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Class Update with New Drug Evaluations: Hepatitis C Direct-acting Antivirals

Date of Review: September 2016
Generic Name: elbasvir/grazoprevir
Generic Name: sofosbuvir/velpatasvir

End Date of Literature Search: August 2016
Brand Name (Manufacturer): Zepatier ® (Merck)
Brand Name (Manufacturer): Epclusa® (Gilead)
Dossiers Received: yes

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
To define place in therapy for 2 new direct-acting antivirals (DAAs) recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of chronic Hepatitis C (CHC) infection. In addition, new comparative evidence for existing DAAs will be reviewed.

Research Questions:
1. Does elbasvir/grazoprevir (EBR/GZR; Zepatier®) or sofosbuvir/velpatasvir (SOF/VEL; Epclusa®) have superior efficacy to placebo and are they more effective/efficacious than other DAAs for the treatment of CHC?
2. Is EBR/GZR or SOF/VEL safer than other DAAs for the treatment of CHC?
3. Is there new comparative evidence for differences in efficacy/effectiveness or harms between available DAAs for the treatment of CHC?
4. Are there specific subpopulations based on severity of disease, comorbidities, or level of fibrosis that may benefit from one particular DAA over another DAA?
5. What is the evidence to support use of non-invasive testing to stage fibrosis, and how do these tests differ in sensitivity and specificity compared to liver biopsies?
6. Is there evidence to support an optimal time to initiate treatment for CHC based on improved effectiveness or less harms?

Conclusions:
- There is moderate quality evidence that 12 weeks of EBR/GZR without ribavirin (RBV) produces a sustained virologic response (SVR) rate of approximately 95% in treatment-naïve CHC patients with genotype (GT) 1 or GT4 with or without HIV coinfection. SVR rates did not significantly differ between patients with or without cirrhosis. However, higher virologic failure occurred in patients with GT1a infection and baseline NS5a resistant amino acid variants (RAVs). Relapse may be reduced with baseline NS5A polymorphism screening.

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- Low quality evidence suggests that 12 weeks of EBR/GZR + RBV may be efficacious in treatment-experienced patients with GT1 who previously failed triple therapy with pegylated interferon and ribavirin plus an early generation protease inhibitor (SVR 96.2%; 95% CI, 89.3 to 99.2%).
- There is low quality evidence for use of EBR/GZR in treatment-experienced patients with GT4, which makes it difficult to determine efficacy in this population. One unpublished trial included 37 treatment-experienced GT4 patients randomized to 12 or 16 weeks of EBR/GZR with or without RBV. SVR rates ranged from 60-100% with the highest SVR rates (8/8) in patients who received EBR/GZR + RBV for 16 weeks. The FDA recommends 16 weeks with RBV based on these data alone due to limited treatment options in treatment-experienced GT4 patients.
- There is low quality evidence based on a phase 3 trial that EBR/GZR can achieve high SVR rates (94.3%; 95% CI, 88.5-97.7%) in GT1 patients with stage 4 or 5 chronic kidney disease (CKD). Although EBR/GZR was generally safe in the population studied, the exclusion criteria were much more restrictive than the other GZR/EBR trials which limit the applicability of these results to real-world patients with CKD.
- GZR exposure is increased in decompensated cirrhosis. EBR/GZR is therefore contraindicated in Child-Pugh B and C cirrhosis due to increased risk for liver toxicity.
- There is low quality evidence that 12 weeks of SOF/VEL results in SVR rates of 95% or higher for treatment-naïve or treatment-experienced CHC patients with GT1, GT2, GT3, GT4, GT5 or GT6. SVR rates did not vary significantly based on age, race, or sex but were numerically lower for patients with GT3, patients with cirrhosis, and patients with prior treatment failure. Confidence intervals were imprecise for GT5 and GT6 due to the low number of patients studied with these 2 genotypes.
- There is low quality evidence that 12 weeks SOF/VEL may be modestly superior to 12 weeks SOF + RBV in patients with GT2 (SVR 99% vs. 95%, respectively; absolute difference 5.2%; 95% CI, 0.2-10.3%; p=0.02). Treatment with 24 weeks of SOF/VEL may also be superior to 24 weeks of SOF + RBV in patients with GT3 (SVR 95% vs. 80%; respectively; absolute difference 14.8%; 95% CI 9.6-20%; p<0.001). There are no other alternative treatment regimens approved for GT2 and there is insufficient comparative data for other treatments available for GT3 (LDV/SOF + RBV or DCV/SOF).
- There are still several limitations in the current evidence for the treatment of CHC:
    - There is still insufficient evidence for the optimal treatment of patients who have had a virologic failure to a previous NS5A or NS5B inhibitor. Risk of DAA resistance is a major concern in this population.
    - There is still a lack of head-to-head trials for most DAA regimens. In some populations, data on DAAs are limited to open-label, uncontrolled, or historically controlled trials.
    - Trials often exclude patients with chronic hepatitis B virus (HBV), HIV, cancer, hepatocellular carcinoma (HCC), decompensated cirrhosis, severe psychiatric, cardiac, pulmonary, or renal comorbidities, and severe alcohol or substance abuse. When decompensated cirrhosis is included, there are very little data in patients with Child-Pugh class C.
    - There is no direct evidence that treatment with antiviral therapy for CHC leads to improved long-term clinical outcomes in incidence of HCC, liver transplantation, or mortality.
- Given the high sensitivity and specificity of image tests to stage fibrosis (specifically, transient elastography [FibroScan], acoustic radiation force impulse imaging [ARFI], shear wave elastography [SWE]) and potential harms of liver biopsy, these less invasive options are favored for prescribers considering CHC treatment with a DAA.

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- Limited data are available according to severity of fibrosis. Studies define patients by cirrhosis status. There is insufficient evidence from clinical trials that patients with early stages of disease (F0-F2) achieve higher SVR rates than those with more advanced disease, or whether delayed treatment leads to poorer long-term clinical outcomes. However, an assessment of the patient's readiness to treat and education on the importance of compliance and follow-up are vital for successful treatment. Factors to consider before deciding to treat early fibrosis stages (F0-F1) include: 1) the slow progression of disease to cirrhosis, 2) limited treatment options for the re-treatment of HCV in cases of relapse or reinfection, and 3) possibility of superior DAA regimens in the pipeline.

Recommendations:

- Proposed amendments to the clinical prior authorization (PA) criteria (Appendix 4) to allow for treatment of preferred DAA regimens in CHC patients with Metavir fibrosis stage 2 or higher was rejected by the Pharmacy and Therapeutics (P&T) Committee. Proposed amendments to deny DAA regimens based on an expected survival of less than 1 year instead of less than 5 years was also rejected by the P&T Committee. Amendments to criteria on alcohol and substance abuse and fibrosis imaging studies were adopted by the P&T Committee.
- Approve SOF/VEL for 12 weeks as a preferred treatment regimen for patients with GT2.
- After evaluation of comparative drug costs in the executive session, make EBR/GZR a preferred regimen for GT1 and GT4, except in decompensation, and make SOF/VEL a preferred regimen for GT3 on the Oregon Health Plan (OHP) fee-for-service Preferred Drug List (PDL). See Table 1 in Appendix 4 for preferred DA regimens.

Previous 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. 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 rivabirin (RBV) or an extended duration of 16 weeks. 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.
- 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. 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.
- 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, HCC, and mortality.

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- 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. These agents should be used with caution in patients with cirrhosis and are contraindicated in decompensated liver disease.

Previous 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.

Background:

Chronic hepatitis C infection 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.[1] The goal of treatment for CHC is to reduce the occurrence of end-stage liver disease and its related complications. However, results from clinical trials designed to evaluate long-term health outcomes are not available. In addition, only about 30% of people with CHC go on to develop cirrhosis and the time to progress to cirrhosis varies at an average of 40 years.[2]

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 based on observational data of an association of SVR and reductions in mortality, liver failure, and cancer.[1] The two major predictors of SVR are viral genotype and pre-treatment viral load.[3] Other factors associated with an increased likelihood of 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. Studies that include patients with decompensated cirrhosis, renal failure or other comorbidities, and minority racial or ethnic groups are lacking though these patients remain the most difficult to successfully treat.[4]

There are no published data to support a specific minimum length of abstinence from illicit substances or alcohol before treatment. In addition, no evidence is available that shows patients who use alcohol, illicit drugs, and marijuana are less likely to achieve SVR if they are adherent to therapy. However, substance use should be part of a readiness to treat assessment because of the higher risk of non-adherence and re-infection.

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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, decreased decompensated liver disease, hepatocellular carcinoma, liver transplant, and all-cause mortality. More recent studies use SVR rate at 12 weeks (SVR12) as the primary endpoint based on evidence that the majority of patients with SVR12 maintain SVR at 24 weeks.[5] SVR12 is generally considered a virologic cure in clinical trials.

Patients at greatest risk for progression 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, developing hepatocellular carcinoma, and are at higher risk for death. Urgency to treat patients with CHC is higher when risk of decompensated cirrhosis or death from liver-related diseases is higher; treatment urgency is also higher in liver transplant recipients with CHC in order to prolong graft survival. Disease progression varies greatly among patients with compensated liver disease and the number needed to treat to prevent adverse long-term outcomes is dependent on several factors. The newer DAAs will be most beneficial in patients at highest risk for cirrhosis-related events.[6] However, treatment of CHC with DAAs at earlier stages of fibrosis incur substantial upfront costs but can be cost-effective long-term if adverse events are avoided from cure.[7] Patients with decompensated liver disease are a challenging population to treat because of symptomatic complications related to cirrhosis (i.e., jaundice, ascites, variceal hemorrhage, or hepatic encephalopathy). Clinical trials define decompensated cirrhosis as Child-Turcotte-Pugh (CTP) class B or C cirrhosis; the majority of decompensated cirrhosis patients included in trials have CTP class B cirrhosis.[8]

Virologic failure is defined as confirmed HCV RNA level at or above the lower limit of quantification (LLOQ) during treatment after previously being below the LLOQ; relapse is defined as confirmed HCV RNA level at or above the LLOQ after treatment after previously achieving an SVR.[9] Virologic failure is typically associated with the emergence of resistance-associated variants (RAVs) that can cause cross resistance to other DAAs in the same class.[10] Baseline RAVs exist in a minority of patients and are found in most patients who fail to achieve SVR with DAA treatment. NS3 variants can cause high-level resistance to other protease inhibitors. In the U.S., the prevalence of baseline NS5A polymorphisms in patients with GT1a and GT1b infection is 8-12% and 11-12%, respectively.[11] Sofosbuvir (SOF), an NS5B inhibitor, appears to have the highest genetic barrier to resistance. Genetic polymorphisms that reduce drug susceptibility have been reported for the NS5A and NS3/4A (protease inhibitor) drug classes. The presence of baseline NS5A RAVs significantly reduce SVR12 rates in patients with GT3 treated with daclatasvir (DCV) plus SOF compared to patients without the NS4A RAV (SVR rates of 54% vs. 92%, respectively).[12]

In the U.S., GT1 infection is found in about 75% of patients with CHC; GT2 and GT3 represent about 20% of CHC patients.[1] 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. Data suggests that fibrosis progression occurs most rapidly in patients with GT3; DAA regimens have also been less effective in patients with this genotype.[8] Therapies to treat CHC have advanced significantly over the past several years. Prior to 2011, the combination of pegylated interferon (PEG-IFN) and ribavirin (RBV) was the standard of care and approximately only 55-60% of patients achieved a SVR. In 2011, the FDA approved the first generation DAAs boceprevir and telaprevir.[13] Since then, a variety of additional DAAs have been approved by the FDA resulting in interferon-free regimens, substantial improvement in adverse events and tolerability, and SVR12 rates that exceed 90% (Table 1). However, newer DAAs are associated with substantial cost. A significant challenge remains identifying patients who will most benefit from treatment since only 5-20% of CHC patients will develop cirrhosis over 20 years.[14] Additionally, the lack of head-to-head trials and the use of single-arm cohort studies make it difficult to compare the relative efficacy of the different DAA regimens available.

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The Oregon Drug Use Review / Pharmacy & Therapeutics (P&T) Committee initially prioritized treatment for the fee-for-service population to patients in greatest need of treatment. Limited real-world experience and data, consideration for the number of patients waiting for treatment and limited provider expertise, and the limited number of alternative treatment options in cases of treatment resistance and patient comorbidities all played a role in prioritizing treatment. As more treatment options become available, real world experience increases, and the community standard evolves, the P&T Committee has opened up treatment in a step-wise fashion to patients with less severe disease. Current drug policies in place approve treatment for patients with fibrosis Metavir stage 3 or 4, or patients with extrahepatic manifestations at any stage of fibrosis, patients in the setting of solid organ transplant, and in patients with fibrosis Metavir stage 2 or greater coinfected with HIV.

Zepatier® (EBR/GZR) is a fixed dose-combination of 2 DAAs which contain 50 mg of elbasvir (EBR) and 100 mg of grazoprevir (GZR) approved for patients with GT1 or GT4. EBR is an NS5A inhibitor and GZR is an NS3/NS4A protease inhibitor.[15] EBR/GZR was also approved for GT1 patients with end stage renal disease (ESRD) on hemodialysis.[11]

Epclusa® (SOF/VEL) is a fixed-dose combination of 400 mg of SOF, a NS5B inhibitor, and 100 mg of velptasvir (VEL), a NS5A inhibitor approved for the treatment of CHC in adult patients with GT1, 2, 3, 4, 5 or 6 with or without cirrhosis, including decompensated cirrhosis.[16]

Table 1. Direct-acting Antiviral Regimens for Chronic Hepatitis C.

