

Class Update with New Drug Evaluation: Direct Antivirals for Hepatitis C

Date of Review: January 2016

Generic Name: daclatasvir

Generic Name: ombitasvir/paritaprevir/ritonavir

End Date of Literature Search: December 2015

Brand Name (Manufacturer): Daklinza® (BMS)

Brand Name (Manufacturer): Technivie® (Abbvie)

Dossier Received: Yes

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

Since the P&T Committee last reviewed the Hepatitis C antivirals, there have been two new drug approvals, updated guidelines, new FDA indications, and a new safety alert. New comparative evidence for the class will be reviewed here.

Research Questions:

1. Are ombitasvir/paritaprevir/ritonavir (OMB/PTV-R; Technivie®) or daclatasvir (Daklinza®) added to sofosbuvir (Sovaldi®) (DCV+SOF) more effective or efficacious than other antiviral agents for the treatment of chronic hepatitis C (CHC) in achievement of sustained virologic response (SVR) and prevention of long-term complications, including hepatocellular carcinoma (HCC), liver-related morbidity, and mortality?
2. Are OMB/PTV-R or DCV+SOF safer than other available agents for the treatment of CHC in adults?
3. What subgroups of patients will benefit most from treatment with OMB/PTV-R or DCV+SOF?

Conclusions:

- DCV+SOF was FDA approved for the treatment of genotype 3 (GT3) CHC based on 1 open-label nonrandomized phase 3 trial. OMB/PTV-R was FDA approved for the treatment of genotype 4 (GT4) CHC based on one open label phase 2b trial. In addition, updated guidelines were released for the treatment of CHC.
- There is low quality evidence from one phase 3 trial with significant methodological flaws, but a high magnitude of effect, that DCV+SOF achieved an SVR of 89% in subjects with GT3 CHC.¹ However, SVR rates were reduced in patients with cirrhosis (63%) compared to those without cirrhosis (96%). As a result, the optimal treatment duration for GT3 patients with cirrhosis is not established. Further data demonstrate that patients with cirrhosis may benefit from the addition of ribavirin (RBV) or an extended duration of 16 weeks.² No other treatment options have shown to be more effective in this population: SOF + ribavirin (RBV) for 24 weeks resulted in lower SVR rates (84%), and ledipasvir/sofosbuvir (LDV/SOF; Harvoni®) + RBV for 12 weeks has only proven to be effective in non-cirrhotic patients.^{3,4}
- There is low quality to insufficient evidence that DCV+SOF is efficacious in GT 1 or GT2 CHC, and insufficient evidence for use in patients with cirrhosis with these genotypes.^{5,6} At this time, there is more evidence to support LDV/SOF in genotype 1 (GT1) and SOF+RBV in genotype 2 (GT2) CHC.

- There is low quality evidence from one phase 2b trial (PEARL-1), with significant methodological flaws, that OMB/PTV-R +/- RBV achieved an SVR of 91-100% in GT4 CHC without cirrhosis.⁷
- There is insufficient evidence that OMB/PTV-R is efficacious in patients with cirrhosis, in patients with genotypes other than GT4, or in treatment-experienced patients with regimens other than pegylated interferon (PEG-IFN) with ribavirin.
- There is insufficient comparative evidence between direct-acting antiviral agents.
- HCV antiviral agents have insufficient evidence for long-term clinical outcomes such as liver transplantation, hepatocellular carcinoma (HCC), and mortality.
- There is low quality evidence that ombitasvir/paritaprevir/ritonavir with dasabuvir (OMB/PTV-R + DAS; Viekira Pak[®]) and OMB/PTV-R may cause serious liver injury, mostly in patients with underlying advanced liver disease.⁸ These agents should be used with caution in patients with cirrhosis and are contraindicated in decompensated liver disease.

Recommendations:

- Continue to prioritize treatment for persons with advanced liver disease (METAVIR stage F3 or F4), as well as those at greatest risk of developing complications of liver disease, including:
 - All patients awaiting a liver transplantation
 - All patients post solid organ transplant
 - HIV coinfection with METAVIR stage F2 or greater
 - Patients with extrahepatic manifestations
- Make DCV preferred and replace LDV/SOF with DCV with SOF and RBV in current prior authorization (PA) for patients with GT3 CHC with cirrhosis.
- Due to extensive drug-drug interactions and safety concerns, make OMB/PTV-R + RBV and OMB/PTV-R + DAS non-preferred.
- Allow treatment approval if prescribed by or in consultation a hepatologist, gastroenterologist, or infectious disease specialist with experience of hepatitis C.
- Approve updated PA criteria in **Appendix 6**.

Previous Conclusions:

- There is low quality evidence 12 weeks of ledipasvir/sofosbuvir (LDV/SOF) results in high SVR12 rates among treatment-naïve (97-99%) and treatment-experienced (94-99%) adults with chronic hepatitis C virus (HCV) GT 1 infection. This is based on 2 poor-quality, open-label studies with a high risk of bias.
- There is low quality evidence that an 8-week regimen of LDV/SOF may have similar sustained virologic response rates as a 12-week regimen of LDV/SOF in treatment-naïve adults with chronic HCV genotype 1 infection who did not have cirrhosis (94% vs. 95%; p=0.52).
- All studies remain small, with imprecise estimates of benefits and harms, particularly in patients with cirrhosis and those 65 years and older. However, there is a large magnitude of benefit seen, and LDV/SOF appears to have potential for improved value over previously approved agents, with higher SVR rates, fewer adverse events, and increased tolerability.
- There is insufficient evidence on the relapse rates associated with LDV/SOF. Larger studies with longer follow-up are needed to adequately assess relapse rates and treatment success.
- There is insufficient to low quality evidence based on one small (n=14) nonrandomized, open-label trial that patients who have viral relapse after SOF plus ribavirin can be successfully re-treated with LDV/SOF for 12 weeks.
- There is insufficient comparative evidence evaluating direct acting antivirals. There is insufficient evidence on long-term clinical outcomes such as liver transplantation, hepatocellular carcinoma, and mortality.

Previous Recommendations:

- Make LDV/SOF a preferred agent on the PDL.
- Implement prior authorization criteria consistent with the community standard to prioritize use so that patients defined by the AASLD guidelines as “highest priority” at high risk for liver-related complications and severe extrahepatic hepatitis are treated. Limit use of LDV/SOF to the following patients (highest priority based on the AASLD guidelines) at this time:
 - Stage 3 and 4 fibrosis without decompensated cirrhosis
 - Those receiving an organ transplant
 - Patients with extrahepatic manifestations, including:
 - Type 2 or 3 cryoglobulinemia with end-organ manifestations (vasculitis)
 - Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis
 - Patients prescribed medication by or in consultation with a hepatologist or gastroenterologist with experience in Hepatitis C.

Background:

Chronic HCV is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma. It is also the leading indication for liver transplantation in the Western world.⁹ The goal of treatment for CHC is to prevent these long-term health complications. However, it remains difficult to design long-term clinical trials that are large enough to provide direct evidence for these outcomes. The SVR rate is defined as the proportion of patients who experience a decline in HCV-RNA to undetectable levels following completion of antiviral treatment, as measured by a sensitive polymerase chain reaction assay. It is the standard marker of successful treatment in clinical trials and is associated with the long-term absence of viremia. There is some evidence of an association of achieving an SVR and reductions in mortality, liver failure, and cancer.⁹ However, this evidence is from observational studies only and those with cirrhosis prior to treatment have been shown to still be at risk for HCC during follow-up. The two major predictors of SVR are viral genotype and the pretreatment viral load. Other factors associated with an increased likelihood of achieving an SVR include female sex, age less than 40 years, non-Black race, lower body weight, absence of insulin resistance, and absence of bridging fibrosis or cirrhosis on liver biopsy. Trials have historically used SVR at week 24 of follow-up (SVR24) as a primary endpoint. SVR24 has been associated with improvements in quality of life and studies have demonstrated that SVR24 is associated with a decrease in decompensated liver disease, hepatocellular carcinoma, liver transplant, and all-cause mortality. More recent studies use SVR at week 12 of follow-up (SVR12) as the primary endpoint, based on evidence that the majority of patients who have an SVR at week 12 maintain it until week 24.¹⁰ Relapse is defined as a patient achieving HCV RNA less than the lower limit of quantitation or the lower limit of detection at the last measurement on treatment but subsequently having a HCV RNA greater than or equal to the lower limit of quantitation or detection post-treatment.¹¹ In addition, genetic variation in both virus and host can affect treatment response.

