled patients with typical and atypical GERD symptoms. All patients underwent upper endoscopy, esophageal high-resolution manometry, and impedance-pH testing. The EGJ-CI was calculated during 3 consecutive respiratory cycles, and the resulting value was divided by cycle duration.

Among the 103 enrolled patients, 42 were male and the median age was 51 ± 15 years. Seventeen patients had erosive esophagitis and 10 had hiatal hernia. Based on impedance-pH results, 22 patients had positive impedance-pH, including 19 with an abnormal acid exposure time and 3 with positive symptom association analysis. Twenty-two patients had functional heartburn, and 47 had non-GERD conditions. EGJ-CI was lower in patients with hiatal hernia (13 ± 6 mmHg × cm) and in those with erosive esophagitis (25 ± 20 mmHg × cm) vs patients without these conditions (62 ± 27 mmHg × cm; *P*<.05). EGJ-CI in patients with an abnormal acid exposure time was 34 ± 22 mmHg × cm, and 21 ± 14 mmHg × cm in patients with a positive symptom association analysis; in patients with a negative pH, EGJ-CI was 55 ± 38 mmHg × cm (*P*<.05).

EGJ-CI was similar for patients with functional heartburn and non-GERD conditions and was similar for patients with abnormal bolus exposure vs others. Receiver-operator characteristic analysis yielded an area under the curve of 0.80 for patients with erosive esophagitis compared with non-GERD patients (*P*<.01) and yielded the same result for the comparison of patients with a positive impedance-pH vs non-GERD patients (*P*<.01). The optimal cutoff values for identifying patients with erosive esophagitis or GERD were 33 mmHg × cm (sensitivity, 89%; specificity, 76%) and 40 mmHg × cm (sensitivity, 73%; specificity, 77%), respectively.

Presence of Gastroesophageal Reflux Disease Influences Composition of Nasal Cavity Microflora in Patients With Rhinosinusitis

Patients with GERD are at increased risk of chronic rhinosinusitis. It is not known how esophageal refluxate impacts the microflora of the nasal cavity and paranasal sinuses. At DDW 2016, Elena Onuchina, MD, of the Irkutsk State Medical Academy of Continuing Education in Irkutsk, Russian Federation presented results of a study that investigated changes to nasal microflora in patients with rhinosinusitis with or without GERD. Patients were diagnosed with rhinosinusitis based on international criteria, and diagnosis of GERD was based on the Montreal consensus.

The study included 64 patients aged 21 to 59 years. Group A included 30 patients with rhinosinusitis and GERD; group B included 34 patients with rhinosinusitis only. The median pH in the pharynx was 4.7 ± 0.4 in group A and 6.4 ± 0.6 in group B (*P*<.01). Growth of microflora was observed in the middle nasal meatus in 100% of patients in group A and 47% of patients group B (OR, 68.39; 95% CI, 3.9-1208.9; *P*<.001). The composition of the microflora in the middle nasal meatus differed between the 2 groups, demonstrated by a greater number of patients with rhinosinusitis and GERD harboring *Staphylococcus aureus* (*P*=.003), *Escherichia coli* (*P*=.029), and *Candida albicans* (*P*=.045). In the paranasal sinuses, growth of microflora was observed with similar frequency in groups A and B (33% and 32%, respectively), and microflora composition was similar.

Presentations in Endoscopy

Administration of Rectal Indomethacin Prior to ERCP Reduces Risk of Post-ERCP Pancreatitis

Administration of indomethacin following endoscopic retrograde cholangiopancreatography (ERCP) has been shown to reduce the incidence of post-ERCP pancreatitis in high-risk patients. However, the efficacy of rectal indomethacin administered before ERCP is unknown. At DDW 2016, Hui Luo, MD, of the Fourth Military Medical University in Xi'an, Shaanxi, China presented results of a prospective, randomized, controlled trial that investigated the efficacy of rectal indomethacin prior to ERCP in patients with a high or low risk of pancreatitis.