Drug Name	Indications	Strength/Route	Dose and Frequency
Daklinza®[17] and Solvaldi®[18]	CHC GT1; GT3	Daclatasvir 60 mg + sofosbuvir 400 mg	1 tablet of each daily x12 weeks
Epclusa®[16]	CHC GT1; GT2; GT3; GT4; GT5; GT6	Sofosbuvir 400 mg/velpatasvir 100 mg	1 tablet once daily x12 weeks
Harvoni®[19]	CHC GT1; GT4; GT5; GT6	Ledipasvir 90 mg/sofosbuvir 400 mg	1 tablet once daily x8, 12, or 24 weeks
Sovaldi®[18]	CHC GT1; GT2; GT3; GT4 Used in combination with other antivirals	Sofosbuvir 400 mg	1 tablet once daily with ribavirin and/or peginterferon alfa x12 weeks
Technivie®[20]	CHC GT4 Without cirrhosis	Ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg	2 tablets once daily x12 weeks
Viekira Pak®[21]	CHC GT1 Without cirrhosis or With compensated cirrhosis	Ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg + dasabuvir 250 mg	2 tablets once daily + 1 dasabuvir tablet twice daily (+/- ribavirin) x12 or 24 weeks
Viekira XR®[22]	CHC GT1	Dasabuvir 200 mg/ombitasvir 8.33 mg/paritaprevir 50 mg/ritonavir 33.33 mg	3 tablets once daily x12 or 24 weeks
Zepatier®[15]	CHC GT1; GT4	Elbasvir 50 mg/ grazoprevir 100 mg	1 tablet once daily x12 or 16 weeks
Abbreviations: CHC = chronic hepatitis C; GT = genotype			

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Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. 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. Randomized controlled trials and abstracts are in **Appendix 2.**

Systematic Reviews:

1. The Canadian Agency for Drugs and Technologies in Health (CADTH) systematically assessed the comparative efficacy and safety of DAA regimens for the treatment of CHC infection (genotypes 1 to 6).[23] Due to a lack of head-to-head trials, a Bayesian network meta-analysis was performed to assess treatments based on indirect evidence. A total of 67 studies were included with the majority reporting on patients with GT1. The authors categorized the available evidence as adequate; however, all but 2 trials had at least one methodological domain with unclear risk of bias. The newest agents, EBR/GZR and SOF/VEL, were not included in this review.

The following conclusions were made for treatment of patients with GT1:

- For treatment-naive patients, SOF + ledipasvir (LDV), paritaprevir/ritonavir + ombitasvir + dasabvir (PAR/RIT + OMB + DAS) ± RBV, and DCV-based regimens were statistically superior to pegylated interferon and ribavirin (PEG-RBV) in achievement of SVR. Patients on SOF + LDV or PAR/RIT + OMB + DAS ± RBV also achieved SVR significantly more often than simeprevir (SIM) +PEG-RBV, SOF + PEG-RBV, and SOF + RBV.
- For treatment-experienced patients, all 3 regimens noted above were superior to PEG-RBV-based treatments, specifically SOF + LDV and PAR/RIT + OMB + DAS ± RBV. There was limited evidence for patients with cirrhosis. There were no significant differences between SOF + LDV and PAR/RIT + OMB + DAS ± RBV.
- For treatment-experienced patients with prior relapse, prior partial response, or null response, PAR/RIT + OMB + DAS ± RBV, SOF + LDV, and DCV-based regimens demonstrated improved SVR rates compared with PEG-RBV-based treatments.
- There was no evidence available for patients with genotype 1 infection and decompensated liver disease.
- Evidence for efficacy of treatments in patients previously treated unsuccessfully with DAA + PEG-RBV regimens were limited to 4 studies that reported SVR rates. The largest study found SVR rates in patients with GT1 and prior treatment failure on DAA + PEG-RBV were 94% with 12 weeks of SOF + LDV (n = 66); 97% with 12 weeks of SOF + LDV + RBV (n = 64); 98% with 24 weeks of SOF + LDV (n = 50); and 100% with 24 weeks of SOF + LDV + RBV (n = 51). Evidence was also available from one trial (n = 80) for the use of 12 weeks of SOF + PEG-RBV for patients with GT1 without cirrhosis and prior experience

with DAA- PEG-RBV, in which the reported SVR rate was 79%. Only one study reported SVR rates for patients previously treated with an all-oral DAA regimen. In this study, all 14 patients with GT1 previously treated with SOF + RBV achieved SVR with 12 weeks of SOF + LDV.

The following conclusions were made for treatment of patients with GTs 2, 3, 4, 5 and 6:

- For patients with GT2, 12 weeks of SOF + RBV significantly improved SVR rates over 24 weeks of PEG-RBV in treatment-naive patients, but 12 weeks of SOF + PEG-RBV did not. In treatment-experienced patients, neither 16 weeks of SOF + RBV nor 12 weeks of SOF + PEG-RBV were significantly different from 12 weeks of SOF + RBV.
- For patients with GT3 regardless of treatment experience, 24 weeks of SOF + RBV, 12 weeks of DCV + SOF, and 12 weeks of SOF + PEG-RBV significantly improved SVR compared with 48 weeks of PEG-RBV, and there were no significant differences between these regimens.
- For patients with GT4, 12 weeks of SOF + PEG-RBV and 24 weeks of SOF + RBV significantly improved SVR rates compared with 48 weeks of PEG-RBV in treatment-naive patients; 12 weeks of SOF + PEG-RBV was statistically superior to 12 weeks of SOF + RBV. There was no data to include 12 weeks of SOF + PEG-RBV in the analysis of treatment-experienced patients.
- Evidence is insufficient for patients with GT2, 3, or 4 and decompensated liver disease.
- Evidence is insufficient to determine the efficacy of DAA-based regimens in patients with GT2, 3, or 4 and previously unsuccessful treatment with a DAA-based regimen.

2. A systematic review evaluated what the effects of interferon-free treatments in treatment-naïve people with CHC with and without cirrhosis.[24] This systematic review was limited to comparisons to SOF (with or without RBV), SIM + SOF, and SOF/LDV. RCTs or systematic reviews of RCTs were eligible for inclusion. Therefore, the majority of the open-label trials, which were part of the FDA approval process, were excluded from this report. RCTs were only found in people with GT2 or 3 as there was insufficient evidence from RCTs for all other treatment regimens and genotypes. GRADE was applied to the evidence for GT 2 and 3. There was no RCT evidence evaluating long-term clinical outcomes including HCC, end-stage liver disease, mortality or quality of life; RCT evidence for any comparisons in subjects with cirrhosis was also insufficient.
    - SOF + RBV may be more effective than placebo at reducing HCV RNA levels at the end of treatment, and increasing SVR12 after the end of treatment in treatment-naïve people with GT2 or 3 without cirrhosis (low quality evidence).
    - SOF + RBV may be more effective than placebo at reducing HCV RNA levels at the end of treatment in treatment-naïve people with GT2 or 3 with cirrhosis (very low quality evidence).
    - SOF + RBV may be more effective than placebo at increasing SVR12 after the end of treatment in treatment-naïve people with GT2 and 3 with cirrhosis. However, this effect appears to be greater for patients with GT2 than for GT3 (very low quality evidence).
    - SOF + RBV appears to be safe and well tolerated with an adverse event profile consistent with RBV alone.

3. A systematic review with meta-analysis assessed HCV recurrence and reinfection rates by risk group.[25] The majority of studies in all groups included subjects treated with PEG/RBV and there has not been a review of the risk of reinfection after use of DAAs. Populations were categorized into 1) low risk populations (mono-HCV infected patients); 2) high-risk populations (≥1 risk factor for reinfection); and 3) HIV/HCV coinfection populations. Risk factors for reinfection

were defined as current or former intravenous drug use, imprisonment, and men who have sex with men. Results were available from 59 studies (n=9049). In the low-risk population, the pooled estimate for the recurrence rate was 1.85/1000 person years of follow-up (PYFU) and the 5-year recurrence risk was 0.95%. In the high-risk population, the pooled estimate for recurrence was 22.32/1000 PYFU with a 5-year recurrence rate of 10.67% and was driven mainly by reinfection (19.06/1000 PYFU) rather than late relapse. There were only 4 studies that identified recurrence in HIV/HCV coinfected patients with a recurrence rate of 32.02/1000 PYFU and 5-year recurrence rate of 15.02%. The authors concluded that the 5-year recurrence risk was higher among high-risk patients (10.67%) and HIV coinfected patients (15.02%) but SVR appears durable in the majority of patients at 5 years post-treatment.

4. Draft guidance was developed by the Oregon Health Evidence Review Commission (HERC) evaluating if noninvasive testing, including imaging and blood tests, for liver fibrosis for CHC should be recommended.[26] No randomized controlled evidence on the use of noninvasive tests compared to liver biopsy was available However, studies were available that compared the diagnostic accuracy of noninvasive tests to the reference standard of liver biopsy and demonstrated good or excellent performance of non-invasive tests for the detection of various levels of fibrosis. Good to excellent performance was defined as an area under the receiver operating curve (AUROC) of ≥ 0.8. The AUROC is an overall measure of how well the noninvasive test compared to the reference standard of a liver biopsy. Imaging tests appear to have a greater ability to distinguish between intermediate stages of fibrosis (between F2 and F3), while blood tests appear to be effective in establishing the presence of significant fibrosis (≥F2) or cirrhosis. Using the GRADE framework, the authors concluded that given the good and excellent performance of the recommended noninvasive imaging tests and potential harms of liver biopsy, the evidence favors offering these tests as an option for those considering therapy with a DAA. Additional testing including a liver biopsy may be necessary for some patients since noninvasive tests sometimes return inconclusive results. Based on the available evidence, resource allocation and patient preferences and values, the authors recommended that:
   - If a fibrosis score of ≥F2 is the threshold for DAA treatment, the following are recommended for coverage (weak recommendation):
     - Imaging tests (Transient elastography [FibroScan®], Acoustic radiation force impulse imaging [AFRI], shear wave elastography (SWE)
     - Blood tests only if imaging tests are unavailable (Enhanced liver fibrosis (ELF), Fibrometer, FIBROSpect II
   - If a fibrosis score of ≥F3 is the threshold for DAA treatment, one of the following are recommended for coverage (strong recommendation):
     - Imaging tests (FibroScan, ARFI, SWE)
   - Magnetic resonance elastography (MRE), which is much more expensive than other imaging tests, is recommended for coverage only when at least one imaging tests has resulted in indeterminate results, and second imaging test is similarly indeterminate, contraindicated or unavailable (weak recommendation).
   - Noninvasive tests should be performed no more often than once per year (weak recommendation).
   - Other imaging and blood tests are not recommended for coverage (strong recommendation).

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Clinical Practice Guidelines:
The World Health Organization (WHO) updated their guidelines for the screening care and treatment of persons with CHC in April 2016.[27] The Veterans Affairs (VA) National Hepatitis C Resource Center updated treatment guidelines in March 2016,[12] and the Guidelines from the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) updated their recommendations for testing, managing, and treating CHC in July 2016.[8] The AASLD/IDSA guidelines are routinely updated to reflect rapidly changing evidence with the DAAs.[8] The AASLD/IDSA 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 has multiple conflicts of interest.

Publication of both the WHO and VA guidelines preceded the approval of SOF/VEL and this agent is only included in the AASLD/IDSA guidelines. The following recommendations are included in these guidelines:

When to Treat:
AASLD/IDSA: Treatment for all patients regardless of disease severity is recommended, except those with short life expectancy that cannot be remediated by treatment or transplantation.[8] 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.

WHO: HCV treatment should be considered for all persons with CHC, including persons who inject drugs. Persons with cirrhosis should be prioritized for treatment because they are at increased risk of HCC and death due to liver failure.[27]

VA: All patients with CHC who did not have medical contraindications are potential candidates for treatment. Patients with advanced liver disease are likely to derive the greatest benefit from treatment.[12] The urgency of treatment should be based on the risk of developing decompensated cirrhosis or dying from liver or liver-related disease, and prolonging graft survival and in transplant recipients. In particular, patients with cirrhosis or advanced fibrosis, selected patients with HCC awaiting liver transplant, post-transplant recipients, patients with serious extra-hepatic manifestations of HCV, and women of childbearing potential who desire to conceive a child in the next 12 months should be considered for antiviral treatment in the near term. Patients with mild liver disease (METAVIR F0-2) have less urgency for treatment in the short-term, but should be informed of current treatments and the potential to cure HCV. Patients with mild liver disease (METAVIR F0-2) and no extra-hepatic manifestations can be treated in the near term if the patient desires treatment and is otherwise a candidate for HCV treatment.

Who Should Treat:
With all-oral shorter course regimens, treatment may be increasingly available outside of specialty clinics. Guidelines recommend that therapy should be managed by medical specialists with experience in the treatment of CHC infection and the physician prescribing should have knowledge of monitoring and ensuring patient adherence with therapy. The VA guideline states treatment can be provided by non-specialists trained in the management of CHC and who have access to specialists for support (Expert Opinion).[12] However, patients with decompensated cirrhosis should be seen by a specialist with experience in the management of advanced disease.

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Alcohol and Drug Abuse Recommendations:
AASLD/IDSA: Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection.[8] Persons identified as abusing alcohol and having alcohol dependence require treatment and consideration for referral to an addiction specialist. For individuals with acute HCV infection who have a history of recent injection drug use, referral to an addiction medicine specialist is recommended when appropriate.