Patients at greatest risk of progressing to cirrhosis have detectable HCV-RNA and liver histology demonstrating fibrosis (METAVIR stage 2 or higher). Patients with compensated cirrhosis are at risk of progressing to decompensation hepatocellular carcinoma, or death. The urgency of treating HCV should be based on the risk of developing decompensated cirrhosis or dying from liver-related disease, and prolonging graft survival in liver transplant recipients. Disease progression varies greatly among patients with compensated liver disease and the number needed to treat to prevent long term outcomes is dependent on the baseline risk for events. The newer costly treatments with high SVR rates will have the most benefit among patients at highest risk of cirrhosis-related events.¹² However, a recent cost effectiveness study found that treating HCV infection at early stages of fibrosis appears to improve health outcomes and to be cost-effective but incurs substantial costs.

In the United States, GT1 infection is found in about 75% of patients with HCV and is associated with a lower response to antiviral treatment than infection with GT2 and GT3, which represent about 20% of HCV patients.⁹ Subgenotypes 1a and 1b are the most common subgenotypes of GT1. Cure rates for GT1a and 1b infection may differ depending on the treatment regimen. Therapies to treat HCV infection have advanced significantly over the past several years. Prior to 2011, the combination of PEG-IFN and RBV was the standard of care and approximately 55-60% of patients achieved a SVR. Severe adverse effects also limited the success of therapy. In 2011, the FDA approved the first generation direct-acting antiviral agents (DAA), boceprevir and telaprevir.¹³ Several randomized controlled trials (RCTs) showed improved SVR rates (63-79%) with triple therapy compared to PEG-IFN+RBV dual therapy. However, these agents still come with several safety concerns and still depend on combination therapy with PEG-IFN+RBV which can result in serious adverse reactions. With the recent development of interferon-free regimens, these therapies have gone out of favor.

In 2013, the second-generation DAAs simeprevir (SMV) and SOF were approved.¹⁰ SOF+RBV, studied together for 24 weeks in those ineligible to receive interferon, was the first interferon-free therapy for the treatment of genotype 1 infection (GT1). These regimens decreased the duration of therapy, decreased adverse events, and again demonstrated improved rates of SVR. In addition, recent data from show real world discontinuation rates of SOF+PEG-IFN+RBV may be up to 5-times greater than rates seen in clinical trials. In 2014, two additional interferon-free therapies were studied, including LDV/SOF and the OMB/PTV-R + DAS regimen. However, these new drugs are expensive, and a significant challenge is identifying which patients will benefit most from receiving treatment since only 5-20% of CHC patients develop cirrhosis over 20 years.¹⁴ Technivie® is a fixed-dose combination that includes ombitasvir, a HCV NS5A inhibitor; paritaprevir, a HCV NS3/4A protease inhibitor; and ritonavir, a potent CYP3A inhibitor that is not active against HCV but boosts concentrations of paritaprevir.¹⁵ It was approved by the FDA for use in combination with ribavirin in GT4 CHC patients without cirrhosis. Treatment options for patients with GT3 CHC remain limited and have required a longer duration of therapy (24 weeks) and the addition of ribavirin. Daclatasvir is a NS5A inhibitor approved for use in combination with sofosbuvir (DCV+SOF) for patients with GT3 CHC. Data suggests that fibrosis progression occurs most rapidly in patients with GT3 CHC and regimens have been less effective for treating this genotype.³

Studies that include patients with decompensated cirrhosis, renal failure, or other comorbidities, and studies that include minority racial and ethnic groups are lacking; yet these patients remain some of the most difficult to treat.¹⁶

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Guidelines:

The guidelines from the American Association for the Study of Liver Diseases (AASLD) and Infectious Disease Society of America (IDSA) are routinely updated to reflect rapidly changing evidence with HCV DAAs.³ The guideline has many limitations with poor methodological quality. The panel lacks non-specialist members and there is no assessment of risk of bias for individual studies. In addition, the authors and sponsors of the guideline had multiple conflicts of interest.

Treatment for all patients regardless of disease severity is recommended, except those with short life expectancy that cannot be remediated by treatment or transplantation. Little evidence exists to support initiation of treatment in patients with limited life expectancy. Prior to treatment, the guideline continues to emphasize the need to assess the patient's understanding of treatment goals and provision of education on adherence and follow-up. The following recommendations for initial treatment of HCV infection are provided:

1. Treatment-naive patients with GT1 infection:
 - a. DCV and SOF for 12 weeks (no cirrhosis) or 24 weeks with or without RBV [Class I, Level B (no cirrhosis); Class IIa, Level B (cirrhosis)]
 - b. LDV/SOF for 12 weeks [Class I, Level A]
 - c. OMB/PTV-R + DAS with RBV (1a only) for 12 weeks (no cirrhosis or cirrhosis and 1b) or 24 weeks (cirrhosis and 1a only) [Class I, Level A]
 - d. SIM and SOF for 12 weeks (no cirrhosis) or 24 weeks with or without RBV (cirrhosis without the Q80K polymorphism or 1b) [Class I, Level A]
2. Treatment-naive patients with GT2 infection:
 - a. DCV and SOF for 12 weeks [Class IIa, Level B]
 - b. SOF and RBV for 12 weeks [Class I, Level A]
 - i. Extending treatment to 16 weeks is recommended in patients with cirrhosis [Class IIb, Level C]
3. Treatment-naive patients with GT3 infection:
 - a. DCV/SOF for 12 weeks (no cirrhosis) or 24 weeks with or without RBV (cirrhosis) [Class I, Level A (no cirrhosis); Class IIa, Level C (cirrhosis)]
 - b. SOF and RBV plus weekly PEG-IFN for 12 weeks for IFN-eligible [Class I, Level A]
 - c. SOF and RBV for 24 weeks [Class I, Level A]
4. Treatment-naive patients with GT4 infection
 - a. LDV/SOF for 12 weeks [Class IIb, Level B]
 - b. OMB/PTV-R with RBV for 12 weeks [Class I, Level B]
 - c. SOF and RBV for 24 weeks [Class IIa, Level B]
 - d. SOF and RBV plus weekly PEG-IFN for 12 weeks for IFN-eligible [Class II, Level B]

New Safety Alerts:

In October 2015, the FDA released a drug safety communication warning that hepatitis C treatments OMB/PTV-R + DAS (Viekira Pak®) and OMB/PTV-R (Technivie®) can cause serious liver injury mostly in patients with underlying advanced liver disease.⁸ As a result, drug labeling was updated to include this risk. A review of adverse events identified cases of hepatic decompensation and liver failure in patients with underlying liver cirrhosis, some of which resulted in liver transplantation or death. These events were reported mostly in patients who had evidence of advanced cirrhosis before starting treatment. These agents should be used with caution in patients with cirrhosis and are contraindicated in decompensated liver disease.

New Formulations or Indications:

In November, the FDA approved an expanded indication for LDV/SOF for the treatment of patients with genotypes 1, 4, 5, and 6, as well as patients co-infected with HIV.¹⁷ It was also approved to be used in combination with RBV for 12 weeks to treat certain patients with CHC and cirrhosis. Supporting RCTs are included in Table 1.

Randomized Controlled Trials:

A total of 20 citations were manually reviewed from the literature search. After further review, 12 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical) or because of unapproved medication. Trials covered in the new drug evaluation section were also excluded. The remaining 5 trials are briefly described in the table below. Full abstracts are included in **Appendix 2**.