The study enrolled 2600 patients with native papilla at 6 centers in China. Patients were randomized to receive rectal indomethacin before or after ERCP. All patients in the pre-ERCP group received a single dose of rectal indomethacin within 30 minutes of the start of ERCP. In the post-ERCP group, only patients with a predicted high risk of post-ERCP pancreatitis received rectal indomethacin immediately after ERCP. The incidence of post-ERCP pancreatitis was 3.6% in the pre-ERCP treatment group and 7.7% in the post-ERCP treatment group (P<.001), and the incidence of moderate-to-severe post-ERCP pancreatitis was 0.8% vs 1.7%, respectively (P=.040). Compared with the post-ERCP group, the pre-ERCP group showed a reduced rate of post-ERCP pancreatitis in high-risk patients (5.4% vs 11.8%; P=.006) and low-risk patients (3.0% vs 6.5%; P<.001). Rates of AEs were similar in the pre- and post-ERCP treatment groups in terms of gastrointestinal bleeding, biliary infection, perforation, and other AEs. The results suggest that use of rectal indomethacin prior to ERCP in all patients without contraindications decreases the risk of post-ERCP pancreatitis without increasing the rate of bleeding events.

Radiation Exposure to Personnel Performing ERCP

ERCP is commonly performed with the patient either lying prone or in the left lateral decubitus position. Radiation scatter is hypothetically increased in patients in the latter position. Many personnel are present during the procedure, and radiation exposure to personnel may differ depending on each person's standing position and the patient's position. At DDW 2016, Worawarut Janjeurmat, MD, of the Thai Red Cross in Bangkok, Thailand presented results of a study that evaluated the absorbed dose of radiation among personnel performing ERCP.

Fifty-two patients undergoing ERCP at a single hospital from April 2015 through October 2015 were randomized to the prone vs left lateral decubitus position. All personnel wore a wrap-around lead apron and thyroid shield. A solid-state dosimeter was positioned over the thyroid shield of each person working around the ERCP table, including the first and second endoscopists and the nurse anesthetist. Following the ERCP procedure, all 3 dosimeters were read and fluoroscopic time was recorded.

Age, sex, body mass index, indication for ERCP, and fluoroscopic time were similar for both groups. Compared with the prone position, the left lateral decubitus position yielded higher mean effective doses per fluoroscopic time (mSv/min) for the first endoscopist (8.98 mSv/min vs 5.15 mSv/min; P=.008) and for the nurse anesthetist (10.67 mSv/min vs 4.96 mSv/min; P=.0001). In order to stay within the new recommended annual dose limit of 20 mSv/yr for the lens of the eye, the calculated maximum number of cases per year without wearing protective eyewear with the patient in the prone vs left lateral decubitus position is 660 and 490 cases for the first endoscopist and 690 and 360 cases for the nurse anesthetist, respectively. Wearing protective eyewear and placing patients in the prone position increases the number of cases that can be safely performed each year by the first endoscopist and the nurse anesthetist.

Optimizing Surveillance Intervals After Radiofrequency Ablation of Barrett Esophagus

Although radiofrequency ablation is an effective treatment for Barrett esophagus, the risk of recurrence remains a concern. Thus, endoscopic surveillance is recommended as frequently as every 3 months during the first year following complete eradication of intestinal metaplasia (CEIM). However, the surveillance intervals are not based on evidence. At DDW 2016, Cary Cotton, MD, of the University of North Carolina School of Medicine in Chapel Hill, North Carolina presented results of a study designed to develop and validate categories of recurrence risk in patients with Barrett esophagus who achieved CEIM by means of treatment with radiofrequency ablation and to propose evidence-based surveillance intervals for use after CEIM.

The initial survival analyses were performed using data available in the United States Radiofrequency

Table 4. Proposed Surveillance Intervals Presented as the Cumulative Time Following CEIM

	Low Risk	Moderate Risk	High Risk
	NDBE or IND With Segment Length <4 cm	NDBE or IND With Segment Length ≥4 cm, all LGD, HGD Under Age 50 Years	HGD 50 Years or Older, All IMC
Confirmation of CEIM	None	3 months	3 months
First surveillance visit	3 years	1 year	9 months
Second surveillance visit	8 years[a]	2.5 years	1.5 years
Third surveillance visit	13 years[a]	4 years[a]	2.5 years

CEIM, complete eradication of intestinal metaplasia; HGD, high-grade dysplasia; IMC, intramucosal adenocarcinoma; IND, indefinite for dysplasia; LGD, low-grade dysplasia; NDBE, nondysplastic Barrett esophagus.