WHO: An alcohol intake assessment is recommended for all persons with HCV infection followed by the offer of a behavioral alcohol reduction intervention for persons with moderate-to-high alcohol intake. Persons who inject drugs should be assessed for antiviral treatment. Persons who inject drugs are at increased risk of HCV-related disease and transmission, as well as for all-cause morbidity and mortality, and therefore require specialized care and should be considered as a priority for HCV treatment.[27]

VA: All patients should be evaluated for current alcohol and other substance use, with validated screening instruments such as AUDIT-C (www.hepatitis.va.gov/provider/tools/audit-c.asp).[12] Patients with a history of substance or alcohol use disorders should be considered for HCV antiviral therapy on a case-by-case basis. There are no published data supporting a minimum length of abstinence as an inclusion criterion for HCV antiviral treatment, while multiple studies show successful treatment of patients who have short durations of abstinence or infrequent use of alcohol. Thus, automatic disqualification of patients as treatment candidates based on length of abstinence is unwarranted and strongly discouraged. The presence of current heavy alcohol use (>14 drinks per week for men or >7 drinks per week for women), binge alcohol use (>4 drinks per occasion at least once a month), or active injection drug use warrants referral to an addiction specialist before treatment initiation. Patients with active substance or alcohol use disorders may be considered for therapy on a case-by-case basis, and care should be coordinated with substance use treatment specialists.[12]

Treatment Discontinuation Guidelines:
The VA guidelines are the only guidelines that recommend discontinuing HCV treatment based on lack of virologic response after 6 weeks of initial treatment. These treatment discontinuation recommendations based on HCV RNA levels are based only on expert opinion.[12]

Testing for Liver Cirrhosis:
AASLD/IDSA: Considers the use of biopsy, imaging, and/or noninvasive markers appropriate to evaluate advanced fibrosis in HCV patients planning on treatment (Class I, Level A).[8] They also recommend that a biopsy should be considered for any patient with discordant results between 2 modalities that would affect clinical decision making. If direct biomarkers or elastography are not available, the AST-to-platelet ratio index (APRI) or FIB-4 index score can help, although neither test is sensitive enough to rule out significant fibrosis.

WHO: In resource-limited settings, it is suggested that the APRI or FIB-4 test be used for the assessment of hepatic fibrosis rather than other noninvasive tests that require more resources such as elastography or FibroTest (Conditional recommendation, low quality of evidence).[27] FibroScan®, which is more accurate than APRI and FIB-4, may be preferable in settings where the equipment is available and the cost of the test is not a barrier to testing.[27]

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Author: Megan Herink, Pharm.D Date: September 2016

VA: Includes clinical findings (low platelet count), abdominal imaging for features of portal hypertension, liver fibrosis imaging (FibroScan and Acoustic Radiation force impulse [APRI]), serum markers of fibrosis (APRI, FIB-4, FibroSure, FibroTest), and liver biopsy as options. Liver biopsy should be reserved for situations in which the risks and limitations of the procedure are outweighed by the benefits of obtaining information via this technique.[12]

Decompensated Cirrhosis:
All guidelines recommend patients with decompensated cirrhosis be considered for treatment on a case by case basis and should involve an experienced specialist who is able to manage complications.

Recommendations for performing pre-treatment resistant testing:
The VA guidelines recommend that NS5A resistance-associated variants (RAV) testing should be performed at baseline prior to initial treatment for GT1a-infected patients who are being treated with EBR/GZR and for GT3 patients who are being treated with DCV.[12] Patients who fail DAA treatment usually have RAVs to one or more classes of DAAs and should have testing done for each of the drug classes before being considered for re-treatment.

Recommended Treatment Options:
Treatment options based on genotype and treatment history are included in the following table:

Table 2: Guideline Recommended Treatment Options

GT	Treatment History	Cirrhosis Status	Veterans Affairs Guidelines[12]	AASLD/IDSA Guidelines[8]	WHO Guidelines[27]
1	***Naïve or Experienced (PEG-INF/RBV only)***	***Non-cirrhotic***	EBR/GZR x 12 weeks ** LDV/SOF x 12 weeks	EBR/GZR x 12 weeks** LDV/SOF x 8-12 weeks OMB/PTV-R + DAS +/- RBV x 12 weeks SOF/VEL x 12 weeks DCV/SOF x 12 weeks	DCV/SOF x 12 weeks LDV/SOF x 8-12 weeks
1		***Cirrhotic***	LDV/SOF + RBV x 8-12 weeks	EBR/GZR x 12 weeks** LDV/SOF x 12 weeks SOF/VEL x 12 weeks	DCV/SOF +/- RBV x 12 weeks LDV/SOF +/- RBV x 12 weeks
1		***Decompensated Cirrhosis***	LDV/SOF + RBV x 12 weeks	LDV/SOF + RBV x 12 week SOF/VEL + RBV x 12 week DCV/SOF + RBV X 12 week	DCV/SOF x 12 weeks
1	***Experienced (prior sofosbuvir)***	***Non-cirrhotic or cirrhosis***	EBR/GZR x 12 weeks +/- RBV	LDV/SOF + RBV X 12 weeks – 24 weeks	N/A
1	***Experienced (Prior NS3A/4A inhibitor)***	***Non-cirrhotic (or cirrhotic CTP A)***	EBR/GZR + RBV x 12 weeks	LDV/SOF X 12 weeks SOF/VEL x 12 weeks DCV/SOF X 12 weeks EBR/GZR + RBV X 12 weeks	N/A
1	***Experienced (Prior NS5A-containing regimen or SMV)***		Test for RAPs to NS5A prior to re-treatment. Consult with an expert based on results.	Deferral of treatment, pending more data. Testing for RAVs should be done.	N/A
2	***Naïve***	***Non-cirrhotic***	SOF + RBV x 12 weeks	SOF/VEL x 12 weeks	SOF + RBV X 12 weeks
2		***Cirrhotic***	SOF + RBV x 16 weeks	SOF/VEL x 12 weeks	SOF + RBV x 16 weeks

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2		***Decompensated***	SOF + RBV x 16 weeks	SOF/VEL + RBV X 12 weeks DCV/SOF + RBV X 12 weeks	SOF + RBV x 16 weeks
2	***Experienced (Prior PEG-IFN/RBV)***	***Non-cirrhotic or Cirrhotic***	SOF + RBV x 16 weeks	SOF/VEL x 12 weeks	N/A
2	***Experienced (SOF + RBV)***	***Non-cirrhotic or Cirrhotic***	The optimal DAA-based therapy for this patient population is not known. Consult with an expert	DCV/SOF x 24 weeks SOF/VEL + RBV X 12 weeks	N/A
3	***Naïve***	***Non-cirrhotic***	LDV/SOF + RBV x 12 weeks*	DCV/SOF x 12 weeks SOF/VEL X 12 weeks	DCV/SOF X 12 weeks
3		***Cirrhotic***	DCV/SOF + RBV x 12 weeks	SOF/VEL + RBV X 12 weeks DCV/SOF + RBV X 12 weeks	DCV/SOF + RBV x 12 weeks
3		***Decompensated Cirrhosis***	DCV/SOF + RBV x 12-24 weeks	SOF/VEL + RBV X 12 weeks DCV/SOF + RBV X 12 weeks	N/A
3	***Experienced (Prior PEG-IFN/RBV only)***	***Non-cirrhotic***	LDV/SOF + RBV X 12 weeks*	DCV/SOF X 12 weeks SOF/VEL X 12 weeks	N/A
3		***Cirrhotic***	DCV/SOF + RBV X 12 weeks- 24 weeks	SOF/VEL x 12 weeks DCV/SOF x 24 weeks	DCV/SOF + RBV x 24 weeks
3	***Experienced (SOF + RBV)***	***Non-cirrhotic or Cirrhotic***	The optimal DAA-based therapy for this patient population is based on expert opinion. Recommend NS5A resistance testing.	DCV/SOF + RBV X 24 weeks SOF/VEL + RBV X 12 weeks	N/A
4	***Naïve***	***Non-cirrhotic***	EBV/GZR x 12 weeks LDV/SOF x 12 weeks	OMB/PTV-R + RBV x 12 weeks SOF/VEL x 12 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks	DCV/SOF x 12 weeks LDV/SOF x 12 weeks
4		***Cirrhotic***	EBV/GZR x 12 weeks LDV/SOF x 12 weeks	OMB/PTV-R + RBV x 12 weeks SOF/VEL x 12 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks	DCV/SOF x 24 weeks DCV/SOF + RBV x 12 weeks LDV/SOF x 24 weeks LDV/SOF + RBV x 12 weeks
4		***Decompensated Cirrhosis***	N/A	LDV/SOF + RBV x 12 weeks SOF/VEL + RBV x 12 week DCV/SOF + RBV X 12 week	N/A
4	***Experienced (Prior PEG-IFN/RBV only)***	***Non-cirrhotic or Cirrhotic***	OMB/PTV-R + RBV x 12 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks	OMB/PTV-R + RBV x 12 weeks SOF/VEL x 12 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks	N/A
5/6	***Naïve or Experienced (Prior PEG-IFN/RBV only)***	***Non-cirrhotic or Cirrhotic***	N/A	SOF/VEL x 12 weeks LDV/SOF x 12 weeks	LDV/SOF X 12 weeks

**No baseline NS5A RAVs Abbreviations: DCV = dacltasvir; EBV/GZR = elbasvir/grazoprevir; LDV/SOF = ledipasvir/sofosbuvir; OMB/PTV-R + DAS = ombitasvir, paritaprevir and ritonavir with dasabuvir; PEG-IFN = pegylated interferon; VEL/SOF = velpatasvir/sofosbuvir; RBV = ribavirin; SOF = sofosbuvir

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Date: September 2016

New Indications:
In February 2016, DCV + SOF was granted FDA approval for the treatment of GT1, treatment of patients co-infected HIV, and those with decompensated cirrhosis (GT1 or 3).[17,28] The expanded approval was based on the ALLY-1[29] and ALLY-2[30] trials.

In February 2016, LDV/SOF also received approval for use in patients with GT1 with decompensated cirrhosis, including those who have undergone liver transplantation.[19] LDV/SOF is now FDA approved for GT1, 4, 5 and 6, HIV coinfection, GT1 and GT4 liver transplant recipients, and GT1 patients with decompensated cirrhosis. Approval was supported by data from the SOLAR-1[31] and SOLAR-2[32] trials.

In July 2016 the FDA approved Viekira XR® as a single tablet version of Viekira Pak® for GT1 infection.[22] The new formulation includes ombitasvir, paritaprevir, and dasabuvir, along with ritonavir as a booster, which are the same ingredients of Viekira Pak®. It was approved based on 6 clinical trials that demonstrated safety and efficacy of the immediate-release formulation. The formulation is contraindicated in patients with moderate to severe hepatic impairment.

Elbasvir/Grazoprevir (EBR/GZR) NEW DRUG EVALUATION**:**
See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
The FDA approved EBR/GZR 100 mg/50 mg based on data from 2 phase 2, 1 phase 2/3, and 3 pivotal phase 3 trials in patients who were treatment naïve, treatment experienced, HIV co-infected, and those with CKD.[11] Additional phase 2 trials also supported efficacy analyses; however they were not included in the FDA's main analysis for approval. Trials included GT1, 4 and 6 patients, but the majority were GT1. SVR12 was the primary endpoint in all trials and was defined as HCV RNA less than lower limit of quantification 12 weeks after the cessation of treatment. Patients with and without cirrhosis were included in all of the trials. Two phase 3 trials were placebo controlled (C-EDGE TN and C-SURVER) to evaluate safety outcomes only and all of the trials were designed to compare SVR12 to historical rates from previously conducted trials of standard of care regimens to define efficacy. The FDA noted that comparisons to historical rates are considered appropriate.[11] In the trials, hepatic fibrosis was staged by biopsy or noninvasive assessment. Cirrhosis was defined as a liver biopsy showing METAVIR stage F4 at any time prior to entry; transient elastography (Fibroscan) performed within 12 months of entry yielding a result >12.5 kPa; or biochemical markers of liver fibrosis (FibroText or FibroSure) yielding a score of >0.75 along with an aspartate aminotransferase-platelet ratio index (APRI) > 2. The overall SVR12 rates in GT1 infected patients are included in Table 3:

Table 3: SVR rates for GT Treatment Naïve Patients[11]

	C-EDGE TN	C-EDGE COINFECTION	C-SURVER (CKD)
GT1 Overall	95% (273/288)	95% (179/189)	94% (115/122)
GT1a	92% (144/157)	94% (136/144)	97% (61/63
GT1b	98% (129/131)	96% (43/45)	92% (54/59)
GT1 No Cirrhosis	94% (207/220)	94$ (148/158)	95% (109/115)
GT1 Cirrhosis	97% (66/68)	100% (31/31)	86% (6/7)

SVR12 results overall ranged from 92-100% depending on the regimen, GT, and prior treatment history. Baseline NS5A resistance testing is strongly recommended for all GT 1a infected patients to decrease the risk of resistance. Overall, 96-97% of GT1a infected subjects with baseline NS5A polymorphisms who failed treatment developed additional resistant mutations, and 58% developed resistance to both NS5A inhibitors and NS3/4A PIs, limiting future treatment options.

C-SALVAGE was an open-label, single-arm phase 2 clinical trial designed to evaluate EBR/GZR + RBV in patients with HCV GT 1 who had previously failed triple therapy with PR plus an earlier-generation PI (boceprevir, telaprevir, or simeprevir).[33] All subjects (n=79) had been unsuccessfully treated with an NS3/4A PI in the past and 66 (84%) of them had a history of virologic failure. The majority of subjects had received either boceprevir or telaprevir. SVR12 rates were 96.2% (95% CI 89.3-99.2%). Relapses occurred in 3 (3.8%) subjects, all of whom had baseline NS3 resistance-associated variants (RAVs). Overall, there were too few virologic failures in this trial to determine the impact of baseline NS5A polymorphism. In addition, it is too small to support an indication for subjects with baseline NS3 resistance substitutions.