Table 1: Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
ION-4 ¹⁸	LDV/SOF x 12 weeks *No comparator group	Adults with HCV/HIV coinfection, treatment-naïve and experienced, 20% cirrhosis; GT1 and GT4	SVR12	<u>SVR12:</u> 322/325 (96%) <u>Relapse:</u> 10/335 (3%)
SIRIUS ¹⁹	LDV/SOF +/- RBV x 12 weeks vs. LDV/SOF x 24 weeks	Treatment-experienced with PEG+RBV and a protease inhibitor; HCV GT1 and compensated cirrhosis	SVR12	<u>SVR12:</u> LDV/SOF + RBV: 74/77 (96%) LDV/SOF: 75/77 (97%)
PHOTON-2 ²⁰	SOF + RBV x 24 weeks (except 12 weeks for treatment-naïve GT2)	Adults with treatment-naïve GT 1, 2, 3 or 4 and treatment-experienced GT2 and GT3; HCV/HIV co-infection	SVR12	<u>SVR12:</u> GT1: 95/112 (85%) GT2: 17/19 (89%) (Treatment-naïve) GT2: 5/6 (83%) (Treatment-experienced) GT3: 52/27 (91%) (Treatment-naïve) GT3: 42/49 (86%) (Treatment-experienced) GT4: 26/31 (84%)
TURQUOISE1 ²¹	OMB/PTV-R + DAS + RBV x 12 weeks vs. 24 weeks	GT1; HCV/HIV co-infection; treatment-naïve or previously treated with PEG+RBV	SVR12	<u>SVR12:</u> 12 week: 29/31 (94%) 24 week: 29/32 (91%)
SOLAR-1 ²²	LDV/SOF + RBV x 12 weeks vs. 24 weeks	GT1 or GT4; advanced liver disease	SVR12	<u>SVR12:</u> Non-transplant: 86-89% Transplant recipients: 96-98%

NEW DRUG EVALUATION: Daclatasvir (Daklinza®)

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Daclatasvir is a NS5A inhibitor and sofosbuvir is a nucleotide NS5B inhibitor that was FDA approved for patients with GT3 HCV.

Clinical Efficacy:

FDA approval of DCV (with SOF) for patients with HCV GT3 was primarily based upon one Phase 3 single-arm (n=152), open-label trial (ALLY-3) conducted in the United States and Puerto Rico.¹ The ALLY-3 trial (details in evidence table) evaluated HCV GT3 patients with compensated liver disease with and without cirrhosis for treatment duration of 12 weeks. The primary efficacy endpoint was SVR12. Overall, DCV with SOF achieved an SVR12 of 89% (135/152). However, SVR12 rates were reduced in HCV GT3 patients with cirrhosis (63%, 20/32) compared to those without cirrhosis (96%, 115/120). As a result, DCV with SOF for 12 weeks may not be a reasonable regimen for those with cirrhosis. No differences in SVR12 rates were noted based upon age, gender, IL28B status, or baseline HCV RNA level. SVR12 rates were lower in patients with the Y93H polymorphism at baseline [54% (7/13); 95% CI 25% to 81%] compared to those without [92% (128/139); 95% CI 86% to 96%]. However, no commercially available assay is available to detect the presence of this polymorphism, leaving the clinical implications of this result unknown.

The ALLY-3 trial has significant methodological flaws, including an open-label design with no active comparator. It did not define a non-inferiority margin for determination of efficacy. The FDA analysis calculated it based on historical data and concluded that DCV with SOF achieved non-inferiority compared to SOF with RBV for 24 weeks (2%; 95% CI -4% to 9%).²³ Based upon these results, the FDA approved the use of DCV with SOF for 12 weeks in HCV GT3 patients with compensated liver disease with or without cirrhosis. However, the FDA stated the optimal duration for HCV GT3 patients with cirrhosis has not been established. The FDA has required a post-marketing requirement to conduct a trial to determine if a longer duration of treatment or addition of RBV improves efficacy in patients with cirrhosis. In a small, unpublished study, 21/24 (6/6 with advanced fibrosis and 15/18 with cirrhosis) patients receiving 12 weeks of DCV+SOF+RBV achieved a sustained virologic response after 4 weeks of treatment (SVR4), whereas 25/26 (8/8 with advanced fibrosis and 17/18 with cirrhosis) patients receiving 16 weeks of DCV+SOF+RBV achieved an SVR4. These data demonstrate that patients with GT3 infection and cirrhosis may benefit from extended treatment duration.² However, longer term and more data are needed to confirm this.

Alternative treatment options for GT3 includes LDV/SOF + RBV based on limited data from the ELECTRON 2 trial demonstrating a high rate of SVR12 (100%) in non-cirrhotics.²⁴

Off-label Uses

DCV with SOF is recommended by the AASLD guidelines as a treatment option for patients with GT1, GT 2, and GT4 based on additional trials.³

The ALLY-2 trial is a phase 3 open-label trial that assessed DCV with SOF for 8-12 weeks for the treatment in patients with GT1, GT2, GT3 and GT4 CHC co-infected with HIV (n=203).⁵ Eighty-three percent of patients had GT1 and 54% were treatment-naïve. Among previously treated patients, 94% had received PEG-IFN therapy. Treatment-naïve patients were randomized to receive either 12 weeks or 8 weeks of DCV with SOF and previously treated subjects received

the regimen for 12 weeks. Ninety-two (46%) patients had a fibrosis score of at least F3 and only 14% had cirrhosis. The SVR12 rate was 96% (95% CI 89.8 to 99.2%) in treatment-naïve patients with GT1 who received 12 weeks of therapy and was 75.6% (95% CI 59.7 to 87.6%) among previously untreated patients who received 8 weeks of treatment. However, only 9 of these patients had cirrhosis. The SVR12 rate in treatment-experienced patients was 97.7% (95% CI 88 to 99.9%). The SVR24 rates were 92% in the two 12-week groups and 72% in the 8-week group; the authors noted this difference due to missing data. Rates of virologic breakthrough was greater in patients treated for 8 weeks versus 12 weeks, which suggests 12 weeks of therapy should be considered for patients with HIV and HCV co-infection. In patients with GT2, GT3, and GT4, SVR12 was 100% (26/26) when treated for 12 weeks and 78% (7/9) when treated for 8 weeks.

A similar open-label phase 2 trial evaluated DCV with SOF in HCV patients with GT1, GT2, or GT3 without cirrhosis at baseline.⁶ This trial included a lead-in period with SOF to determine whether it would decrease the emergence of DCV-resistant variants. Forty-four patients were infected with HCV GT2 or GT3 and 167 with GT1. Patients were randomized to receive SOF for 1 week, then DCV with SOF for 23 weeks; DCV with SOF for 24 weeks; or DCV with SOF and RBV for 24 weeks. The majority of patients had moderate fibrosis (F2 or F3). In patients with GT2 or GT3, SVR12 was 91% (40/44) and with GT1, SVR12 was 98% in previously untreated subjects and 95% in previously treated.

Overall, patients with cirrhosis were not adequately represented in these studies and the optimal duration of treatment for patients with cirrhosis remains unclear.

Other treatment options for GT1 have more supporting data, include LDV/SOF (SVR12 94-99% in non-cirrhosis and 94-100% in cirrhosis) and OMB/PTV-R + DAS (SVR12 96-100% in non-cirrhosis and 89-100% in cirrhosis).⁴

Current treatment options for GT2 include SOF + RBV for 12 weeks or 16 weeks with cirrhosis. At this time there is more evidence to support this regimen.³

Clinical Safety:

Overall, the limited short-term data for DCV does not show cause for any serious safety concerns and because DCV was the third NS5A inhibitor the FDA Advisory committee was not required to meet prior to approval of DCV. Overall, approximately 1900 patients with HCV infection have been treated with DCV in combination with other HCV agents in clinical trials. The safety assessment described in the prescribing information was primarily based on the Phase 3 clinical trial (ALLY-3) in patients with GT3 CHC with compensated liver disease with and without cirrhosis.²⁵

The most common adverse reactions in the ALLY-3 trial were headache, nausea and fatigue. All adverse reactions were mild to moderate in severity. One subject experienced a serious adverse event that was considered unrelated to DCV and no subjects discontinued therapy for adverse events. Adverse events that occurred in at least 5% of patients are included below²⁵:

Adverse Reaction	n (%) n=152
Headache	21 (14%)
Fatigue	21 (14%)
Nausea	12 (8%)
Diarrhea	7 (5%)

Further review has identified a potential drug-drug interaction with use of amiodarone co-administered with SOF in combination with another DAA, including DCV that can result in potential severe bradycardia. The FDA has updated labeling to include a warning to avoid the combination of amiodarone with DCV and SOF.

Pharmacology and Pharmacokinetic Properties of Daclatasvir²⁵:

Parameter	
Mechanism of Action	Inhibitor of HCV nonstructural protein 5A (NS5A).
Oral Bioavailability	67%
Distribution and Protein Binding	Vd: 47 L; Protein binding ~99%
Elimination	Feces (88%, 53% unchanged); urine (6.6%, primarily unchanged)
Half-Life	12 to 15 hours
Metabolism	Substrate of CYP3A, with CYP3A4 being the primary CYP isoform responsible for metabolism.