[a]Recommendations greater than 3 years are fixed at previous interval due to insufficient data on recurrence in registries.

Adapted from Cotton CC et al. Evidence-based surveillance intervals following radiofrequency ablation (RFA) of Barrett's esophagus: an analysis of recurrence in the US RFA registry with validation in the UK national Halo Registry [DDW abstract 887]. *Gastrointest Endosc*. 2016;83(5)(suppl).

Ablation Registry, which reports outcomes of Barrett esophagus patients treated with radiofrequency ablation at 148 centers. Recurrence was defined as the diagnosis of high-grade dysplasia or worse histology in the esophagus or gastric cardia following CEIM. The best-fitting model was validated for the area under the receiver operating characteristic curve in the United Kingdom National Halo Registry, which reports outcomes in patients with dysplastic Barrett esophagus at 28 centers. Risk categories based on patient age, baseline histology, and Barrett esophagus segment length were created and calibrated using both cohorts. The yield of surveillance intervals was then simulated for the proposed risk categories of high, moderate, and low.

The analytic cohorts included 2952 patients from the United States registry and 412 from the United Kingdom registry. All patients had achieved CEIM, and findings were available from at least 1 endoscopy thereafter. The best-fitting Poisson model of advanced neoplasia recurrence included the patient's worst baseline pathologic grade, baseline age, and, in patients with nondysplastic Barrett esophagus, baseline segment length. Simulation of the proposed surveillance intervals for the respective risk categories in each cohort demonstrated a low incidence of invasive adenocarcinoma prior to the scheduled surveillance. Proposed surveillance intervals following CEIM for the high, moderate, and low risk categories are shown in Table 4.

Improving Biopsy Techniques to Increase Diagnostic Sensitivity in Patients With Suspected Malignant Biliary Strictures

Tissue sampling of biliary strictures by ERCP is associated with limited specificity for cancer detection. Peroral cholangioscopy (POC) combined with endoscopic ultrasound–guided fine needle aspiration biopsy (EUS-FNAB) potentially offers increased diagnostic sensitivity and specificity over ERCP in the context of suspected malignant biliary strictures. At DDW 2016, Yun Nah Lee, MD, of the Soonchunhyang University School of Medicine in Bucheon, South Korea presented findings from a study that compared the diagnostic utility of POC-guided forceps biopsy vs EUS-FNAB on the stricture location in patients with suspected malignant biliary strictures.

Patients with suspected malignant biliary strictures were initially diagnosed by means of ERCP with transpapillary forceps biopsy. Based on stricture location in the suprapancreatic or intrapancreatic common bile duct, patients were classified as having a proximal or distal type of stricture, respectively. In cases where transpapillary forceps biopsy failed to confirm the malignancy, proximal-type strictures were reassessed by POC-guided forceps biopsy, and distal-type strictures were reassessed by EUS-FNAB using a core biopsy needle.

Of the 120 included patients, 78 had proximal-type strictures and 42 had distal-type strictures. The diagnostic accuracy for the entire study population was 70.8% and was significantly higher in patients with proximal-type strictures (76.9% vs 59.5%; P=.038). One (4.2%) technical failure occurred among the 24 patients with proximal type-strictures that was negative by transpapillary forceps biopsy. Among the 23 patients with a proximal-type stricture and negative forceps biopsy, the diagnostic accuracy of EUS-FNAB was 95.7% compared with 97.6% in the 19 patients with a distal-type stricture and negative forceps biopsy (P=.076). The overall diagnostic accuracies of the combined biopsy approaches were 98.7% for proximal-type strictures and 97.6% for distal-type strictures (P=.583).