C-EDGE TN was a phase 3 trial multinational evaluating EBR/GZR for 12 weeks (immediate treatment group [ITG) without RBV vs. placebo (deferred treatment group [DTG]) in treatment-naïve (TN) monoinfected patients with and without cirrhosis and with GT1, GT4, or GT6 infection.[34] The DGT received GZR/EBR for 12 weeks following unblinding at week 4. Approximately half of the clinical sites (49%) were in the United States and the majority of patients had HCV GT 1. Overall, SVR12 rates were 95% in the immediate treatment group. SVR12 rates were 92% in patients with GT1a, 99% in those with GT1b, 100% (18/18) with GT4, and 80% (8/10) in those with GT6. SVR12 was achieved in 97% of cirrhotic patients (68/70) and 94% of noncirrhotic patients (231/246). Overall, the majority of patients had less severe disease (66% F0-F2) partly due to extensive exclusion criteria. However, 92 (22%) of patients did have cirrhosis. Subgroup analysis did not identify meaningful effects of age, sex, race, ethnicity, or IL28B genotype on treatment outcome. Virologic failure occurred in 13 (4%) patients, including 1 breakthrough and 12 relapses. NS3 resistance variants were detected in 57% of patients with GT1a and 19% of those with GT1b; however, there did not seem to be an association between baseline NS4 resistance and virologic failure. NS5A resistance variants were identified in 19 (12%) of GT1a infected patients and SVR12 was only achieved in 11 of 19 (58%) of these patients compared with 99% of patients without baseline NS5A resistance variants, suggesting an association between virologic failure (> 5 fold loss of EBR susceptibility) and baseline NS5A resistance. SVR12 rates were 91% in those with cirrhosis.

C-EDGE COINFECTION was a phase 3 open-label trial that assessed EBR/GZR for 12 weeks in TN cirrhotic and non-cirrhotic subjects with HCV GT 1, 4, or 6 and HIV coinfection.[35] This was a non-randomized, single arm trial that compared SVR12 to the historical rate of 70%, derived from the phase 2 trial of sofosbuvir in HCV GT1 subjects with HIV (Photon-1). However, the SVR rate among TN patients with GT 1 was 76% in the Photon-1 trial.[36] The majority of patients were male, white with F0-F2 disease. Sixteen percent of subjects had cirrhosis and 11% with advanced fibrosis (F3). Overall, 207/218 (95%) achieved SVR12. Seven (3.2%) subjects experienced virologic failure, all due to relapse and all of whom were non-cirrhotic. All 35 subjects with cirrhosis achieved SVR12 and SVR rates in GT 1a and 1b were similar, unlike the C-EDGE TN trial. Baseline NS4 resistance-associated variants (RAV) were detected in 41% (74) of subjects with GT1, but did not seem to effect rates of SVR12. In patients with GT1, 13/15 patients with baseline NS5A RAV achieved SVR12 (87%) compared to 98% without.

C-SURFER is a randomized, phase 2/3 placebo-controlled trial in stage 4 or 5 CKD patients with GT 1 HCV, with or without prior treatment experience (majority were TN) and with or without cirrhosis.[37] This is the first trial of a DAA in patients with advanced CDK (76.2% on dialysis). The most common etiologies of renal disease were hypertension (39.1%) and type 2 diabetes (19.6%). Similar to other trials, those with decompensated liver disease were excluded as well as subjects receiving peritoneal dialysis or new or worsening cardiovascular or cerebrovascular disease or uncontrolled diabetes (HgA1C > 8.5%). Subjects were randomized to ITG or DGT (unblended after receiving placebo during the initial 4 weeks). The placebo comparison was for safety and efficacy data remains observational. SVR rates were compared to a historical rate of 45% based on studies of HCV subjects with stage 3-5 CKD treated with interferon monotherapy and non-CKD subjects treated with PR. The exclusion criteria were much more restrictive than the other GZR/EBR trials (see evidence table) and limit the generalizability of these results to real world patients with CKD. There was a larger representative of black patients (45%) and fewer cirrhotics (6%) compared to other trials. Overall 115 subjects achieved SVR12 (94%). One subject (0.9%) failed due to relapse. The remaining 6 virologic failures were due to missing data for reasons unrelated to treatment. Two additional relapses were found after follow-up through week 24.[11] All 3 patients who relapsed had at least one of the key RAVs at baseline.

Additional Trials:

A phase III, open label recently published RCT compared GZR/EBR to SOF plus pegylated interferon/ribavirin in patients with HCV GT 1 or 4 infection.[38] Since pegylated interferon/ribavirin is no longer considered standard of care for HCV GT 1 or 4, the clinical relevance of this trial is low. Patients were either treatment naïve or failed treatment with pegylated interferon/ribavirin and both cirrhotic and noncirrhotic patients were included. Those with HIV, HBV, decompensated liver disease or HCC were excluded. Overall SVR12 rates were 99.2% (129/129; 95% CI 95.6-99.9) and 90.5% (114/126; 95% CI 84-95) in the EBR/GZR and SOF groups, respectively establishing both noninferiority and superiority of EBR/GZR. As expected, there were significantly higher rates of adverse events reported in those receiving pegylated interferon/ribavirin (92.9%) compared to EBR/GZR (51.9%).

EBR/GZR was studied in a double-blind, placebo-controlled RCT in 301 treatment naïve patients with CHC GT 1, 4, or 6 who were receiving opioid agonist therapy (methadone, buprenorphine, or buprenorphine-naloxone) in persons who inject drugs. Patients actively using drugs of potential abuse while receiving opioid agonist therapy were excluded from the trial. Patients were randomly assigned to the ITG group (blinded EBR/GZR for 12 weeks; n=201) or the DTG (placebo for 12 weeks followed by 12 weeks of open label treatment with EBR/GZR; n=100). To ensure adherence, study medication was dispensed every 2 weeks and patients were asked to complete an electronic study medication diary. In clinical practice, replicating this kind of follow-up is difficult in this patient population and therefore SVR results and adherence may be lower than results seen in clinical trials. The SVR12 rate was 91.5% (184/201; 95% CI 86.8 to 95) in the ITG and

89.5% (95% CI 81.5 to 94.8) in the DTG. Five patients in the ITG had probable reinfection and 1 patient in the DTG. Through follow-up week 24, the reinfection rate was 4.6 reinfections (95% CI 1.7 to 10) per 100 person years. This increased risk of reinfection is a considerable concern in high-risk populations. Over 50% of patients had positive results on a urine drug screen with no meaningful differences in SVR between those that did not.

Unpublished Trials:

C-EDGE TE was a phase 3 randomized, parallel-group, open-label clinical trial.[11,39] It remains unpublished and cannot be assessed for quality. The trial compared GZR/EBR +/- RBV for 12 weeks to EBR/GZR +/- RBV for 16 weeks (n=420). The patient population consisted of TE cirrhotic and non-cirrhotic subjects who failed prior treatment with PR (43% null responders, 21% partial responders, 35% relapsers). Discontinuations due to adverse events were higher in subjects on RBV and on extended therapy for 16 weeks (3.8%). There was an imbalance across groups with respect to HCV GT and race. There were higher rates of black subjects in the 12 week treatment groups (22.5%) compared to 16 week treatment groups (11.4%) and a higher number of Asian subjects in the 16 week group. Asian race is associated with higher GZR exposures, which may impact safety. Similar to previous studies, there were very few subjects with either GT4 or GT6. SVR12 results and number of subjects experiencing virologic failure are included in Table 4:

Table 4: SVR12 rates of EBR/GZR +/- RBV for 12 to 16 weeks

Treatment Duration	12 weeks		16 weeks	
	EBR/GZR (n=105)	EBR/GZR + RBV (104)	EBR/GZR (n=105)	EBR/GZR + RBV (N=106)
SVR Achieved (%) 95% CI	97 (92.4%) 85.5-96.7	98 (94.2%) 87.9-97.9	97 (92.4%) 85.5-96.7	103 (97.2%) 92-99.4
Virologic failure	6 (5.6%)	6 (5.8%)	7 (6.7%)	0 (0%)
SVR Achieved (%) • GT 1a • GT 1b • GT 4	 90.2% (79.8-96.3) 100% (89.7-100) 77.8% (40-97.2)	 93.3% (83.8-98.2) 96.6% (82.2-99.9) 93.3% (68.1-99.8)	 93.8% (82.8-98.7) 95.8% (85.8-99.5) 60.0% (14.7-94.7)	 94.8% (85.6-98.9) 100% (90.3-100) 100% (63.1-100)
Abbreviations: EBR = elbasvir; GZR = grazoprevir; RBV = ribavirin; SVR = sustained virologic response				

All of the virologic failures in the 12 week groups were due to relapse; the majority with GT 1a. Four of the 7 failures in the 16 week treatment group without RBV were due to relapse. The longer treatment duration of 16 weeks in addition to RBV appeared to improve efficacy and minimize the risk of relapse and overcome the effect of baseline NS5A polymorphisms as SVR 12 rate remained 100% even in those with resistance variants. Similar to the previous trial, the presence of baseline NS5A polymorphisms appears to explain the majority of virologic failures. There was a higher SVR12 rate in the 16 week + RBV arm for GT4 subjects. However, the number of subjects was relatively small overall (37) and imbalanced between groups.

C-SCAPE was a phase 2 open-label clinical trial that assessed the efficacy and safety of EBR/GZR +/- RBV for 12 weeks in TN non-cirrhotic subjects with HCV GT 4, 5, and 6 infection (n=19).[11,40] This was a small study with one discontinuation due to an adverse event and one due to lack of efficacy. The majority of subjects had HCV GT 4 (n=38) and SVR rates were 100% and 90% with and without RBV, respectively. It is hard to determine if the addition of RBV was beneficial in this population as groups were not balanced at baseline. There were more patients with severe fibrosis (F3) in the RBV group compared to the majority of subjects not receiving RBV with F0-F2 fibrosis. This trial helped support efficacy in GT 4 infected subjects (52.6%), but overall the trial enrolled very few numbers. Virologic failure occurred in ¾ of HCV GT 5-infected subjects and as a result, subsequent studies did not enroll GT 5 subjects.

Clinical Safety:
EBR/GZR was generally well tolerated in short term studies with the most significant concern being increased transaminase elevations occurring at or after 8 weeks of treatment initiation, occurring in less than 1% of patients with the FDA approved dose. Phase 2 trials demonstrated higher rates of increases with higher doses that were studies. GZR exposure is increased in decompensated cirrhosis and therefore EBR/GZR is contraindicated in Child-Pugh B and C cirrhosis due to an increased risk of liver toxicity.

The most common reported adverse events (>5%) in clinical trials with EBR/GZR were fatigue, headache, and nausea (Table). These rates were similar in the trial including subjects on hemodialysis. In patients receiving EBR/GZR + RBV for 16 weeks, the most common adverse events were anemia (8%) and headache (6%). During clinical trials with EBR/GZR ± RBV, 1% of patients experienced ALT elevations of >5 times the ULN, generally at or after treatment week 8. ALT elevations were typically asymptomatic and most resolved with ongoing or completion of therapy. Higher rates of late ALT elevations occurred in the following subgroups: females (2% [10/608]), Asian race (2% [4/164]), and age 65 years or older (2% [3/177]).

Table 5. Adverse Reactions Reported In ≥5% of Treatment-Naïve Subjects with HCV

Adverse Reaction	EBR/GZR (n=316)	Placebo (n=105)
Fatigue	11%	10%
Headache	10%	9%
Nausea	9%	8%

GZR is a substrate of OATP1B1/3 transporters and drugs that inhibit these transporters may result in a significant increase in the plasma concentrations of GZR. In addition, EBR and GZR are substrates of CYP3A and P-gp.

Table 6: Pharmacology and Pharmacokinetic Properties: [41]

Parameter	
Mechanism of Action	GZR is an NS3/4A Protease Inhibitor, and EBR is an NS5A replication inhibitor. GZR/EBR is a fixed dose combination of direct-acting antiviral agents against the hepatitis C virus.
Distribution and Protein Binding	Extensively bound to plasma proteins (EBR > 99.9%, GZR > 98.8%), both bind to albumin and alpha1-acid glycoprotein. VD 680 L (EBR) and 1250 L (GZR).
Metabolism	Partially eliminated by oxidative metabolism, primarily by CYP3A.
Half-Life	24 hours (EBR) and 31 hours (GZR)
Elimination	Primary route of elimination is through feces

Abbreviations: IL-5 = interleukin 5; kg = kilograms; L = liters; Vd = volume of distribution

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Hepatocellular Carcinoma
2) Mortality
3) Liver Transplant
4) Decompensated Liver Disease
5) Discontinuation Rates Due to Adverse Events
6) Severe Adverse Events

Primary Study Endpoints:
1) Sustained Virologic Response at 12 after the end of treatment (SVR12)

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Table 7. Clinical Efficacy Evidence Table (EBR/EZR)

Ref./ Study Design	Drug Regimen/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARI/ NNH	Quality Rating Risk of Bias/Applicability
1. Buti, et al.[33,42] Open-label, single arm C-SALVAGE Phase 2	1. EBR 50 mg/GZR 100 mg daily + weight based RBV twice daily 12 weeks	Demographics: Treatment-experienced Mean age 54.4 42% women 43% cirrhotics 38% GT 1a Key Inclusion Criteria: -HCV GT1, prior regimen containing an approved DAA + PR, HCV RNA > 10,000 IU/ml Key Exclusion Criteria: -Decompensated liver disease, hepatocellular carcinoma, HIV or hepatitis B co-infection, uncontrolled DM (HgA1C > 10%), elevated PT, CrCl < 50ml/min, Hg < 95 g/L, thrombocytopenia, ALT > 10 x ULN, hypoalbuminemia, clinically-relevant drug or alcohol abuse within 12 months	FAS 1. 79 Attrition 1. 0%	Primary Endpoint: SVR12 76 (96.2%; 95% CI 89.3-99.2) *Patients with prior virologic failure:* 63 (95.5%; 95% CI 87.3-00.1)	N/A	Safety Outcomes D/C due to AE: 1 (1.2%) Serious AE: 5 (6.3%)	NA for all	**Risk of Bias** Selection bias: (high) non-randomized Performance bias: (high) open-label. Detection bias: (unclear) open-label; objective outcome Attrition bias: (low) overall attrition low and similar across groups based on mITT analysis; missing outcome data were imputed as failures unless flanked by visits where HCV RNA levels were both < 15 IU/ml. Reporting bias: (unclear) funded by Merck. Merck involved in trial design, study execution, data collection, statistical analyses, and drafting of the report. **Applicability**: Patient: extensive exclusion criteria may limit applicability of study results to patients with more severe disease. Intervention: Optimal treatment duration unknown other phase 3 trial in TE patients explored 16 weeks with or without ribavirin. Comparator: This study lacked an active comparator control. . Outcomes: Surrogate outcome of SVR 12 used to evaluate efficacy. Setting: 77.2% (61) of the sites were not in the U.S.