Abbreviations: HCV = hepatitis C virus; L = liters; Vd = volume of distribution

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

- 1) Hepatocellular Carcinoma
- 2) Mortality
- 3) Liver Transplant
- 4) Discontinuation Rates Due to Adverse Events

Primary Study Endpoint:

- 1) Sustained Virologic Response at week 12 after the end of treatment (SVR12)

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. ALLY-3 ¹ OL phase 3 study	1. DCV 60 mg + SOF 400 mg once daily x 12 weeks	<p><u>Demographics:</u> 59% male Median age 55 90% white 21% cirrhotics 66% treatment naïve 61% with non –CC IL28B GT</p> <p><u>Key Inclusion Criteria:</u> Adults ≥ 18 y/o, treatment naïve or treatment experienced, chronic genotype 3 infection, HCV-RNA levels ≥ 10,000 IU/ml</p> <p><u>Key Exclusion Criteria:</u> Treatment experienced with a NS5A inhibitor, previous intolerance to SOF, coinfection with HIV or HBV, HCC, decompensation</p>	ITT 152	<p><u>SVR12 (Total):</u> 1. 135/152 (89%); 95% CI 83-93%</p> <p>Without Cirrhosis: 115/120 (96%); 95% CI 91-99%</p> <p>With Cirrhosis: 20/32 (63%); 95% CI 44-79%</p> <p><u>SVR12 (Treatment-naïve):</u> 1. 91/101 (90%); 95% CI 83-95%</p> <p>Without Cirrhosis: 80/82 (98%); 95% CI 91-100%</p> <p>With Cirrhosis: 11/19 (58%); 95% CI 34-80%</p> <p><u>SVR12 (Treatment-experienced):</u> 44/51 (86%); 95% CI 74-94%</p> <p>Without Cirrhosis: 35/38 (92%); 95% CI 74-94%</p> <p>With Cirrhosis: 9/13 (69%); 95% CI 39-91% p=0.52</p>	NA	<p><u>Discontinuations due to Adverse Events:</u> 0</p> <p><u>Serious AE:</u> 1 (1%)</p> <p><u>Relapse:</u> 1) 11 (5.1%) 2) 9 (4.2%) 3) 3 (1.4%)</p>	NA	<p>Risk of Bias (low/high/unclear): <u>Selection Bias:</u> high; nonrandomized; no comparator group <u>Performance Bias:</u> high; open-label; no comparator group <u>Detection Bias:</u> high; open label <u>Attrition Bias:</u> low; overall low attrition <u>Reporting Bias:</u> unclear</p> <p>Applicability: <u>Patient:</u> Almost all white patients; included patients with more moderate disease severity with a low percentage of cirrhotics and overall higher baseline HCV RNA level <u>Intervention:</u> Appropriate intervention <u>Comparator:</u> No comparator and the study did not define a noninferiority margin for determination of efficacy. Unable to assess safety based on trial design. <u>Outcomes:</u> Surrogate outcome of SVR 12 used to evaluate efficacy. <u>Setting:</u> Monitoring and follow-up difficult to mirror in clinical practice in the hepatitis C patient population.</p>

<p>ALLY-2⁵ OL phase 3 study</p>	<p><u>Treatment-naïve</u> 1. DCV 60 mg + SOF 400 mg once daily x 12 weeks</p> <p>2. DCV 60 mg + SOF 400 mg once daily x 8 weeks</p> <p><u>Treatment- experienced</u> 1. DCV 60 mg + SOF 400 mg once daily x 12 weeks</p>	<p><u>Demographics:</u> 87% male 34% black 14% cirrhosis 46% ≥ F3 83% GT1</p> <p><u>Key Inclusion Criteria:</u> Adults ≥ 18 y/o, HIV coinfection, HCV-RNA levels ≥ 10,000 IU/ml</p> <p><u>Key Exclusion Criteria:</u> Treatment experienced with a NS5A inhibitor; decompensated cirrhosis, pregnancy, h/o cancer, HCC, uncontrolled diabetes (HgA1C > 8.5%), active substance abuse, active severe psychiatric disorders, abnormal laboratory values (ALT, albumin, platelets, Hg), CrCl < 50 ml/min</p>	<p><u>ITT</u> 1. 101 2. 50 1. 52</p>	<p><u>SVR12:</u> <i>Treatment-naïve:</i> 1. 98 (97%; 95% CI 91.6-99.4%) 2. 38 (76%; 95% CI 61.8-86.9%) <i>Treatment experienced:</i> 51 (98.1%; 95% CI 89.7-100%)</p>	<p>N/A</p>	<p><u>Discontinuations due to Adverse Events:</u> 0</p> <p><u>Serious AE:</u> <i>Treatment-naïve:</i> 1. 1 (1%) 2. 0 (0%)</p> <p><i>Treatment- experienced:</i> 3 (6%)</p>	<p>N/A NS</p>	<p>Risk of Bias (low/high/unclear): <u>Selection Bias:</u> high; only treatment-naïve patients randomized. <u>Performance Bias:</u> high; open-label; <u>Detection Bias:</u> high; open label <u>Attrition Bias:</u> low; overall low attrition ; ITT used <u>Reporting Bias:</u> unclear</p> <p>Applicability: <u>Patient:</u> Majority of patients GT1; less than 10% with cirrhosis in previously untreated patients. Significant exclusion criteria limit generalizability to patient population (renal dysfunction, significant diabetes, etc.) <u>Intervention:</u> Appropriate intervention <u>Comparator:</u> No active comparator group to assess efficacy and safety of medication <u>Outcomes:</u> Surrogate outcome of SVR 12 used to evaluate efficacy. <u>Setting:</u> Monitoring and follow-up difficult to mirror in clinical practice in the hepatitis C patient population.</p>
<p><u>Abbreviations</u> [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; CrCl = creatinine clearance; DCV = daclatasvir; GT = genotype; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HIV = human immunodeficiency; ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OL = open label; OMB = ombitasvir; PTV = paritaprevir; R = ritonavir; RBV = ribavirin; SOF = sofosbuvir; SVR12 = sustained virologic response at 12 weeks after treatment; TN = Treatment naïve; TE = treatment experienced</p>								

NEW DRUG EVALUATION: ombitasvir/paritaprevir/ritonavir (OMB/PTV-R) (Technivie®)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

OMB/PTV-R was approved for GT4 CHC without cirrhosis based on one randomized, open-label phase 2b study.⁷ Treatment-naïve patients were randomly assigned to receive treatment with or without RBV for 12 weeks, while treatment-experienced patients only received the treatment regimen with ribavirin for 12 weeks after investigators realized the addition of RBV to the regimen was superior in this population. Treatment-experienced patients were limited to those who had failed treatment with PEG-IFN with ribavirin. All genotype 1b-infected patients without cirrhosis were enrolled and completed treatment before enrolment of GT4 treatment-naïve patients to allow for a sequential evaluation of the 2 DAA regimens in these populations. Patients with cirrhosis were excluded from the study. There was no significant difference in SVRxx rates in treatment-naïve patients between those who received RBV and those who did not (100% vs. 91%; Mean difference -9.16%; 95% CI, -19.61 to 1.29%; P=0.086). All treatment-experienced patients who received ribavirin achieved SVRxx. Three treatment-naïve patients without RBV had virological failure and no patients who received RBV had virological failure. Overall, the patient population studied had more mild disease, with 77% fibrosis F0-F2 and no cirrhotics. Most patients were European, limiting the generalizability of the results to clinical practice.

Clinical Safety:

Overall, treatment was well tolerated but safety data are based on short-term studies composed of few patients. The most commonly reported adverse reactions with an incidence greater than 10% in clinical trials were headache, asthenia, fatigue, nausea and insomnia.²⁶ No patients reported any serious adverse events related to study drug or adverse events resulting in discontinuation of therapy. The following table displays adverse reactions that occurred in greater than 5% of subjects.²⁶

Adverse Reaction	PEARL-1 ^{7,26}	
	Ombitasvir, paritaprevir, ritonavir + RBV 12 weeks 12 weeks N=91 %	Ombitasvir, paritaprevir, ritonavir 12 weeks N=44 %
Asthenia	29	25
Fatigue	15	7
Nausea	14	9
Insomnia	13	5
Pruritus	7	5
Skin reactions	7	5

Elevated liver enzymes to greater than 5-times the upper limit of normal occurred in approximately 1% of subjects which were typically asymptomatic. The long-term effects of OMB/PTV-R on liver function are unknown.