Response Durability After Complete Eradication of High-Grade Dysplasia in Patients With Barrett Esophagus

Liquid nitrogen spray cryotherapy is a safe and effective therapy for high-grade dysplasia associated with Barrett esophagus, with high rates of complete eradication observed at 2-year follow-up. However, longer-term durability has not been adequately assessed. At DDW 2016, Fariha Ramay, MD, of the University of Maryland School of Medicine in Baltimore, Maryland presented results of a retrospective study that evaluated the efficacy, durability, and rate of neoplastic progression with 5 years' follow-up after endoscopic liquid nitrogen spray cryotherapy in patients with Barrett esophagus and high-grade dysplasia.

Patients from a single center with Barrett esophagus and high-grade dysplasia of any length were treated with liquid nitrogen spray cryotherapy. Included patients had received 1 or more treatments and had at least 5 years of follow-up records after the last ablation. The 31 included patients had a median follow-up of 65.5 months (IQR, 60.4-80.3 months). All patients initially exhibited complete eradication of high-grade dysplasia. Initial rates of complete eradication were 90.3% for dysplasia and 64.5% for intestinal metaplasia. At 5 years, complete eradication rates were 93.5% for high-grade dysplasia, 87.1% for dysplasia, and 73.3% for intestinal metaplasia, and rates at the last follow-up were 96.8%, 93.6%, and 80.7%, respectively. Response durability was 80.6%, defined as the proportion of patients who maintained complete eradication of high-grade dysplasia without retreatment. Two of the 6 recurrences of high-grade dysplasia occurred more than 2 years after the initial eradication. Among the 28 patients with initial complete eradication of dysplasia, 11 (39.3%) had recurrent dysplasia, which was most common in the area just below the neosquamocolumnar junction. Initial Barrett esophagus segment length was significantly associated with an increased likelihood of dysplasia recurrence (r=0.43; *P*=.02). One patient (3.2%) progressed to adenocarcinoma after cryotherapy.

Initial Results of a Large, Prospective Trial of Colorectal Endoscopic Submucosal Dissection

At DDW 2016, Yoji Takeuchi, MD, of the Osaka Medical Center for Cancer and Cardiovascular Disease in Osaka, Japan presented initial findings from a prospective multicenter cohort trial of colorectal endoscopic submucosal dissection in patients with colorectal cancer. The study enrolled all consecutive lesions planned for colorectal endoscopic submucosal dissection at 20 institutions in Japan from February 2013 through January 2015. Outcomes were categorized as curative resection or noncurative resection as stipulated in the Japanese 2010 guidelines. Curative resection was further subcategorized as complete curative resection, indicating R0 resection with lateral and vertical margins free from tumor, and all other outcomes were categorized as incomplete curative resection.

Table 5. Outcomes From 1939 Completed Colorectal Endoscopic Submucosal Dissections

	Median (IQR)
Procedure Outcomes, n (%)	
Procedure time, min	76 (40-100)
Resected specimen size, mm	37 (30-47)
Resected lesion size, mm	30 (22-40)
Outcomes Among Epithelial Lesions, n (%)	
Complete curative resection	1513 (78.3)
Incomplete curative resection	226 (11.7)
Noncurative resection	193 (10)
Complications, n (%)	
Delayed bleeding	43 (2.2)
Intraoperative perforation	49 (2.5)
Delayed perforation	22 (1.1)

IQR, interquartile range.

Adapted from Takeuchi Y et al. Short-term outcomes of colorectal endoscopic submucosal dissection: preliminary results of a prospective, largest-scale, Japanese multicenter long-term cohort trial [DDW abstract 51]. *Gastrointest Endosc.* 2016;83(5)(suppl).

A total of 1965 colorectal endoscopic submucosal dissections were performed in 1883 patients. The median age was 69 years (range, 15-91 years), and 58.4% were male. The median predicted size of the lesions was 30 mm (IQR, 20-40 mm). Lesions were located in the proximal or distal colon in 55.3% and 19.2% of patients, respectively, and in the rectum in 25.4%. Morphology was laterally spreading tumor of either granular type in 48.9% and nongranular type in 37.2% and was protruded or recurrent in 13.9%.