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2. Zeuzem, et al.[34] RCT, PC, PG C-EDGE	1. EBR/GZR daily (ITG) 2. Placebo* followed by deferred EBR/GZR x 12 weeks (DTG) 12 weeks *Placebo was used for safety comparison only	Demographics: Treatment-naïve Mean age 52.6 46% women 37% nonwhite 91% GT1 22% Cirrhosis 66% F0-F2 Key Inclusion Criteria: -age ≥18 y, HCV RNA levels > 10^4 IU/ml Key Exclusion Criteria: -Decompensated liver disease, hepatocellular carcinoma, HIV or hepatitis B co-infection, uncontrolled DM (HgA1C > 10%), elevated PT, CrCl < 50ml/min, Hg < 95 g/L, thrombocytopenia, ALT > 10 x ULN, hypoalbuminemia	mITT 1. 316 2. 105 Attrition 1. 0% 2. 0%	Primary Endpoint: SVR12 1. 299 (95%) P<0.0001 -GT 1a: 144/157 (92%) -GT1b: 129/131 (99%) -GT4: 18/18 (100%) -GT6: 68/70 (97%) *Cirrhosis:* Yes: 68/70 (97%) No: 231/246 (93.9%)	NA for all	Safety Outcomes D/C due to AE: 1. 1% 2. 1% Serious AE: 1. 9 (2.8%) 2. 3 (2.9%)	NS NS	**Risk of Bias** Selection bias: (low) randomized 3:1 to immediate (tx) or deferred (placebo) therapy through a central interactive voice-response system and a computer-generated random allocation schedule. Baseline characteristics similar between groups, except almost twice as many elderly subjects in the DTG Performance bias: (low) Matching placebo used. Patients, clinical site, and sponsor personnel were blinded for first 4 weeks. 4 weeks after treatment, treatment allocation was unblended and patients in placebo group received open-label treatment. Detection bias: (unclear): Unblinded medical team monitored virologic failures and serious adverse events. However, primary outcome objective so less likely to be effected by unblinding. Attrition bias: (low) overall attrition low and similar across groups based on mITT analysis; missing outcome data were imputed as failures uless the values immediately before and after the missing result were both successes, in which case the absent value was imputed as a success. Appropriate statistical tests used. Reporting bias: (unclear) funded by Merck. Merck involved in trial design, study execution, data collection, statistical analyses, and drafting of the report. **Applicability**: Patient: extensive exclusion criteria may limit applicability of study results to patients with more severe disease. Very little representation of non-GT1 patients. Intervention: No concerns Comparator: This study lacked an active comparator control. Historical comparator of SVR rate of 73% was used but not applicable today as peginterferon no longer preferred treatement option. Outcomes: Surrogate outcome of SVR 12 used to evaluate efficacy. Setting: 60 centers in Australia, Czech Republic, France, Germany, Israel, Puerto Rico, South Korea, Sweden, Taiwan, and the U.S. (24)

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3. Rockstroh et al.[35] Open-label, single arm, MC Phase 3 C-EDGE CO-INFECTION	EBR/GZR Daily 12 weeks	Baseline Demographics: Mean age: 49 y Female: 16% White 77%, Black 17% HCV GT 1a 66%, GT 1b 20%, GT 4 13%, GT 6 0.5% F0-F2 73% Key Inclusion Criteria: -age ≥18 y, HCV RNA levels > 10,000 IU/ml, HIV coinfection, either naïve to ART or on stable ART with tenofovir or abacavir, and either emtricitabine or lamibudine plus raltegravir, dolutegravir, or rilpivirine Key Exclusion Criteria: -decompensated liver disease, Child-Pugh class B or C, or with a Child-Turcotte-Pugh score of >6 points, HBV, HCC, h/o malignant disease, clinically-relevant drug or alcohol abuse within 12 months, CrCl <50 ml/min, Hg < 9.5 g/dl, platelets < 50 x 10^3 uL, albumin < 3.0 g/dl, INR > 1.7, HbA1c > 10%, ALT/AST >10x ULN, use of CYP3A/P-gp inducers, OATB inhibitors, statins	FAS 218 Attrition 0	Primary Endpoint: SVR12: 207/218 (95%; 95% CI 91.2-97.5%) P<0.0001* -GT 1a: 136/144 (94.4%) -GT1b: 42/44 (95.5%) -GT4: 27/28 (96.4%) *Cirrhosis:* Yes: 35/35 (100%) No: 23(172/183) (94%) *compared to historical rate of 73% Secondary Endpoints: SVR24	NA for all	Safety Outcomes D/C due to AE: 0 Serious AE: 6 (0.3%)	NA for all	**Risk of Bias** Selection bias: (high) non-randomized Performance bias: (high) open-label Detection bias: (low) statisticians and GSK personnel blinded to data. Power assumptions appropriate. Appropriate statistical tests utilized. Attrition bias: (low) overall attrition low and similar across groups based on mITT analysis; imputation of missing data unclear but few dropped out early. Appropriate statistical tests used. Reporting bias: (unclear) funded by GSK; data analyzed by GSK. Pre-specified primary outcome reported as relative risk reduction. **Applicability**: Patient: Over 70% of patients with F0-F2; results have limited applicability to patients with more severe disease. Intervention: Unclear if addition of RBV or extended duration would benefit HIV coinfected patients. Comparator: No comparator group. Outcomes: Surrogate outcome of SVR 12 used to evaluate efficacy. Setting: 37 centers across Austrlia (2), Canada (2), Denmark (3), France (3), Germany (3), Israel (3), Spain (3), United Kingdom (2) and the U.S. (18).

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4. Roth et al.[37] RCT, PC Phase 2/c C-SURVER	1. EBR/GZR daily (ITG) 2. Placebo* followed by deferred EBR/GZR x 12 weeks (DTG) 12 weeks *Placebo was used for safety comparison only	Demographics: Treatment-naïve Mean age 56 26.8% women 53.7% nonwhite 51.9% GT1a 6% Cirrhosis 69.4% F0-F2 76.2% dialysis Key Inclusion Criteria: -age ≥18 y, HCV RNA levels > 10^4 IU/ml, liver disease staging with either liver biopsy, fibroscan, or FibroSure AND APRI, CKD Key Exclusion Criteria: -Decompensated liver disease, peritoneal dialysis, hepatocellular carcinoma, HIV or hepatitis B co-infection, uncontrolled DM (HgA1C > 8.5%), significant CV disorder, severe active peripheral vascular disease, recent stroke, elevated PT, Hg < 95 g/L, thrombocytopenia, ALT > 10 x ULN, hypoalbuminemia, taking a prohibited medication**, substance abuse to any of the following: alcohol, IV drugs, inhalational (not including marijuana), psychotropics, narcotics, cocaine, OTC or prescription drugs within 1 year	mITT 1. 122 2. 113 Attrition 0 (0%)	Primary Endpoint: SVR12 (ITG only) 1. 115 (94.3%; 95% CI 88.5-97.7) P<0.001* *Compared to historical rate of 45%	NA	Safety Outcomes D/C due to AE: 1. 0 (0%) 2. 5 (4.4%) Serious AE: 1. 16 (14%) 2. 19 (17%)	NA for all	**Risk of Bias** : Selection bias: (low) randomized 1:1 to immediate (tx) or deferred (placebo) therapy through a central interactive voice-response system and a computer-generated random allocation schedule. Baseline characteristics similar between groups. Performance bias: (high) Matching placebo used. Patients, clinical site, and sponsor personnel were blinded for first 4 weeks. 4 weeks after treatment, treatment allocation was unblended and patients in placebo group received open-label treatment. Detection bias: (low) Unblinded medical team monitored virologic failures and serious adverse events. However, primary outcome objective so less likely to be effected by unblinding. Attrition bias: (low) overall attrition low. Reporting bias: (unclear) funded by Merck. Merck involved in trial design, study execution, data collection, statistical analyses, and drafting of the report. **Applicability**: Patient: extensive exclusion criteria may limit applicability of study results to patients with more severe disease as well as patients with severe DM or CVD. Small number of TE and cirrhotic subjects. Intervention: The lack of RBV does not seem to compromise efficacy in this population. Unclear if extending to 16 weeks in those with RAVs would be beneficial. Limited treatment options for those with CKD. Comparator: This study lacked an active comparator control. Historical comparator of SVR rate of 45% was used but not applicable today as peginterferon no longer preferred treatement option. Outcomes: Surrogate outcome of SVR 12 used to evaluate efficacy. Setting: Multinational trial in 79 centers in 12 countries: U.S. (48 sites), Canada, Israel, France, Lithuania, Spain, Australia, Estonia, Korea, Netherlands, Sweden, Argentina

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Abbreviations: AE = adverse events; ALT = alanine aminotransferase; APRI = AST to platelet ratio index; ARI = absolute risk increase; ARR = absolute risk reduction; CI = confidence interval; CKD = chronic kidney disease; CrCl = creatinine clearance; CV = cardiovascular; DB = double-blind; DAA = direct acting antiviral; D/C = discontinue; DM = diabetes mellitus; DTG = deferred treatment group; EBR = elbasvir; EF = ejection fraction; FAS = full analysis set; FDA = U.S. Food and Drug Administration; GT = genotype; GZR = grazoprevir; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; h/o = history of; HG = hemoglobin; ICS = inhaled corticosteroid; ITG = immediate treatment group; ITT = intention to treat; IV = intravenous; MC = multi-centered; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; OR = odds ratio; PC = placebo-controlled; PBO = placebo;; PG = parallel group; PP = per protocol; PT=prothrombin time; RBV = ribavirin; RCT = randomized controlled trial; RR = relative risk; RRR = relative risk reduction; SAE = serious adverse event; SE = standard error; SVR12 = sustained virologic response at 12 weeks after therapy completed; TE = treatment experienced; TN = treatment naïve; ULN = upper limit of normal; wk = weeks; wt = weight; y = years; µL = microliters.
*derived from phase 3 trials of simeprevir/peginterferon + ribavirin in treatment-naïve monoinfected patients
** Known hepatotoxic drugs (etofoxine, isoniazid, nitrofurantoin, phenytoin), herbal supplements, strong CYP3A4/P=gp inhibitors (clarithromycin, erythromycin, telithromycin, azole antifungals, nifedipine, nefazodone), strong and moderate CYYP4A/P=gp inducers (nafcillin, rifampin, carbamazepine, phenytoin, phenobarbital, bosentan, modafinil, St. John's Wort), OATP inhibitors (cyclosporine, rifampin, gemfibrozil, eltrombopag, lapatinib), HIV medications, statins (simvastatin, fluvastatin, rosuvastatin, atorvastatin, pitavastatin, pravastatin doses > 10 mg).

Sofosbuvir/Velpatasvir NEW DRUG EVALUATION**:**
See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Three phase 3 trials evaluated the safety and efficacy of SOF/VEL that contributed to FDA approval.[43] ASTRAL-1 included GT 1, 2, 4, 5 or 6 and two additional phase 3 trials were conducted in patients with GT 2 (ASTRAL 2), and GT 3 (ASTRAL-3).[43] The FDA requested studies with an active comparator for both GT 2 and 3. Cirrhosis was defined as: liver biopsy showing cirrhosis (Metavir score = 4 or Ishak score ≥ 5), FibroTest score > 0.75 AND an APRI > 2, or Fibroscan with a result of > 12.5 kPa. In the absence of a definitive diagnosis, liver biopsy or Fibroscan was required. In addition, a long list of medications were not allowed or advised to use with caution, including proton-pump inhibitors and statins, respectively. VEL solubility decreases as pH increases and drugs that increase gastric pH are expected to decrease concentration of VEL. This includes antacids, H2-receptor antagonists, and proton pump inhibitors.[16] Pooled analysis of these 3 trials resulted in SVR12 rates of 95% of higher in subjects without decompensated cirrhosis. SVR12 rates were comparable with the exception of GT3. Subgroup analysis showed that cirrhosis, prior treatment failure, and the presence of baseline NS5A polymorphisms were associated with numerically higher rates of treatment failure. [43]

The ASTRAL-1 trial is a phase 3 randomized, double-blind, placebo controlled trial, comparing an immediate treatment group (ITG) with SOF/VEL for 12 weeks to a deferred treatment group (DTG) of placebo followed by treatment with SOF/VEL in subjects with GT 1, 2, 4 or 6.[44] Due to the low prevalence of GT 5 infection, these subjects were not randomized but placed directly in the ITG. Subjects in the placebo group were eligible for deferred treatment after the 12 week blinded period. The placebo group was included to evaluate the safety profile of SOF/VEL. The efficacy analysis was designed to compare SVR of SOF/VEL to a performance goal of 85% which was not a historical control but rather a benchmark based on general trend of treatment. The clinical relevance of this ambiguous value is unclear. Both TN and TE patients were included in the trial and 19% had cirrhosis. Of the 32% who had received previous treatment, 28% received PR plus a protease inhibitor and 61% had received PR. Subjects previously on a NS5A or NS5B inhibitor were excluded from the trial. Overall SVR rates were 98% to 100% regardless of HCV genotype (See evidence table). Confidence intervals were wider for subjects with GT 5 or GT 6, consistent with the low number of subjects included in the trial with these genotypes. Only 2 subjects experienced a virologic failure, both of whom had baseline NS5A RAVs. This trial

had extensive exclusion criteria and excluded medications (see evidence table) that limits the overall generalizability of results. The majority of subjects were from the US which increases applicability but resulted in lower recruitment of non-GT1 HCV genotypes, which are less common in the US.