Pharmacology and Pharmacokinetic Properties²⁶:

Parameter	
Mechanism of Action	Ombitasvir inhibits HCV NS5A and interferes with viral RNA replication and virion assembly. Paritaprevir inhibits HCV NS3/4A protease and interferes with HCV coded polyprotein cleavage necessary for viral replication. Ritonavir is not active against HCV but is a potent CYP3A inhibitor that increases peak and trough plasma drug concentrations of paritaprevir and overall drug exposure (ie, AUC).
Oral Bioavailability	Ombitasvir: ~48%; Paritaprevir: ~53%; Ritonavir: Not evaluated
Distribution and Protein Binding	Ombitasvir: Vd: 173 L; Paritaprevir: Vd: 103 L; Ritonavir: Vd: Not evaluated
Elimination	Ombitasvir: Feces (~90%, mainly as unchanged drug); urine (<2%, mainly as unchanged drug) Paritaprevir: Feces (~88%, mainly as metabolites); urine (~9%, mainly as metabolites) Ritonavir: Feces (~86%); urine (~11%)
Half-Life	Ombitasvir: 21 to 25 hours; Paritaprevir: 5.5 hours; Ritonavir: 4 hours
Metabolism	Ombitasvir: Metabolized by amide hydrolysis and oxidative metabolism Paritaprevir: Metabolized by CYP3A4 and to a lesser extent CYP3A5 Ritonavir: Metabolized by CYP3A and to a lesser extent CYP2D6

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

- 1) Hepatocellular Carcinoma
- 2) Mortality
- 3) Liver Transplant
- 4) Discontinuation Rates Due to Adverse Events

Primary Study Endpoint:

- 1) Sustained Virologic Response at week 12 after the end of treatment (SVR12)

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. PEARL-1 ⁷ phase 2b, randomized, OL	<p><u>Treatment-naïve</u></p> <p>1. OMB/PTV-R x 12 weeks</p> <p>2. OMB/PTV-R + RBV x 12 weeks</p> <p><u>Treatment-experienced</u></p> <p>1. OMB/PTV-R + RBV x 12 weeks</p>	<p><u>Demographics:</u> 86% from Europe Age 48 years</p> <p><u>Key Inclusion Criteria:</u> Adults ≥18 y/o, treatment-naïve or treatment-experienced, chronic genotype 4 infection, HCV-RNA levels ≥ 10,000 IU/mL</p> <p><u>Key Exclusion Criteria:</u> Cirrhosis, HBV, HIV, other causes of liver disease</p>	<p><u>mITT</u></p> <p><u>TN</u></p> <p>1. 44</p> <p>2. 42</p> <p><u>TE</u></p> <p>1. 49</p>	<p><u>SVR12:</u></p> <p><i>Treatment-naïve</i></p> <p>1. 91% (95% CI 78.3-97.5%)</p> <p>2. 100% (95% CI 91.6-100%)</p> <p>Mean difference -9.16%; 95% CI -19.61 to 1.29%, P=0.086</p> <p><i>Treatment-experienced</i></p> <p>1. 100% (95% CI 92.7-100%)</p>	NA	<p><u>Discontinuations due to Adverse Events:</u></p> <p>0</p> <p><u>Serious AE:</u></p> <p>0</p>	NA	<p>Risk of Bias (low/high/unclear):</p> <p><u>Selection Bias:</u> high; only treatment naïve subjects were randomized to receive therapy with ribavirin or no ribavirin using a computer generated randomization list. Treatment experienced subjects were not randomized. More patients in the group w/o RBV had F0-F1 fibrosis score (86% vs. 79%)</p> <p><u>Performance Bias:</u> high; open-label</p> <p><u>Detection Bias:</u> high; open label</p> <p><u>Attrition Bias:</u> low; overall low attrition and ITT performed</p> <p><u>Reporting Bias:</u> unclear</p> <p>Applicability:</p> <p><u>Patient:</u> Almost all white patients; included patients with more mild disease severity (77% F0-F2) with a low percentage of cirrhotics and overall higher baseline HCV RNA level; majority of patients from Europe (86%). Treatment experienced patients were limited to those who have failed treatment with PEG/RBV.</p> <p><u>Intervention:</u> Appropriate intervention</p> <p><u>Comparator:</u> No active comparator group besides addition of RBV to truly assess efficacy of OMB/PTV-R</p> <p><u>Outcomes:</u> Surrogate outcome of SVR 12 used to evaluate efficacy.</p> <p><u>Setting:</u> Multicenter sites in Europe and US</p>

Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency; ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OL = open label; OMB = ombitasvir; PTV = paritaprevir; R = ritonavir; RBV = ribavirin; SVR12 = sustained virologic response at 12 weeks after treatment; TN = Treatment-naïve; TE = treatment-experienced

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	HARVONI	LEDIPASVIR/SOFOSBUVIR	Y
ORAL	TAB DS PK	VIEKIRA PAK	OMBITA/PARITAP/RITON/DASABUVIR	Y
SUB-Q	KIT	PEGINTRON	PEGINTERFERON ALFA-2B	Y
SUB-Q	PEN IJ KIT	PEGINTRON REDIPEN	PEGINTERFERON ALFA-2B	Y
SUB-Q	PEN INJCTR	PEGASYS PROCLICK	PEGINTERFERON ALFA-2A	Y
SUB-Q	SYRINGE	PEGASYS	PEGINTERFERON ALFA-2A	Y
SUB-Q	VIAL	PEGASYS	PEGINTERFERON ALFA-2A	Y
ORAL	CAPSULE	REBETOL	RIBAVIRIN	Y
ORAL	CAPSULE	RIBASPHERE	RIBAVIRIN	Y
ORAL	CAPSULE	RIBAVIRIN	RIBAVIRIN	Y
ORAL	TABLET	COPEGUS	RIBAVIRIN	Y
ORAL	TABLET	MODERIBA	RIBAVIRIN	Y
ORAL	TABLET	RIBASPHERE	RIBAVIRIN	Y
ORAL	TABLET	RIBAVIRIN	RIBAVIRIN	Y
ORAL	TABLET	SOVALDI	SOFOSBUVIR	Y
ORAL	CAPSULE	OLYSIO	SIMEPREVIR SODIUM	N
ORAL	SOLUTION	REBETOL	RIBAVIRIN	N
ORAL	TAB DS PK	MODERIBA	RIBAVIRIN	N
ORAL	TAB DS PK	RIBASPHERE RIBAPAK	RIBAVIRIN	N

Appendix 2: Abstracts of Clinical Trials

Naggie, et al. Ledipasvir and Sofosbuvir for HCV in patients Coinfected with HIV-1. *N Engl J Med* 2015; 373:705-13.

BACKGROUND: Effective treatment for hepatitis C virus (HCV) in patients coinfecting with human immunodeficiency virus type 1 (HIV-1) remains an unmet medical need.

METHODS: We conducted a multicenter, single-group, open-label study involving patients coinfecting with HIV-1 and genotype 1 or 4 HCV receiving an antiretroviral regimen of tenofovir and emtricitabine with efavirenz, rilpivirine, or raltegravir. All patients received ledipasvir, an NS5A inhibitor, and sofosbuvir, a nucleotide polymerase inhibitor, as a single fixed-dose combination for 12 weeks. The primary end point was a sustained virologic response at 12 weeks after the end of therapy.

RESULTS: Of the 335 patients enrolled, 34% were black, 55% had been previously treated for HCV, and 20% had cirrhosis. Overall, 322 patients (96%) had a sustained virologic response at 12 weeks after the end of therapy (95% confidence interval [CI], 93 to 98), including rates of 96% (95% CI, 93 to 98) in patients with HCV genotype 1a, 96% (95% CI, 89 to 99) in those with HCV genotype 1b, and 100% (95% CI, 63 to 100) in those with HCV genotype 4. Rates of sustained virologic response were similar regardless of previous treatment or the presence of cirrhosis. Of the 13 patients who did not have a sustained virologic response, 10 had a relapse after the end of treatment. No patient had confirmed HIV-1 virologic rebound. The most common adverse events were headache (25%), fatigue (21%), and diarrhea (11%). No patient discontinued treatment because of adverse events.

CONCLUSIONS: Ledipasvir and sofosbuvir for 12 weeks provided high rates of sustained virologic response in patients coinfecting with HIV-1 and HCV genotype 1 or 4. (Funded by Gilead Sciences; ION-4 ClinicalTrials.gov number, [NCT02073656](#).)

Bourliere, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS) *Lancet Infect Dis* 2015; 15:397-404.