For the 1939 completed colorectal endoscopic submucosal dissections, median procedure time was 63 min (IQR, 40-100 min; Table 5). En bloc resection was achieved in 96.9% of procedures. Median resected specimen size and tumor size were 37 mm (IQR, 30-47 mm) and 30 mm (IQR, 22-40 mm), respectively. The median hospitalization period was 6 days (IQR, 5-7 days). Rates of intraoperative perforation, postoperative bleeding, and delayed perforation were 2.5%, 2.2%, and 1.1%, respectively.

Of the 1932 epithelial lesions, rates of complete curative resection, incomplete curative resection, and noncurative resection were 78.3%, 11.7%, and 10.0%, respectively. Failure to achieve en bloc resection was independently associated with protruded type or recurrent lesions (OR, 3.95) and with tumor location in the colon (OR, 2.85). Survival data and the rate of colon preservation will be presented in 2020.

Presentations in IBS

Results From a Randomized, Controlled Trial Comparing the Low-FODMAP Diet to NICE Guidelines in Adults With IBS-D

In patients with irritable bowel syndrome (IBS), the degree of benefit conferred by restricting intake of fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs) remains unclear. At DDW 2016, Shanti Eswaran, MD, of the University of Michigan in Ann Arbor, Michigan presented results from the first prospective, randomized, controlled trial of the low-FODMAP diet in adults in the United States with IBS and diarrhea (IBS-D).

The trial included adult patients with IBS-D based on Rome III criteria. Eligible patients had a mean daily abdominal pain score of 4 or greater and a Bristol stool scale score of at least 5. Patients were initially evaluated for eligibility during a 2-week screening period. Eligible patients were then randomized to 4 weeks of a low-FODMAP diet or a control diet based on modified National Institute for Health and Care Excellence (NICE) guidelines for IBS-D patients. Patients randomized to the control diet were allowed to eat foods with FODMAPs.

The 171 enrolled patients had a median age of 42.6 years (range, 19-75 years) and 71% were female. Eighty-three patients were randomized and completed the study, of whom 45 followed the low-FODMAP diet and 38 followed the NICE IBS diet recommendations. At baseline, patients had similar demographics, symptom severity, and FODMAP intake. The primary endpoint was not reached, as 54% and 47% of patients in the low-FODMAP or control diet groups, respectively, reported adequate relief of their IBS-D symptoms for at least 50% of the intervention weeks (P=.5764). The low-FODMAP diet yielded a significantly greater proportion of responders based upon abdominal pain (57% vs 23%; P=.0018) and composite endpoint (31% vs 10%; P=.0223). Stool consistency did not differ significantly between the 2 cohorts (P=.1678). Five patients dropped out of the low-FODMAP arm vs 2 in the control diet arm. No AEs were reported with either diet intervention.

Improved Outcomes Observed in IBS-D Patients Who Followed a Low-FODMAP Diet for 4 Weeks

Patients with IBS have not only gastrointestinal symptoms but also increased psychological comorbidity and sleep disturbance and reduced work productivity and health-related quality of life. At DDW 2016, Shanti Eswaran, MD, of the University of Michigan in Ann Arbor, Michigan presented results of a single-blinded, randomized, controlled trial that investigated the impact of a low-FODMAP diet on these factors in patients with IBS-D.

The trial included adult patients with IBS-D based on Rome III criteria. Criteria for eligibility included a mean daily abdominal pain score of 4 or greater and a Bristol stool scale score of at least 5. A 2-week screening period was held to evaluate patients for eligibility; patients meeting the criteria were randomized to either 4 weeks of a low-FODMAP diet or a control diet based upon modified NICE guidelines for patients with IBS-D. Patients randomized to the control diet were allowed to eat foods with FODMAPs.