The ASTRAL-2 and ASTRAL-3 trials were two identical randomized, phase 3, open-label noninferiority studies involving HCV GT 2 or 3, respectively.[45] Patients who had previously failed treatment with PEG +/- RBV and treatment naïve patients were included, as well as those with compensated cirrhosis. SOF/VEL for 12 weeks was compared to SOF + RBV for 12 or 24 weeks for GT 2 and 3, respectively. Non-inferiority using a margin of 10% was used for each comparison. Previous studies with SOF + RBV for 12 weeks in GT 2 HCV have demonstrated SVR12 rates of 95% in treatment naïve and 82% in treatment experienced subjects. In patients with GT 2, VEL/SOF was found to be superior to SOF/RBV for 12 weeks in SVR rates (99% vs. 94%; absolute difference 5.2 percentage points; 95% CI 0.02 to 10.3; p=0.02). There were no virologic failures among subjects receiving SOF/VEL and 6 in the SOF + RBV group. In subjects with GT 3, SOF/VEL for 12 weeks was superior to SOF + RBV for 24 weeks in achieving SVR (95% vs. 80%; absolute difference of 14.8 percentage points; 95% CI 9.6 to 20.0; p<0.001). Eleven subjects receiving SOF/VEL had virologic failure. Across all groups, SVR rates were lowest among those with cirrhosis and previous treatment and in GT 3 subjects. In GT3, those with cirrhosis had SVR rates of 91.3% and 66.3% for the SOF/VEL and SOF/RBV groups, respectively. SVR rates for treatment experienced with GT 3 were 90.1% and 63.4%. All clinical sites for ASTRAL-2 were in the US, while approximately 75% of subjects in ASTRAL-3 were enrolled in sites in Europe and Australia/New Zealand where GT3 HCV is more prevalent. This resulted in an underrepresentation of Black subjects. All subjects with a baseline NS5A polymorphism responded favorably to treatment and there does not seem to be a role for NS5A screening prior to treatment. There is insufficient evidence if the addition of RBV may benefit subjects with GT3 HCV or if extending treatment for cirrhotics will be effective in reducing relapse. The FDA requested a further clinical trial to evaluate for a clinically meaningful difference between SOF/VEL and SOF/VEL + RBV in GT3 cirrhotics.[43]

The ASTRAL-4 trial was a phase 3 open-label trial assessing SOF/VEL with or without ribavirin for 12 or 24 weeks in patients with HCV genotypes 1 through 6 and with decompensated cirrhosis (Child-Pugh-Turcotte [CPT] class B).[46] Patients were randomized to receive: 1) SOF/VEL x 12 weeks, 2) SOF/VEL + RBV x 12 weeks, or 3) SOF/VEL x 24 weeks. The primary outcome was SVR12 and the secondary end point was change from baseline in the CPT and Model for End-Stage Liver Disease (MELD) scores at 12 weeks after the end of treatment. For SVR rates, each treatment group was compared to the assumed spontaneous rate of 1%; however, the study was not designed or powered to detect significant differences in rates of SVR among the treatment groups. A post-hoc comparison did not detect any significant differences in rates of SVR between the 3 treatment groups. Twenty two (8.2%) of patients had virologic failure; the majority of subjects had a relapse. Of those with virologic failure, 9 patients had baseline NS5A or NS5B RAVs. There were too few subjects with genotypes 4, 5, or 6 to make generalizing conclusions in these subgroups. Overall SVR rates were 83%, 94% and 86% for those receiving SOF/VEL for 12 weeks, SOF/VEL + RBV for 12 weeks, and SOF/VEL for 24 weeks, respectively. SVR rates were lowest in those with GT3 (50-85%), but rates were improved with the addition of RBV. Forty seven percent of patients had an improvement in the CPT score over baseline and 51% had an improved MELD score. Only patients with moderate hepatic decompensation were included in the study; results cannot be generalized to those with more severe liver disease. In addition, all 47 sites were within the US which resulted in the majority of patients having GT 1. Severely decompensated patients (CPT C) were not included in study.

Clinical Safety:

Phase 3 trials evaluated over 1300 patients treated with SOF/VEL. The most common adverse events were headache, fatigue, nausea, insomnia, nasopharyngitis and diarrhea and subjects who received RBV experienced higher rates of adverse events associated to RBV therapy. [16,43] Adverse reactions observed in at least 5% of patients and more commonly than placebo are included in table 8. Most rates were comparable in both groups. In subjects with decompensated cirrhosis, the most common adverse events were fatigue (32%), anemia (26%), nausea (15%), headache (21%), insomnia (11%), and diarrhea (10%). Decreases in

hemoglobin to less than 10g/dl and 8.5 g/dl were observed in 23% and 7% of subjects treated with SOF/VEL and ribavirin, respectively. There were low rates of discontinuations due to adverse events (<2%) and serious adverse events when given without RBV (2%). In patients with decompensated cirrhosis, there were much higher rates of serious adverse events (17%), consistent with advanced underlying liver disease. Still, few subjects discontinued SOF/VEL due to adverse events (3% overall).

Table 8. Adverse Reactions Reported In ≥5% of Subjects and More Commonly than Placebo

Adverse Reaction	SOF/VEL 12 week (n=1035)	Placebo (n=116)
Headache	296 (29%)	33 (28%)
Fatigue	217 (21%)	23 (20%)
Nausea	135 (13%)	13 (11%)
Nasopharyngitis	121 (12%)	12 (10%)
Insomnia	87 (8%)	11 (9%)
Asthenia	58 (6%)	9 (8%)
Cough	57 (6%)	4 (3%)
Upper respiratory tract infection	50 (5%)	3 (3%)
Irritability	49 (5%)	4 (3%)
Constipation	47 (5%)	3 (3%)

Similar to SOF, there is a safety warning regarding the risk of serious symptomatic bradycardia related to co-administration of SOF with amiodarone and another DAA. Both SOF and VEL are substrates for P=glycoprotein (P-gp) and breast cancer resistance protein (BCRP). VEL is also a substrate of CYP2B6, CYP2C8 and CYP3A as well as an inhibitor of P-gp, BCRP and OATP2B1. Therefore, there are many potential drug-drug interactions to be aware of and concomitant drugs that were not included in clinical trials.

Table 9: Pharmacology and Pharmacokinetic Properties:

Parameter	
Mechanism of Action	SOF is a NS5B inhibitor, and VEL is an NS5A replication inhibitor. SOF/VEL is a fixed dose combination of direct-acting antiviral agents against the hepatitis C virus.
Distribution and Protein Binding	SOF 61-65% protein bound; VEL > 99.5%
Metabolism	SOF: Cathepsin A, CES1, HINT1; VEL: CYP2B6, CYP2C8, CYP3A4
Half-Life	SOF: 0.5 h; VEL: 15 h
Elimination	SOF: glomerular filtration and active tubular secretion, 80% excreted in urine; VEL: biliary excretion as parent; 94% excreted in feces

Abbreviations: IL-5 = interleukin 5; L = liters; ml =milliliters

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Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Hepatocellular Carcinoma
2) Mortality
3) Liver Transplant
4) Decompensated Liver Disease
5) Discontinuation Rates Due to Adverse Events
6) Serious Adverse Events

Primary Study Endpoints:
2) Sustained Virologic Response at 12 after the end of treatment (SVR12)

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Table 10. Clinical Evidence Table (SOF/VEL)

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Feld et al.[44] DB, PC, MC Phase 3 ASTRAL-1	1. SOF/VEL (ITG) 2. Placebo (DTG) 12 weeks	Demographics: 34% GT 1a 19% GT 1b 17% GT 2 19% GT 4 6% GT 5 7% GT 6 79% white 60% male 19% Cirrhosis Key Inclusion Criteria: -age ≥18 y, HCV RNA levels > 10^4 IU/ml Key Exclusion Criteria: -Clinically-significant illness, decompensated cirrhosis, HCC, psychiatric hospitalization, suicide attempt or period of disability within last 5 years, malignancy, ALT/AST > 10 x ULN, bilirubin > 1.5 x ULN, Platelets < 50,000/uL, HbA1c > 8.5%, CrCl < 60 ml/min, Hg < 11 g/dL-12 g/dl, albumin < 3 g/dL, INR > 1.5 x ULN, prior tx with SOF or other NS5B/NS5A inhibitor, HBV or HIV, clinically-relevant alcohol or drug abuse within 12 months, use of prohibited concomitant medications*	ITT: 1. 624 2. 116 Attrition: 1. 0 2. 0	Primary Endpoint: SVR12 (ITG only) 1. 99% (95% CI 98 to > 99) P<0.001* *Compared to performance goal of 85% *GT 1a 98% (95 to >99)* *GT 1b 99% (95to 100)* *GT 2 100% (97 to 100)* *GT 4 100% (97 to 100)* *GT 5 97% (85 to >99)* *GT 6 100% (91 to 100)* *Cirrhosis:* 99% (95 to >99)	N/A	Outcome: D/C due to AE: 1. 1 (0.2%) 2. 2 (2%) Serious AE: 1. 15 (2%) 2. 0 (0%)	NS NS	**Risk of Bias**: Selection Bias: (low) randomized 5:1 by computerized central randomization and interactive response technology. Subjects with GT 5 not randomized. Groups generally well balanced; however efficacy comparison not done between groups so differences unlikely to bias results. Performance Bias: (low) patients and investigators remained masked. SOF/VEL and placebo identical in appearance. Detection Bias: (unclear) Funder's clinical staff masked until analysis; unclear of outcome assessors blinded. Attrition Bias: (low) overall attrition low and similar across groups Reporting Bias: (unclear) Funded and designed by Gilead Sciences. Gilead was involved in data collection, study conduct, and statistical analyses, as well as writing of the manuscript. **Applicability**: Patient: Extensive and elusive exclusion criteria limits applicability of study results. Only patients with moderate liver disease were included (CPT B). Severely decompensated patients (CPT C) not included in study. Few patients with GTs 5 & 6 and mostly younger white men. Intervention: No concerns Comparator: Primary efficacy endpoint compared to performance goal of 85%. It is unclear how this goal was decided on. Outcomes: Surrogate outcome of SVR 12 used to evaluate efficacy. Setting: 81 sites in the U.S., Canada, Europe, and Hong Kong; 51% in Europe and 46% in North America.

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2. Foster et al.[45] Open-label, phase 3, noninferiority trial Astral-2 & Astral-3	ASTRAL-2 (GT2) 1. SOF/VEL 2. SOF/RBV 12 weeks ASTRAL:-3 (GT3) 1. SOF/VEL x 12 weeks 2. SOF/RBV x 24 weeks	Demographics: *GT2:* 14% cirrhosis 15% previous treatment *GT3:* 30% cirrhosis 26% previous treatment Key Inclusion Criteria: -age ≥18 y, HCV RNA levels > 10^4 IU/ml, GT 2 (ASTRAL-2), GT3 (ASTRAL-3), Key Exclusion Criteria: See Feld, et al.	ITT: 1. 135 2. 134 Attrition: 1. 1 2. 2 ITT: 1. 278 2. 280 Attrition: 1. 1 2. 5	Primary Endpoint: SVR12 *Genotype 2:* Sof/Vel: 133/134 (99%; 95% CI 96-100) Sof/RBV: 124 (94%; 95% CI 88-97) Absolute difference 5.2%; 95% CI 0.2to 10.3 P=0.02 *Genotype 3:* 1. 264/277 (95%; 95% CI 92-98) 2. 221/275 (80%; 95% CI 75-85) Absolute difference 14.8%; 95% CI 9.6 to 20.0 P<0.001 Relapse: *Genotype 2:* Sof/Vel: 0 (0%) Sof/Rbv: 6 (5%) *Genotype 3:* 1. 11 (4%) 38 (14%)	NS for all	Outcome: D/C due to AE: 1. 1 (%) 2. 0 (0%) Serious AE: 1. 2 (1.5%) 2. 2 (1.5%) GT3: D/C due to AE: 1. 0 (0%) 2. 9 (3%) Serious AE: 1. 6 (2%) 2. 15 (5%)	NS for all	**Risk of Bias:** Selection Bias: (low) randomized 1:1 by computerized central randomization and interactive response technology. Groups similar at baseline. Performance Bias: (high) open-label study Detection Bias: (high) open-label study Attrition Bias: (low) overall attrition low and similar across groups; full analysis set used for efficacy analysis. Missing data counted as a success only if data point preceded and followed by values that are deemed successes, otherwise counted as a failure. Reporting Bias: (unclear) Funded and designed by Gilead Sciences. Gilead was involved in data collection, study conduct, and statistical analyses, as well as writing of the manuscript. **Applicability**: Patient: Extensive and elusive exclusion criteria limits applicability of study results. Mostly white males. Patients previously treated with another NS5A or NS5B inhibitor were excluded; unknown the effect of newer DAA's in this population. Intervention: No concerns; appropriate dose of SOF and VEL based on phase 2 studies. Comparator: SOF+RBV current standard of care for GT2, but other agents now available and used for GT3 Outcomes: Surrogate outcome of SVR 12 used to evaluate efficacy. Setting: ASTRAL-2: 51 sites in the US; ASTRAL-3: 76 sites in the US, Canada, Europe, Australia, and New Zealand