BACKGROUND: Patients with cirrhosis resulting from chronic hepatitis C virus (HCV) infection are at risk of life-threatening complications, but consistently achieve lower sustained virological response (SVR) than patients without cirrhosis, especially if treatment has previously failed. We assessed the efficacy and safety of the NS5A inhibitor ledipasvir and the nucleotide polymerase inhibitor sofosbuvir, with and without ribavirin.

METHODS: In this multicentre, double-blind trial, between Oct 21, 2013, and Oct 30, 2014, we enrolled patients with HCV genotype 1 and compensated cirrhosis who had not achieved SVR after successive treatments with pegylated interferon and protease-inhibitor regimens at 20 sites in France. With a computer-generated randomisation sequence, patients were assigned in a 1:1 ratio to receive placebo matched in appearance to study drugs for 12 weeks followed by once daily combination fixed-dose tablets of 90 mg ledipasvir and 400 mg sofosbuvir plus weight-based ribavirin for 12 weeks, or ledipasvir-sofosbuvir plus placebo once daily for 24 weeks. The primary endpoint was SVR 12 weeks after the end of treatment (SVR12), for which 95% CIs were calculated with the Clopper-Pearson method. This study is registered with ClinicalTrials.gov, number [NCT01965535](#).

FINDINGS: Of 172 patients screened, 155 entered randomisation, 77 were assigned to receive ledipasvir-sofosbuvir plus ribavirin and 78 ledipasvir-sofosbuvir. 114 (74%) were men, 151 (97%), were white, 98 (63%) had HCV genotype 1a, and 145 (94%) had non-CC IL28B alleles. SVR12 rates were 96% (95% CI 89-99) for patients in the ledipasvir-sofosbuvir plus ribavirin group and 97% (91-100) in the ledipasvir-sofosbuvir group. One patient discontinued treatment because of adverse events while receiving only placebo. The most frequent adverse events were asthenia and headache, pruritus, and fatigue.

INTERPRETATION: Ledipasvir-sofosbuvir plus ribavirin for 12 weeks and ledipasvir-sofosbuvir for 24 weeks provided similarly high SVR12 rates in previous non-responders with HCV genotype 1 and compensated cirrhosis. The shorter regimen, when given with ribavirin, might, therefore, be useful to treat treatment-experienced patients with cirrhosis if longer-term treatment is not possible

Molina, et al. Sofosbuvir plus ribavirin for treatment of hepatitis C virus in patients co-infected with HIV (PHOTON-2): a multicentre, open-label, non-randomised, phase 3 study *Lancet* 2015; 385:1098-106.

BACKGROUND: Although interferon-free regimens are approved for patients co-infected with HIV and genotype-2 or genotype-3 hepatitis C virus (HCV), interferon-based regimens are still an option for those co-infected with HIV and HCV genotypes 1 or 4. These regimens are limited by clinically significant toxic effects and drug interactions with antiretroviral therapy. We aimed to assess the efficacy and safety of an interferon-free, all-oral regimen of sofosbuvir plus ribavirin in patients with HIV and HCV co-infection.

METHODS: We did this open-label, non-randomised, uncontrolled, phase 3 study at 45 sites in seven European countries and Australia. We enrolled patients (aged ≥ 18 years) co-infected with stable HIV and chronic HCV genotypes 1-4, including those with compensated cirrhosis. Once-daily sofosbuvir (400 mg) plus twice-daily ribavirin (1000 mg in patients with bodyweights < 75 kg and 1200 mg in those with weights ≥ 75 kg) was given for 24 weeks to all patients except treatment-naive patients with genotype-2 HCV, who received a 12-week regimen. The primary efficacy endpoint was sustained virological response 12 weeks after treatment. We did analysis by modified intention to treat. This study is registered with ClinicalTrials.gov, number NCT01783678.

FINDINGS: Between Feb 7, 2013, and July 29, 2013, we enrolled 275 eligible patients, of whom 262 (95%) completed treatment; 274 patients were included in the final analysis. Overall rates of sustained virological response 12 weeks after treatment were 85% (95% CI 77-91) in patients with genotype-1 HCV, 88% (69-98) in patients with genotype-2 HCV, 89% (81-94) in patients with genotype-3 HCV, and 84% (66-95) in patients with genotype-4 HCV. Response rates in treatment-naive patients with HCV genotypes 2 or 3 (89% [95% CI 67-99] and 91% [81-97], respectively) were similar to those in treatment-experienced patients infected with those genotypes (83% [36-100] and 86% [73-94], respectively). There was no emergence of sofosbuvir-resistance mutations in patients with HCV viral relapse. Six (2%) patients discontinued treatment because of adverse events. The most common adverse events were fatigue, insomnia, asthenia, and headache. Four (1%) patients had serious adverse events regarded as related to study treatment. Additionally, four (1%) patients receiving antiretroviral treatment had a transient HIV viral breakthrough; however, none required changes in antiretroviral regimen.

INTERPRETATION: Sofosbuvir and ribavirin provided high rates of sustained virological response after 12 weeks of treatment in treatment-naive and treatment-experienced patients co-infected with HIV and HCV genotypes 1-4. The characteristics of this interferon-free combination regimen make sofosbuvir plus ribavirin a useful treatment option for this patient population.

Sulkowski, et al. *JAMA* 2015 Mar 24-31;313(12):1223-31. doi: 10.1001/jama.2015.1328.

IMPORTANCE: Patients co-infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) are at high risk for liver disease progression. However, interferon-based treatments for HCV infection have significant toxicities, limiting treatment uptake.

OBJECTIVE: To assess the all-oral 3 direct-acting antiviral (3D) regimen of ombitasvir, paritaprevir (co-dosed with ritonavir [paritaprevir/r]), dasabuvir, and ribavirin in HCV genotype 1-infected adults with HIV-1 co-infection, including patients with cirrhosis.

DESIGN, SETTING, AND PARTICIPANTS: TURQUOISE-I is a randomized, open-label study. Part 1a of this pilot study was conducted at 17 sites in the United States and Puerto Rico between September 2013 and August 2014 and included 63 patients with HCV genotype 1 and HIV-1 co-infection who were HCV treatment-naive or had history of prior treatment failure with peginterferon plus ribavirin therapy. The study allowed enrollment of patients, including those with cirrhosis, with a CD4+ count of 200/mm³ or greater or CD4+ percentage of 14% or more and plasma HIV-1 RNA suppressed while taking a stable atazanavir- or raltegravir-inclusive antiretroviral regimen.

INTERVENTIONS: Ombitasvir/paritaprevir/r, dasabuvir, and ribavirin for 12 or 24 weeks of treatment as randomized.

MAIN OUTCOMES AND MEASURES: The primary assessment was the proportion of patients with sustained virologic response (HCV RNA <25 IU/mL) at posttreatment week 12 (SVR12).

RESULTS: Among patients receiving 12 or 24 weeks of 3D and ribavirin, SVR12 was achieved by 29 of 31 (94%; 95% CI, 79%-98%) and 29 of 32 patients (91%; 95% CI, 76%-97%), respectively. Of the 5 patients who did not achieve SVR, 1 withdrew consent, 2 had confirmed virologic relapse or breakthrough, and 2 patients had clinical history and phylogenetic evidence consistent with HCV reinfection. The most common treatment-emergent adverse events were fatigue (48%), insomnia (19%), nausea (18%), and headache (16%). Adverse events were generally mild, with none reported as serious or leading to discontinuation. No patient had a confirmed HIV-1 breakthrough of 200 copies/mL or greater during treatment.

CONCLUSIONS AND RELEVANCE: In this open-label, randomized uncontrolled study, treatment with the all-oral, interferon-free 3D-plus-ribavirin regimen resulted in high SVR rates among patients co-infected with HCV genotype 1 and HIV-1 whether treated for 12 or 24 weeks. Further phase 3 studies of this regimen are warranted in patients with co-infection.

Charlton, et al. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease*Gastroenterology* 2015; 149:649-59.

BACKGROUND & AIMS: There are no effective and safe treatments for chronic hepatitis C virus (HCV) infection of patients who have advanced liver disease.

METHODS: In this phase 2, open-label study, we assessed treatment with the NS5A inhibitor ledipasvir, the nucleotide polymerase inhibitor sofosbuvir, and ribavirin in patients infected with HCV genotypes 1 or 4. Cohort A enrolled patients with cirrhosis and moderate or severe hepatic impairment who had not undergone liver transplantation. Cohort B enrolled patients who had undergone liver transplantation: those without cirrhosis; those with cirrhosis and mild, moderate, or severe hepatic impairment; and those with fibrosing cholestatic hepatitis. Patients were assigned randomly (1:1) to receive 12 or 24 weeks of a fixed-dose combination tablet containing ledipasvir and sofosbuvir, once daily, plus ribavirin. The primary end point was sustained virologic response at 12 weeks after the end of treatment (SVR12).