The study was comprised of 171 patients with a median age of 42.6 years (range, 19-75 years), and 71% were female. Eighty-three patients were randomized and completed the study; 45 patients followed the low-FODMAP diet and 38 followed standard IBS recommendations. Patients had similar demographics, FODMAP intake, and symptom severity at baseline. At 4 weeks, the proportion of patients with a greater than 10-point improvement in IBS quality-of-life score was greater in the low-FODMAP group compared with the control diet group (58% vs 24%; P=.0032; Table 6). The mean total IBS quality-of-life score was also improved in the patients

Table 6. IBS-QOL Mean Scores After Dietary Intervention

	Low-FODMAP Diet	Control IBS Diet	*P* value
Total IBS-QOL	68.9	59.0	.0228
Dysphoria	73.1	62.6	.0449
Interference with activity	49.5	38.0	.0058
Body image	70.0	54.2	.0040
Health worry	72.9	73.4	.9054
Food avoidance	32.7	35.1	.6432
Social reaction	72.5	65.9	.1813
Sexual interaction	80.6	67.2	.0430
Relationship	79.2	68.5	.0250

FODMAP, fermentable oligo-, di-, and monosaccharides and polyols; IBS, irritable bowel syndrome; IBS-QOL, irritable bowel syndrome quality of life.

Adapted from Eswaran SL et al. A low FODMAP diet improves quality of life, reduces activity impairment, and improves sleep quality in patients with irritable bowel syndrome and diarrhea: results from a United States randomized, controlled trial [DDW abstract 821]. *Gastroenterology.* 2016;150(4)(suppl).

who adopted the low-FODMAP diet (68.9% vs 59.0%; *P*=.0228). Additionally, patients who followed the low-FODMAP diet reported superior reductions in dysphoria (73.1% vs 62.6%; *P*=.0449) and interference with activity (49.5% vs 38.0%; *P*=.0058), and improvements in body image (70.0% vs 54.2%; *P*=.0040), sexual interaction (80.6% vs 67.2%; *P*=.0430), and relationships (79.2% vs 68.5%; *P*=.0250). Patients following the low-FODMAP diet also experienced greater improvements in sleep quality (*P*=.0336) and exhibited a trend toward reduced anxiety (*P*=.0679). Based on the Work Productivity and Activity Index questionnaire, only activity impairment improved significantly in the patients who consumed the low-FODMAP diet (*P*=.0398).

A Large US Survey Reveals Prevalence and Predictors of IBS

IBS has been reported in up to 20% of people in the United States. However, these studies have been limited by a lack of rigorous large-scale sampling. At DDW 2016, Christopher Almario, MD, of Cedars-Sinai Medical Center in Los Angeles, California presented results of a study designed to determine the prevalence and predictors of IBS, as well as the distribution of concomitant gastrointestinal symptoms in people with IBS. The study conducted a survey by means of My GI Health, a mobile application that uses a previously validated computer algorithm known as Automated Evaluation of GI Symptoms (AEGIS), to systematically collect patient gastrointestinal symptoms. A survey research firm was engaged to recruit a representative sample of Americans to complete AEGIS. Participants were guided through the National Institutes of Health GI Patient Reported Outcome Measurement Information System (PROMIS) surveys, with added questions regarding comorbidities and demographics. The primary outcome was prevalence of IBS based upon Rome III criteria and self-reported physician diagnosis.

Of the 71,813 participants who completed AEGIS, 1411 (2.0%) met Rome III IBS criteria and an additional 2211 (3.1%) did not meet Rome III criteria but self-reported a physician diagnosis of IBS. IBS that met Rome III criteria was more likely in women, non-Hispanic whites, younger people, those who were married, and those with comorbidities (Table 7). The risk of IBS was not associated with education level, employment status, or household income. Participants with Rome III IBS were more likely to report concomitant bowel incontinence, heartburn and/or reflux, bloating, and nausea compared with age- and sex-matched controls without Rome III IBS (n=22,558). Those with Rome III IBS had significantly higher PROMIS scores compared with those without Rome III IBS (adjusted *P*<.001), as reflected by more severe heartburn/reflux and bloating. PROMIS scores for incontinence and nausea did not differ significantly between the 2 groups.