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3. Curry et al.[46] Open-label Phase 3 ASTRAL-4	1. SOF/VEL x 12 weeks 2. SOF/VEL + RBV x 12 weeks 3. SOF/VEL x 24 weeks	Demographics: 60% GT 1a 18% GT 1b 4% GT 2 15% GT 3 3% GT 4 Mean age 58 Key Inclusion Criteria: -age ≥18 y, HCV RNA levels > 10^4 IU/ml, decompensated cirrhosis Key Exclusion Criteria: -Clinically-significant illness, HCC, significant pulmonary disease or cardiac disease, psychiatric hospitalization, suicide attempt or period of disability within last 5 years, malignancy, ALT/AST > 10 x ULN, bilirubin > 5 mg/dl, Platelets < 30,000/uL, CrCl < 50 ml/min, Hg <10g/dl, albumin < 3 g/dL, INR > 1.5 x ULN, prior tx with SOF or other NS5B/NS5A inhibitor, HBV or HIV, clinically-relevant alcohol or drug abuse within 12 months, use of prohibited concomitant medications*	ITT: 1. 90 2. 87 3. 90 Attrition: 1. 0 2. 0 3. 0	Primary Endpoint: SVR12 (ITG only) 1. 83%; 95% CI 74 to 90) 2. 94%; 95% CI 87 to 98) 3. 86%; 95% CI 77 to 98) P<0.001 for all comparisons* *Compared to assumed spontaneous rate of HCV clearance of 1%	NA for all	Outcome: D/C due to AE: 1. 1 (1.1%) 2. 4 (4.6%) 3. 4 (4.4%) Serious AE: 1. 17 (19.9%) 2. 14 (16.1%) 3. 16 (17.8%)	NS for all	**Risk of Bias**: Selection Bias: (low) randomized but unclear on method of randomization used. Fewer males in Group 1. However efficacy comparison not done between groups so differences unlikely to bias results. Performance Bias: (high) open-label Detection Bias: (high) open-label; objective primary outcome used for efficacy analysis Attrition Bias: (low) overall attrition low and similar across groups; if missing data point was preceded and followed by values deemed successes, then the missing data point was termed a success; otherwise it was termed a failure. Reporting Bias: (unclear) Funded and designed by Gilead Sciences. Gilead was involved in data collection, study conduct, and statistical analyses, as well as writing of the manuscript. **Applicability**: Patient: Extensive and elusive exclusion criteria limits applicability of study results. Only moderate liver disease; majority of GT 1 patients included, possibly because only study sites in the U.S. were included. Intervention: No concerns Comparator: Primary efficacy endpoint compared to assumed spontaneous rate of 1%. More relevant if study would have compared treatment regimens to each other. Outcomes: Surrogate outcome of SVR 12 used to evaluate efficacy. Setting: 47 sites in the U.S.

Abbreviations: AE = adverse events; ALT = alanine aminotransferase; APRI = AST to platelet ratio index; ARI = absolute risk increase; ARR = absolute risk reduction; CI = confidence interval; CKD = chronic kidney disease; CPT = child turcotte-pugh; CrCl = creatinine clearance; CV = cardiovascular; DB = double-blind; DAA = direct acting antiviral; D/C = discontinue; DM = diabetes mellitus; DTG = deferred treatment group; EF = ejection fraction; FAS = full analysis set; FDA = U.S. Food and Drug Administration; GT = genotype; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; h/o = history of; HG = hemoglobin; ICS = inhaled corticosteroid; ITG = immediate treatment group; ITT = intention to treat; IV = intravenous; MC = multi-centered; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; OR = odds ratio; PC = placebo-controlled; PBO = placebo;; PG = parallel group; PP = per protocol; PT=prothrombin time; RBV = ribavirin; RCT = randomized controlled trial; RR = relative risk; RRR = relative risk reduction; SAE =

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serious adverse event; SE = standard error; SOF = sofosbuvir; SVR12 = sustained virologic response at 12 weeks after therapy completed; TE = treatment experienced; TN = treatment naïve; ULN = upper limit of normal; VEL = velpatasvir; wk = weeks; wt = weight; y = years; µL = microliters.
*Hematologic stimulating agents (erythropoiesis-stimulating agents, granulocyte colony stimulating factor), chronic immunosuppressants, herbal supplements, inhibitors or inducers of P-gyp or CYP, proton-pump inhibitors, anticonvulsants, modafinil, sulfasalazine, methotrexate,

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Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

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Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	DAKLINZA	DACLATASVIR DIHYDROCHLORIDE	Y
ORAL	TABLET	DAKLINZA	DACLATASVIR DIHYDROCHLORIDE	Y
ORAL	TABLET	HARVONI	LEDIPASVIR/SOFOSBUVIR	Y
ORAL	TABLET	SOVALDI	SOFOSBUVIR	Y
ORAL	TAB DS PK	VIEKIRA PAK	OMBITA/PARITAP/RITON/DASABUVIR	N
ORAL	TABLET	TECHNIVIE	OMBITASVIR/PARITAPREV/RITONAV	N
ORAL	TABLET	ZEPATIER	ELBASVIR/GRAZOPREVIR	N
ORAL	CAPSULE	OLYSIO	SIMEPREVIR SODIUM	N

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Appendix 2: Summary of Randomized Controlled Trials

Randomized Controlled Trials:
A total of 10 citations were manually reviewed from the literature search. After further review, 5 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 sections were also excluded and are summarized above. The remaining 5 trials are briefly described in the table below.

Table 1: Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Results (Primary Outcome; SVR12)	
ALLY-1[29] Open-label, phase 3	DCV/SOF + RBV x 12 weeks	Compensated/decompensated cirrhosis (n=60) or post-liver transplantation (n=53) (treatment naïve or experienced) HCV GT 1, 2, 3, 4, 5 or 6	SVR12: *Advanced Cirrhosis:* 50/60 (83%; 95% CI 71.5-91.7)	*Posttransplantation:* 50/53 (94%; 95% CI 84.3-98.8)
ELECTRON-2[47] Open-label, phase 2	LDV/SOF vs. LDV/SOF + RBV x 12 weeks	HCV GT 3 or 6 (n=126), treatment naïve and treatment experienced	SVR12: *Treatment Naïve GT3* LDV/SOF: 16/25 (64%; 95% CI 43-82) LDV/SOF + RBV: 26/26 (100%; 95% CI 87-100) *Treatment Experienced GT3* LDV/SOF + RBV: 41/50 (82%; 95% CI 69-91)	*GT 6 (Treatment Naïve and Experienced)* LDV/SOF: 24/25 (96%; 95% CI 80-100)
Wilson, et al.[48] Phase 2, open-label	LDV/SOF x 12 weeks	HCV GT 1 with treatment failure to short course LDV/SOF based regimens without liver cirrhosis (n=34)	SVR12: 31/34 (91.2%)	
OPTIMIST-2[49] Open-label, phase 3	SMV/SOF x 12 weeks	HCV GT1 and compensated cirrhosis, treatment-naïve and treatment experienced	SVR12: 83% (95% CI 76-91)	
SOLAR-2[32] Phase 2, open label	LDV/SOF + RBV for 12 -24 weeks	Cohort A (decompensated cirrhosis CTP B or C) Cohort B (post liver transplantation) GT 1 or 4	SVR12: *Cohort A; GT 1; CTP B* 12 wks: 20 (87%; 90% CI 70-96) 24 wks: 22 (96%; 81-100)	*Cohort A; GT 1; CTP C* 12 wks: 17 (85%; 66-96) 24 wks: 18 (78%; 60-91) *Cohort B; GT1; without cirrhosis* 12 wks: 42 (93%; 84-98) 24 wks: 44 (100%; 84-98)

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Abstracts of Randomized Controlled Trials:

1. Poordad F, Schiff Er, Vierling JM, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. *Hepatology. 2*016 May;63(5):1493-505. Epub 2016 Mar 7.

Abstract: Chronic hepatitis C virus (HCV) infection with advanced cirrhosis or post-liver transplantation recurrence represents a high unmet medical need with no approved therapies effective across all HCV genotypes. The open-label ALLY-1 study assessed the safety and efficacy of a 60-mg once-daily dosage of daclatasvir (pan-genotypic NS5A inhibitor) in combination with sofosbuvir at 400 mg once daily (NS5B inhibitor) and ribavirin at 600 mg/day for 12 weeks with a 24-week follow-up in two cohorts of patients with chronic HCV infection of any genotype and either compensated/decompensated cirrhosis or posttransplantation recurrence. Patients with on-treatment transplantation were eligible to receive 12 additional weeks of treatment immediately after transplantation. The primary efficacy measure was sustained virologic response at posttreatment week 12 (SVR12) in patients with a genotype 1 infection in each cohort. Sixty patients with advanced cirrhosis and 53 with posttransplantation recurrence were enrolled; HCV genotypes 1 (76%), 2, 3, 4, and 6 were represented. Child-Pugh classifications in the advanced cirrhosis cohort were 20% A, 53% B, and 27% C. In patients with cirrhosis, 82% (95% confidence interval [CI], 67.9%-92.0%) with genotype 1 infection achieved SVR12, whereas the corresponding rates in those with genotypes 2, 3, and 4 were 80%, 83%, and 100%, respectively; SVR12 rates were higher in patients with Child-Pugh class A or B, 93%, versus class C, 56%. In transplant recipients, SVR12 was achieved by 95% (95% CI, 83.5%-99.4%) and 91% of patients with genotype 1 and 3 infection, respectively. Three patients received peritransplantation treatment with minimal dose interruption and achieved SVR12. There were no treatment-related serious adverse events.

Conclusion: The pan-genotypic combination of daclatasvir, sofosbuvir, and ribavirin was safe and well tolerated. High SVR rates across multiple HCV genotypes were achieved by patients with post-liver transplantation recurrence or advanced cirrhosis.

2. Gane EJ, Hyland RH, An D, et al. Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV genotype 3 or 6 infection. *Gastroenterology.* 2015 Nov;149(6):1454-1461.e1. doi: 10.1053/j.gastro.2015.07.063. Epub 2015 Aug 7.

BACKGROUND & AIMS: We performed a phase 2 clinical trial to evaluate the efficacy and safety of ledipasvir and sofosbuvir, with or without ribavirin, in patients infected with hepatitis C virus (HCV) genotype 3 or 6.

METHODS: We performed an open-label study of 126 patients with HCV genotype 3 or 6 infections at 2 centers in New Zealand from April 2013 through October 2014. Subjects were assigned 1 of 4 groups that received 12 weeks of treatment. Previously untreated patients with HCV genotype 3 were randomly assigned to groups given fixed-dose combination tablet of ledipasvir and sofosbuvir (n = 25) or ledipasvir and sofosbuvir along with ribavirin (n = 26). Treatment-experienced patients with HCV genotype 3 (n = 50) received ledipasvir and sofosbuvir and ribavirin. Treatment-naïve or treatment-experienced patients with HCV genotype 6 (n = 25) received ledipasvir and sofosbuvir. The primary end point was the percentage of patients with HCV RNA ≤15 IU/mL 12 weeks after stopping therapy (sustained virologic response at 12 weeks [SVR12]).

RESULTS: Among treatment-naïve genotype 3 patients, 16 of 25 (64%) receiving ledipasvir and sofosbuvir alone achieved SVR12 compared with all 26 patients (100%) receiving ledipasvir and sofosbuvir and ribavirin. Among treatment-experienced patients with HCV genotype 3, forty-one of fifty achieved an SVR12 (82%). Among patients with HCV genotype 6, the rate of SVR12 was 96% (24 of 25 patients). The most common adverse events were headache, upper respiratory infection, and fatigue. One patient with HCV genotype 3 discontinued ledipasvir and sofosbuvir because of an adverse event (diverticular perforation), which was not considered treatment related.

CONCLUSIONS: In an uncontrolled, open-label trial, high rates of SVR12 were achieved by patients with HCV genotype 3 infection who received 12 weeks of ledipasvir and sofosbuvir plus ribavirin, and by patients with HCV genotype 6 infection who received 12 weeks of sofosbuvir and ledipasvir without ribavirin. Current guidelines do not recommend the use of ledipasvir and sofosbuvir, with or without ribavirin, in patients with HCV genotype 3 infection.

3. Luetkemeyer AF, McDonald C, Ramgopal M, Noviello S, Bhore R, Ackerman P. 12 Weeks of Daclatasvir in Combination With Sofosbuvir for HIV-HCV Coinfection (ALLY-2 Study): Efficacy and Safety by HIV Combination Antiretroviral Regimens. *Clin Infect Dis.* 2016 Jun 15;62(12):1489-96. doi: 10.1093/cid/ciw163. Epub 2016 Mar 29.

   BACKGROUND: Highly effective hepatitis C virus (HCV) direct-acting antiviral therapies that do not require modification of human immunodeficiency virus (HIV) antiretroviral regimens are needed. We evaluated the efficacy and safety of daclatasvir + sofosbuvir (DCV + SOF) for 12 weeks by antiretroviral (ARV) regimen in HIV-HCV-coinfected patients.

   METHODS: In the randomized, open-label ALLY-2 study, HIV-HCV-coinfected patients received 8 or 12 weeks of once-daily DCV 60 mg (dose-adjusted as-necessary for concomitant ARVs) + SOF 400 mg. Results were stratified by ARV class for the 151 patients who received 12 weeks of DCV + SOF.