RESULTS: We enrolled 337 patients, 332 (99%) with HCV genotype 1 infection and 5 (1%) with HCV genotype 4 infection. In cohort A (nontransplant), SVR12 was achieved by 86%-89% of patients. In cohort B (transplant recipients), SVR12 was achieved by 96%-98% of patients without cirrhosis or with compensated cirrhosis, by 85%-88% of patients with moderate hepatic impairment, by 60%-75% of patients with severe hepatic impairment, and by all 6 patients with fibrosing cholestatic hepatitis. Response rates in the 12- and 24-week groups were similar. Thirteen patients (4%) discontinued the ledipasvir and sofosbuvir combination prematurely because of adverse events; 10 patients died, mainly from complications related to hepatic decompensation.

CONCLUSION: The combination of ledipasvir, sofosbuvir, and ribavirin for 12 weeks produced high rates of SVR12 in patients with advanced liver disease, including those with decompensated cirrhosis before and after liver transplantation. ClinTrials.gov: [NCT01938430](https://clinicaltrials.gov/ct2/show/study/NCT01938430).

Appendix 3: Highlights of Prescribing Information (Daclatasvir)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DAKLINZA safely and effectively. See full prescribing information for DAKLINZA.

DAKLINZA™ (daclatasvir) tablets, for oral use
Initial U.S. Approval: 2015

INDICATIONS AND USAGE

DAKLINZA is a hepatitis C virus (HCV) NS5A inhibitor indicated for use with sofosbuvir for the treatment of chronic HCV genotype 3 infection. (1)

Limitations of Use:

- Sustained virologic response (SVR) rates are reduced in patients with cirrhosis. (14)

DOSAGE AND ADMINISTRATION

- 60 mg taken orally once daily with or without food in combination with sofosbuvir. (2.1)
- Recommended treatment duration: 12 weeks. (2.1)
- Dose modification: Reduce dosage to 30 mg once daily with strong CYP3A inhibitors and increase dosage to 90 mg once daily with moderate CYP3A inducers. (2.2)

DOSAGE FORMS AND STRENGTHS

- Tablet: 60 mg and 30 mg (3)

CONTRAINDICATIONS

- Strong inducers of CYP3A, including phenytoin, carbamazepine, rifampin, and St. John's wort. (4)

WARNINGS AND PRECAUTIONS

- Bradycardia When Coadministered with Sofosbuvir and Amiodarone: Serious symptomatic bradycardia may occur in patients taking amiodarone with sofosbuvir in combination with another HCV direct-acting agent, including DAKLINZA, particularly in patients also receiving beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with DAKLINZA in combination with sofosbuvir is not recommended. In patients with no alternative treatment options, cardiac monitoring is recommended. (5.2, 6.2, 7.3)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 10\%$) observed with DAKLINZA in combination with sofosbuvir were headache and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drug Interactions: Coadministration of DAKLINZA can alter the concentration of other drugs and other drugs may alter the concentration of daclatasvir. Consult the full prescribing information before use for contraindicated drugs and other potential drug-drug interactions. (2.2, 4, 5.1, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 7/2015

Appendix 4: Highlights of Prescribing Information (Ombitasvir, paritaprevir and ritonavir)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TECHNIVIE safely and effectively. See full prescribing information for TECHNIVIE.

TECHNIVIE (ombitasvir, paritaprevir and ritonavir) tablets, for oral use
Initial U.S. Approval: 2015

RECENT MAJOR CHANGES

Indications and Usage, Removed-Limitations of Use (1)	10/2015
Dosage and Administration, Testing Prior to Initiation of TECHNIVIE (2.1)	10/2015
Dosage and Administration, Recommended Dosage in Adults (2.2)	10/2015
Dosage and Administration, Dosage in Patients with Hepatic Impairment (2.3)	10/2015
Contraindications (4)	10/2015
Warnings and Precautions (5.1)	10/2015

INDICATIONS AND USAGE

TECHNIVIE is a fixed-dose combination of ombitasvir, a hepatitis C virus NS5A inhibitor, paritaprevir, a hepatitis C virus NS3/4A protease inhibitor, and ritonavir, a CYP3A inhibitor and is indicated in combination with ribavirin for the treatment of patients with genotype 4 chronic hepatitis C virus (HCV) infection without cirrhosis. (1)

DOSAGE AND ADMINISTRATION

- Testing Prior to Initiation: Assess baseline hepatic laboratory and clinical parameters. (2.1)
- Recommended dosage: Two tablets taken orally once daily (in the morning) with a meal without regard to fat or calorie content. TECHNIVIE is recommended to be used in combination with ribavirin. (2.2)

Patient Population	Treatment	Duration
Genotype 4 without cirrhosis	TECHNIVIE + ribavirin*	12 weeks

*TECHNIVIE administered without ribavirin for 12 weeks may be considered for treatment-naïve patients who cannot take or tolerate ribavirin [see Microbiology (12.4) and Clinical Studies (14)].

DOSAGE FORMS AND STRENGTHS

Tablets: 12.5 mg ombitasvir, 75 mg paritaprevir, 50 mg ritonavir. (3)

CONTRAINDICATIONS

- The contraindications to ribavirin also apply to this combination regimen. (4)

- Patients with moderate to severe hepatic impairment. (4, 5.1, 8.6, 12.3)
- Co-administration with drugs that are: highly dependent on CYP3A for clearance; moderate and strong inducers of CYP3A. (4)
- Known hypersensitivity to ritonavir (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome). (4)

WARNINGS AND PRECAUTIONS

- **Hepatic Decompensation and Hepatic Failure in Patient with Cirrhosis:** Hepatic decompensation and hepatic failure, including liver transplantation or fatal outcomes, have been reported mostly in patients with advanced cirrhosis. Discontinue treatment in patients who develop evidence of hepatic decompensation. (5.1)
- **ALT Elevations:** Discontinue ethinyl estradiol-containing medications prior to starting TECHNIVIE (alternative contraceptive methods are recommended). Perform hepatic laboratory testing on all patients during the first 4 weeks of treatment. For ALT elevations on TECHNIVIE, monitor closely and follow recommendations in full prescribing information. (5.2)
- **Risks Associated With Ribavirin Combination Treatment:** The warnings and precautions for ribavirin also apply to this combination regimen. (5.3)
- **Drug Interactions:** The concomitant use of TECHNIVIE and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of TECHNIVIE. (5.4)

ADVERSE REACTIONS

The most commonly reported adverse reactions (incidence greater than 10% of subjects, all grades) observed with treatment with ombitasvir, paritaprevir and ritonavir with ribavirin for 12 weeks were asthenia, fatigue, nausea and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Co-administration of TECHNIVIE can alter the plasma concentrations of some drugs and some drugs may alter the plasma concentrations of TECHNIVIE. The potential for drug-drug interactions must be considered before and during treatment. Consult the full prescribing information prior to and during treatment for potential drug interactions. (4, 5.4, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2015

Appendix 5: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to December Week 1 2015, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 10, 2014

1 Hepatitis C/ or hepatitis c virus.mp. or Hepatitis C, Chronic 43,112

2 Antiviral Agents/ or direct acting antivirals.mp 49116

3 sofosbuvir.mp 283

4 ledipasvir.mp 74

5 ombitasvir.mp. 33

6 daclatasvir.mp. 129

7 dasabuvir.mp. 27

8 1 or 2 44131

9 3 or 4 or 5 or 6 or 7 or 8 49149

10 9 and 10 12809

11 limit 11 to (english language and humans and yr="2015 -Current" and (clinical trial, phase ii or clinical trial, phase iii or controlled clinical trial or meta analysis or systematic reviews)) 20

12 from 12 keep 2, 11, 17-18, 20-24, 27-28, 31... 8

Hepatitis C Direct-Acting Antivirals

Goals:

- Approve use of cost-effective treatments supported by the medical evidence.
- Prioritize populations in greatest need of treatment who will benefit the most from therapy.
- Provide consistent patient evaluations across all hepatitis C treatments.