Table 7. Predictors of Having Rome III–Positive IBS

Variable	Rome III–Positive IBS (n=1411)	Odds Ratio (95% CI)[a]
Age	N/A	0.993 (0.989-0.997)
Sex		
Female	2.5%	reference
Male	1.2%	0.57 (0.50-0.65)
Race/Ethnicity		
Non-Hispanic whites	2.4%	reference
Non-Hispanic blacks	0.8%	0.36 (0.27-0.49)
Latinos	1.2%	0.56 (0.46-0.69)
Asians	0.4%	0.20 (0.11-0.34)
Other	1.7%	0.77 (0.57-1.05)
Marital Status		
Single	1.3%	reference
Divorced or widowed	2.6%	1.40 (1.15-1.71)
Married	2.2%	1.30 (1.12-1.51)
Number of Comorbidities		
0	1.3%	reference
1	3.4%	2.44 (2.16-2.76)
2	5.0%	3.47 (2.93-4.11)
≥3	11.9%	8.34 (6.18-11.3)

[a]The logistic regression model included all variables listed in the table above. IBS, irritable bowel syndrome.

Adapted from Almario CV et al. Prevalence and predictors of irritable bowel syndrome in the United States [DDW abstract 822]. *Gastroenterology*. 2016;150(4)(suppl).

Responses to Eluxadoline Over 12 or 24 Weeks in IBS-D Patients From Two Phase 3 Trials

Opioid receptors, including μ-, δ-, and κ-opioid receptors, in the gastrointestinal tract contribute to the regulation of gastrointestinal motility, secretion, and visceral sensation. Eluxadoline is a mixed μ-opioid receptor and κ-opioid receptor agonist and δ-opioid receptor antagonist that is locally active in the enteric nervous system. The drug significantly improved IBS-D symptoms based on a composite endpoint in two phase 3 studies and is approved for the treatment of IBS-D in adults. At DDW 2016, William Chey, MD, of the University of Michigan in Ann Arbor, Michigan presented results from 2 double-blind, randomized, placebo-controlled phase 3 trials (IBS-3001 and IBS-3002) that evaluated the durability of response in IBS-D patients treated with eluxadoline.

The two phase 3 studies included patients with IBS-D based on Rome III criteria. Patients were randomized to

Table 8. Composite Response Rates Over Longer Treatment Intervals in Patients Who Were Composite Responders or Nonresponders During Month 1

	Placebo (n=101)		Eluxadoline 75 mg twice daily (n=184)		Eluxadoline 100 mg twice daily (n=189)	
	Responder, n (%)	Nonresponder, n (%)	Responder, n (%)	Nonresponder, n (%)	Responder, n (%)	Nonresponder, n (%)
Month 3	69 (68.3)	32 (31.7)	134 (72.8)	50 (27.2)	142 (71.7)	56 (28.3)
Month 6	50 (49.5)	51 (50.5)	116 (63.0)	68 (37.0)	113 (57.1)	85 (42.9)
Weeks 1-12	78 (77.2)	23 (22.8)	150 (81.5)	34 (18.5)	154 (77.8)	44 (22.2)
Weeks 1-26	67 (66.3)	34 (33.7)	136 (73.9)	48 (26.1)	140 (70.7)	58 (29.3)

Adapted from Chey W et al. A 1-month trial with eluxadoline for IBS-D predicts a durable response: continuation analysis of response in two phase 3 studies [DDW abstract Su1204]. *Gastroenterology*. 2016;150(4)(suppl).

twice-daily treatment with eluxadoline (75 mg or 100 mg) or placebo. Patients rated IBS symptoms daily, including worst abdominal pain (0-10 scale) and stool consistency using the Bristol Stool Scale (7 types). The primary efficacy endpoint was composite response, defined as simultaneous daily improvement in abdominal pain (based upon a reduction of at least 30% in worst abdominal pain score vs baseline), and stool improvement, based upon a Bristol Stool Scale score of less than 5; these responses had to occur on the same day for at least 50% of the days from weeks 1 through 12 and from weeks 1 through 26. Composite endpoints were calculated separately for patients who were responders or nonresponders pooled from both trials during weeks 1 to 4 (month 1).

The pooled intent-to-treat analysis set included 2423 patients with IBS-D. In month 1, the proportion of composite responders in the placebo, eluxadoline (75 mg), and eluxadoline (100 mg) groups were 12.5% (101/809), 22.8% (184/808), and 24.6% (198/806), respectively. For the 75-mg and 100-mg doses of eluxadoline, the majority of patients who were composite responders in month 1 showed sustained responses during month 3 (72.8% and 71.7%, respectively) and month 6 (63.0% and 57.1%, respectively; Table 8). Among the patients who responded during month 1, responses during weeks 1 to 12 and weeks 1 to 26 were observed in 81.5% and 73.9% of the patients in the 75 mg, twice daily eluxadoline group and were observed in 77.8% and 70.7% of patients in the 100 mg, twice daily eluxadoline group, respectively. Of the patients who failed to achieve a response during month 1, fewer than 20% subsequently demonstrated a response during weeks 1 to 12 or weeks 1 to 26. In the pooled analysis, 765 patients (31.5%) had discontinued from the studies by 6 months, of whom 95.9% were nonresponders over weeks 1 to 26. The authors proposed that trials of 1-month duration may be adequate to determine the proportions of patients who are likely to respond to eluxadoline treatment.

An Investigation of the Mechanisms That Confer a Benefit in IBS Patients Treated With Rifaximin

Rifaximin (550 mg 3 times daily) administered for 2 weeks yielded significant improvements in the symptoms of nonconstipated IBS patients, including bloating, abdominal pain, and diarrhea, but the mechanisms that lead to these improvements have not been identified. At DDW 2016, Andres Acosta, MD, PhD, of the Mayo Clinic in Rochester, Minnesota presented results of a randomized, double-blind, placebo-controlled, parallel-group study that examined the effects of rifaximin (500 mg 3 times daily) vs placebo for 14 days in 24 patients with nonconstipated IBS. All patients completed baseline and on-study evaluations of colonic transit (by scintigraphy), mucosal permeability (by urinary lactulose-mannitol excretion after oral administration), bile acids, short-chain fatty acids, and fecal microbiome measured on a random stool sample. Sugars in the urine and organic acids in stool were measured and validated by means of mass spectrometry and liquid chromatography.

No significant effects emerged in terms of bowel symptoms, small bowel or colonic permeability, or overall colonic transit at 24 hours. Rifaximin was associated with accelerated emptying of the ascending colon (6.9 ± 0.9 hours vs 14.9 ± 2.6 hours; P=.033) and accelerated overall colonic transit at 48 hours (geometric center, 4.7 ± 0.2 hours vs 4.0 ± 0.3 hours; P=.046). Rifaximin did not alter the concentration of fecal bile acids, the proportion of individual bile acids, or the level of acetate propionate in stool. A decrease in stool butyrate concentration was observed in patients taking rifaximin (P=.06). Patients treated with rifaximin yielded a small decrease in microbial richness, and this reduction in richness over time was detectable as an interaction between time and study arm in a mixed linear model (P=.048). However, the overall effect of rifaximin on the microbiota appeared modest. The mechanisms that confer the clinical benefit of rifaximin in patients with nonconstipated IBS remain to be elucidated.

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Mansueto P et al. Nutrition in Clinical Practice. 2015; 30(5): 665-82. Halmos EP et al. Gastroenterology. 2014; 146:67-75.

INTRODUCING

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- **43.5%** reduction in sensation of heaviness, pressure, and fullness at 4 weeks[4]
- Over **90%** of patients indicated improvement of symptoms[4]

Nonprescription FDgard™...Effectiveness, Tolerability, Retail Access, and Affordability

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Studies were conducted using caraway oil and peppermint oil (l-Menthol) similar to FDgard™

References:

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Results may vary. Medical foods do not require preapproval by the FDA but must comply with regulations. Use under medical supervision. The company will strive to keep information current and consistent, but may not be able to do so at any specific time.

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