Length of Authorization:

- 6 weeks

Requires PA:

- All direct-acting antivirals for treatment of Hepatitis C

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization?	Yes: Go to Renewal Criteria	No: Go to #2
2. What diagnosis is being treated?	Record ICD10 code.	
3. Is the request for treatment of Hepatitis C infection?	Yes: Go to #4	No: Pass to RPh; deny for appropriateness.
4. Has the patient had all of the following appropriate pre-treatment testing? <ul style="list-style-type: none"> • Genotype testing in past 3 years; <u>AND</u> • Baseline HCV RNA level in the past 6 months; <u>AND</u> • HIV status in past 6 months; <u>AND</u> • Pregnancy test if a woman of child-bearing age in past 30 days 	Yes: Record results and go to #5	No: Pass to RPh. Request updated testing before approving treatment.

Approval Criteria

<p>5. Has the patient failed treatment with any HCV NS5A inhibitor (including daclatasvir plus sofosbuvir, ledipasvir/sofosbuvir, or paritaprevir/ritonavir/ombitasvir plus dasabuvir)?</p> <p>Note: Patients who failed treatment with sofosbuvir +/- ribavirin or pegylated interferon can be retreated (See table below)</p>	<p>Yes: Pass to RPh; deny for appropriateness.</p> <p>Note: If patient needs urgent retreatment, resistance testing must be done to indicate susceptibility to prescribed regimen for retreatment</p>	<p>No: Go to #6</p>
<p>6. What regimen is requested?</p>	<p>Document and go to #7</p>	
<p>7. Is the regimen prescribed by, or in consultation with, a hepatologist, gastroenterologist, or infectious disease specialist with experience in treatment of Hepatitis C?</p>	<p>Yes: Go to #8</p>	<p>No: Pass to RPh; deny for appropriateness.</p> <p>Forward to DMAP for further manual review to determine appropriateness of prescriber.</p>
<p>8. Does the patient have:</p> <ul style="list-style-type: none"> • A biopsy, transient elastography (Fibroscan[®]) or serum test (FibroSure[®]) to indicate advanced fibrosis (METAVIR F3) or cirrhosis (METAVIR F4); OR • Radiologic, laboratory (APRI score > 1.5 or FIB-4 score >3.25), or clinical evidence (ascites, portal hypertension) of cirrhosis; AND • Expected survival from non-HCV-associated morbidities of greater than 5 years? 	<p>Yes: Go to #12</p>	<p>No: Go to #9</p>

Approval Criteria

<p>9. Does the patient have one of the following extrahepatic manifestations of Hepatitis C (with documentation from a relevant specialist that their condition is related to HCV) and have an expected survival from non-HCV-associated morbidities greater than 5 years?</p> <p>a. Type 2 or 3 cryoglobulinemia with end-organ manifestations (i.e., leukocytoclastic vasculitis); <u>OR</u></p> <p>b. Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis; <u>OR</u></p> <p>c. Porphyria cutanea tarda</p>	<p>Yes: Go to #12</p>	<p>No: Go to #10</p>
<p>10. Does the patient have Hepatitis C in the transplant setting, including the following scenarios:</p> <p>a) Patient is listed for a transplant and it is essential to prevent recurrent hepatitis C infection post-transplant; <u>OR</u></p> <p>b) Post solid organ transplant; <u>AND</u></p> <p>c) Expected survival from non-HCV-associated morbidities of greater than 5 years?</p>	<p>Yes: Go to #12</p>	<p>No: Go to # 11</p>
<p>11. Does the patient have HIV coinfection and METAVIR stage F2 or greater (APRI \geq 1.0) <u>AND</u> the patient is under treatment by a specialist with experience in HIV?</p>	<p>Yes: Go to #12</p>	<p>No: Pass to RPh; deny for medical appropriateness.</p> <p>Note: Other scenarios not included can be brought to the OHP Medical Director on a case-by-case basis.</p>
<p>12. Has the patient been evaluated for current alcohol and substance use with a validated screening instrument?</p>	<p>Yes: Go to #13</p>	<p>No: Pass to RPh; deny for medical appropriateness.</p> <p>Request current evaluation for alcohol and substance use before treatment.</p>

Approval Criteria		
13. Is the patient actively using illicit drugs or abusing alcohol?	Yes: Go to #14	No: Go to #15
14. Is the patient enrolled in a treatment program under the care of an addiction specialist?	Yes: Go to #15	No: Pass to RPh; deny for medical appropriateness.
15. Does the patient have significant renal impairment (CrCl \leq 30 mL/min) or end-stage renal disease?	Yes: Pass to RPh; deny for appropriateness.	No: Go to #16 Note: Treatment may be considered in patients with genotype 1 with paritaprevir/ritonavir/ombitasvir and dasabuvir in those without cirrhosis and for whom the urgency to treat is high.
16. Will the patient and provider comply with all case management and adherence monitoring requirements required by the Oregon Health Authority, including measuring and reporting of a post-treatment viral load?	Yes: Go to #17	No: Pass to RPh; deny for appropriateness.
17. Is the prescribed drug regimen a recommended regimen based on the patient's genotype and cirrhosis status (see Table 1)?	Yes: Approve for 6 weeks to allow for 4 week HCV RNA level	No: Pass to RPh; deny for appropriateness.

Renewal Criteria		
1. Has the patient been adherent to and tolerated initial therapy?	Yes: Go to #2	No: Pass to RPh; deny for medical appropriateness.

Renewal Criteria		
2. Is the HCV RNA level at week 4 detectable (HCV RNA is ≥ 25 IU/mL)?	Yes: Reassess HCV RNA in 2 weeks. Go to #3	No: Approve for additional 2-10 weeks based on genotype and regimen (Table 1).
3. Has the HCV RNA increased (i.e., >1 log ₁₀ IU/mL from nadir)?	Yes: Discontinue treatment.	No: Approve for additional 2-10 weeks based on genotype and regimen (Table 1).
Note: HCV RNA levels must be assessed at 12 weeks after completion of treatment to determine whether SVR was achieved.		

Table 1: Recommended Treatment Regimens for Chronic Hepatitis C.

Genotype	Cirrhosis Status	Approved Regimen [^]	Duration of Treatment
Genotype 1			
Treatment-naïve	NO	<ul style="list-style-type: none"> LDV/SOF 	8-12 weeks <i>Note: If HCV RNA < 6 million IU/mL, give LDV/SOF for 8 weeks</i>
	YES	<ul style="list-style-type: none"> LDV/SOF 	12 weeks
Treatment-experienced	NO	<ul style="list-style-type: none"> LDV/SOF 	12 weeks
	YES	<ul style="list-style-type: none"> LDV/SOF + RBV 	12 weeks
Genotype 2			
Naïve or Experienced	YES/NO	<ul style="list-style-type: none"> SOF + RBV 	12 weeks*
Genotype 3			
Naïve or Experienced	NO	<ul style="list-style-type: none"> LDV/SOF + RBV 	12 weeks
Naïve or Experienced	YES	<ul style="list-style-type: none"> DCV + SOF + RBV 	12 weeks
Genotype 4			
Naïve or Experienced	NO	<ul style="list-style-type: none"> LDV/SOF 	12 weeks
Naïve or Experienced	YES	<ul style="list-style-type: none"> LDV/SOF 	12 weeks
Genotype 6			
Naïve or Experienced	YES/NO	<ul style="list-style-type: none"> LDV/SOF 	12 weeks

*Previous non-responders to PEG/RBV with cirrhosis may benefit by extension of therapy to 16 weeks

Abbreviations: DCV = daclatasvir (Daklinza®); LDV/SOF = ledipasvir and sofosbuvir (Harvoni®); RBV = ribavirin; SOF = sofosbuvir (Sovaldi®)

^Approved regimens are:

- DCV: 1 tablet once daily
- RBV: twice daily weight-based dosing;
- LDS/SOFL: 1 tablet once daily;
- SOF: 1 tablet once daily

Clinical Notes:

Rarely, genotyping assays may indicate the presence of a mixed infection (e.g., genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are sparse. Awaiting availability of a pangenotypic regimen may be considered. Until then, when treatment is necessary, the choice of antiviral combination and duration of treatment should maximize efficacy against each genotype represented in the assay. When the correct combination or duration is unclear, expert consultation should be sought

Ribavirin-containing regimens are absolutely contraindicated in pregnant women and in the male partners of women who are pregnant. Documented use of two forms of birth control in patients and sex partners for whom a ribavirin-containing regimen is chosen is required.

P&T/DUR Review: 1/16 (MH); 5/15; 3/15; 1/15; 9/14; 1/14
Implementation: TBD; 10/15; 4/15; 1/15; 9/14; 7/14; 3/14