   RESULTS: Fifty-one patients were HCV treatment experienced, 100 were treatment naive, 89% male and 33% black. HCV genotypes were: genotype 1a (GT1a; 69%), GT1b (15%), GT2 (8%), GT3 (6%), and GT4 (2%). Sustained virologic response 12 weeks post-treatment (SVR12) was 97% and was similar across ARV regimens (P = .774): protease inhibitor-based, 97% (95% confidence interval [CI], 90%-99.7%); nonnucleoside reverse transcriptase inhibitor-based, 100% (95% CI, 91%-100%); and integrase inhibitor based, 95% (95% CI, 83%-99.4%). SVR12 among patients receiving either tenofovir disoproxil fumarate or abacavir as part of their antiretroviral therapy regimen was 98% (95% CI, 93%-99.5%) and 100% (95% CI, 85%-100%), respectively. Age, gender, race, cirrhosis, HCV treatment history, GT , and baseline HCV RNA did not affect SVR12. No discontinuations were attributed to treatment-related adverse events.

   CONCLUSIONS: DCV + SOF x12 weeks is a highly efficacious, all-oral, pan-GT HCV treatment for HIV-HCV coinfected patients across a broad range of ARV regimens.

4. Wilson EM, Kattakuzhy S, Sidharthan S, Sims Z, Tang L, McLaughlin M, et al. Successful Retreatment of Chronic HCV Genotype-1 Infection With Ledipasvir and Sofosbuvir After Initial Short Course Therapy With Direct-Acting Antiviral Regimens. *Clin Infect Dis*. 2016 Feb 1;62(3):280-8. doi: 10.1093/cid/civ874. Epub 2015 Oct 31.

BACKGROUND: The optimal retreatment strategy for chronic hepatitis C virus (HCV) patients who fail directly-acting antiviral agent (DAA)-based treatment is unknown. In this study, we assessed the efficacy and safety of ledipasvir (LDV) and sofosbuvir (SOF) for 12 weeks in HCV genotype-1 (GT-1) patients who failed LDV/SOF-containing therapy.

METHODS: In this single-center, open-label, phase 2a trial, 34 participants with HCV (GT-1) and early-stage liver fibrosis who previously failed 4-6 weeks of LDV/SOF with GS-9669 and/or GS-9451 received LDV/SOF for 12 weeks. The primary endpoint was HCV viral load below the lower limit of quantification 12 weeks after completion of therapy (sustained virological response [SVR]12). Deep sequencing of the NS3, NS5A, and NS5B regions were performed at baseline, at initial relapse, prior to retreatment, and at second relapse with Illumina next-generation sequencing technology.

RESULTS: Thirty-two of 34 enrolled participants completed therapy. Two patients withdrew after day 0. Participants were predominantly male and black, with median baseline HCV viral load of 1.3 × 10(6) IU/mL and Metavir fibrosis stage 1 and genotype-1a. Median time from relapse to retreatment was 22 weeks. Prior to retreatment, 29 patients (85%) had NS5A-resistant variants. The SVR12 rate was 91% (31/34; intention to treat, ITT) after retreatment. One patient relapsed.

CONCLUSIONS: In patients who previously failed short-course combination DAA therapy, we demonstrate a high SVR rate in response to 12 weeks of LDV/SOF, even for patients with NS5A resistance-associated variants

5. Manns M, Samuel D, Gane EJ, Mutimer D, McCaughan G, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. Lancet Infect Dis. 2016 Jun;16(6):685-97. doi: 10.1016/S1473-3099(16)00052-9. Epub 2016 Feb 18.

BACKGROUND: Treatment options are limited for patients infected by hepatitis C virus (HCV) with advanced liver disease. We assessed the safety and efficacy of ledipasvir, sofosbuvir, and ribavirin in patients with HCV genotype 1 or 4 and advanced liver disease.

METHODS: We did an open-label study at 34 sites in Europe, Canada, Australia, and New Zealand. Cohort A included patients with Child-Turcotte-Pugh class B (CTP-B) or CTP-C cirrhosis who had not undergone liver transplantation. Cohort B included post-transplantation patients who had either no cirrhosis; CTP-A, CTP-B, or CTP-C cirrhosis; or fibrosing cholestatic hepatitis. Patients in each group were randomly assigned (1:1) using a computer-generated randomisation sequence to receive 12 or 24 weeks of ledipasvir (90 mg) and sofosbuvir (400 mg) once daily (combination tablet), plus ribavirin (600-1200 mg daily). The primary endpoint was the proportion of patients achieving a sustained virological response 12 weeks after treatment (SVR12). All patients who received at least one dose of study drug were included in the safety analysis and all patients who received at least one dose of study drug and did not undergo liver transplantation during treatment were included in the efficacy analyses. Estimates of SVR12 and relapse rates and their two-sided 90% CI (Clopper-Pearson method) were provided. This exploratory phase 2 study was not powered for formal comparisons among treatment groups; no statistical hypothesis testing was planned or conducted. The trial is registered with EudraCT (number 2013-002802-30) and ClinicalTrials.gov (number NCT02010255).

FINDINGS: Between Jan 14, 2014, and Aug 19, 2014, 398 patients were screened. Of 333 patients who received treatment, 296 had genotype 1 HCV and 37 had genotype 4 HCV. In cohort A, among patients with genotype 1 HCV, SVR12 was achieved by 20 (87%, 90% CI 70-96) of 23 CTP-B patients with 12 weeks of treatment; 22 (96%, 81-100) of 23 CTP-B patients with 24 weeks of treatment; 17 (85%, 66-96) of 20 CTP-C patients (12 weeks treatment); and 18 (78%, 60-91) of 23 CTP-C patients (24 weeks treatment). In cohort B, among patients with genotype 1 HCV, SVR12 was achieved by 42 (93%, 84-98) of 45 patients without

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cirrhosis (12 weeks treatment); 44 (100%, 93-100) of 44 patients without cirrhosis (24 weeks treatment); 30 (100%, 91-100) of 30 CTP-A patients (12 weeks treatment); 27 (96%, 84-100) of 28 CTP-A patients (24 weeks treatment); 19 (95%, 78-100) of 20 CTP-B patients (12 weeks treatment); 20 (100%, 86-100) of 20 CTP-B patients (24 weeks treatment); one (50%, 3-98) of two CTP-C patients (12 weeks treatment); and four (80%, 34-99) of five CTP-C patients (24 weeks treatment). All five patients with fibrosing cholestatic hepatitis achieved SVR12 (100%, 90% CI 55-100). Among all patients with genotype 4 HCV, SVR12 was achieved by 14 (78%, 56-92) of 18 patients (12 weeks treatment) and 16 (94%, 75-100) of 17 patients (24 weeks treatment). Seven patients (2%) discontinued ledipasvir-sofosbuvir prematurely due to adverse events. 17 patients died, mainly from complications of hepatic decompensation.

INTERPRETATION: Ledipasvir-sofosbuvir and ribavirin provided high rates of SVR12 for patients with advanced liver disease, including those with decompensated cirrhosis before or after liver transplantation.

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Appendix 3: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZEPATIER safely and effectively. See full prescribing information for ZEPATIER.

ZEPATIER™ (elbasvir and grazoprevir) tablets, for oral use
Initial U.S. Approval: 2016

----------INDICATIONS AND USAGE----------

ZEPATIER is a fixed-dose combination product containing elbasvir, a hepatitis C virus (HCV) NS5A inhibitor, and grazoprevir, an HCV NS3/4A protease inhibitor, and is indicated with or without ribavirin for treatment of chronic HCV genotypes 1 or 4 infection in adults. (1)

----------DOSAGE AND ADMINISTRATION----------

- Testing prior to initiation:
  - Genotype 1a: Testing for the presence of virus with NS5A resistance-associated polymorphisms is recommended. (2.1)
  - Obtain hepatic laboratory testing. (2.1)
- Recommended dosage: One tablet taken orally once daily with or without food. (2.2)

Dosage Regimens and Durations for ZEPATIER in Patients with Genotype 1 or 4 HCV with or without Cirrhosis

Patient Population	Treatment	Duration
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* without baseline NS5A polymorphisms†	ZEPATIER	12 weeks
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* with baseline NS5A polymorphisms†	ZEPATIER + ribavirin	16 weeks
Genotype 1b: Treatment-naïve or PegIFN/RBV-experienced*	ZEPATIER	12 weeks
Genotype 1a or 1b: PegIFN/RBV/PI-experienced‡	ZEPATIER + ribavirin	12 weeks
Genotype 4: Treatment-naïve	ZEPATIER	12 weeks
Genotype 4: PegIFN/RBV-experienced*	ZEPATIER + ribavirin	16 weeks

*Peginterferon alfa + ribavirin.
†Polymorphisms at amino acid positions 28, 30, 31, or 93.
‡Peginterferon alfa + ribavirin + HCV NS3/4A protease inhibitor.

- HCV/HIV-1 co-infection: Follow the dosage recommendations in the table above. (2.2)
- Renal Impairment, including hemodialysis: No dosage adjustment of ZEPATIER is recommended. Refer to ribavirin prescribing information for ribavirin dosing and dosage modifications. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 50 mg elbasvir and 100 mg grazoprevir (3)

----------CONTRAINDICATIONS----------

- Patients with moderate or severe hepatic impairment (Child-Pugh B or C). (4)
- OATP1B1/3 inhibitors, strong CYP3A inducers, and efavirenz. (4)
- If ZEPATIER is administered with ribavirin, the contraindications to ribavirin also apply. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- ALT elevations: Perform hepatic laboratory testing prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, perform additional hepatic laboratory testing at treatment week 12. For ALT elevations on ZEPATIER, follow recommendations in full prescribing information. (5.1)
- Risk associated with ribavirin combination treatment: If ZEPATIER is administered with ribavirin, the warnings and precautions for ribavirin also apply. (5.2)

---------- ADVERSE REACTIONS ----------

In subjects receiving ZEPATIER for 12 weeks, the most commonly reported adverse reactions of all intensity (greater than or equal to 5% in placebo-controlled trials) were fatigue, headache, and nausea. In subjects receiving ZEPATIER with ribavirin for 16 weeks, the most commonly reported adverse reactions of moderate or severe intensity (greater than or equal to 5%) were anemia and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Co-administration of ZEPATIER with moderate CYP3A inducers is not recommended as they may decrease the plasma concentration of ZEPATIER. (7)
- Co-administration of ZEPATIER with certain strong CYP3A inhibitors is not recommended as they may increase the plasma concentration of ZEPATIER. (7)
- Consult the full prescribing information prior to and during treatment for potential drug interactions. (4, 5.3, 7, 12.3)

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

Revised: 1/2016

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EPCLUSA safely and effectively. See full prescribing information for EPCLUSA.

EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use
Initial U.S. Approval: 2016

----------INDICATIONS AND USAGE----------

EPCLUSA is a fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor, and is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection (1):

- without cirrhosis or with compensated cirrhosis
- with decompensated cirrhosis for use in combination with ribavirin

----------DOSAGE AND ADMINISTRATION----------

- Recommended dosage: One tablet (400 mg of sofosbuvir and 100 mg of velpatasvir) taken orally once daily with or without food (2.1)
- See recommended treatment regimen and duration in patients with genotypes 1, 2, 3, 4, 5, or 6 HCV in table below: (2.1)

Patient Population	Recommended Treatment Regimen
Patients without cirrhosis and patients with compensated cirrhosis (Child-Pugh A)	EPCLUSA for 12 weeks
Patients with decompensated cirrhosis (Child-Pugh B and C)	EPCLUSA + ribavirin for 12 weeks

- A dosage recommendation cannot be made for patients with severe renal impairment or end stage renal disease (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 400 mg sofosbuvir and 100 mg velpatasvir (3)

----------CONTRAINDICATIONS----------

EPCLUSA and ribavirin combination regimen is contraindicated in patients for whom ribavirin is contraindicated (4)

----------WARNINGS AND PRECAUTIONS----------

Bradycardia with amiodarone coadministration: Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with EPCLUSA is not recommended. In patients without alternative viable treatment options, cardiac monitoring is recommended. (5.1, 7.3)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with EPCLUSA for 12 weeks are headache and fatigue. (6.1)
- The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with EPCLUSA and ribavirin for 12 weeks in patients with decompensated cirrhosis are fatigue, anemia, nausea, headache, insomnia, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- P-gp inducers and/or moderate to potent CYP inducers (e.g., rifampin, St. John's wort, carbamazepine): May decrease concentrations of sofosbuvir and/or velpatasvir. Use of EPCLUSA with P-gp inducers and/or moderate to potent CYP inducers is not recommended (5.2, 7)
- Consult the full prescribing information prior to use for potential drug interactions (5.1, 5.2, 7)

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

Revised: 06/2016

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Hepatitis C Direct-Acting Antivirals

Goals:

- Approve use of cost-effective treatments supported by the medical evidence.
- Provide consistent patient evaluations across all hepatitis C treatments.
- Ensure appropriate patient selection based on disease severity, genotype, and patient comorbidities.

Length of Authorization:

- 8-12 weeks

Requires PA:

- All direct-acting antivirals for treatment of chronic Hepatitis C

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of chronic Hepatitis C infection?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is expected survival from non-HCV-associated morbidities more than 5 years?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.

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Approval Criteria		
4. Has all of the following pre-treatment testing been performed: a. Genotype testing in past 3 years; b. Baseline HCV RNA level in past 6 months; c. Current HIV status of patient; d. Pregnancy test in past 30 days for a woman of child-bearing age; and e. History of previous HCV treatment and outcome? Note: Direct-acting antiviral agents can re-activate hepatitis B in some patients. Please screen before treatment and monitor carefully during and after treatment for flare-up of hepatitis.	**Yes:** Record results of each test and go to #5	**No**: Pass to RPh. Request updated testing.
5. Has the patient failed treatment with any of the following HCV NS5A inhibitors: a. Daclatasvir plus sofosubvir; b. Ledipasvir/sofosbuvir; c. Paritaprevir/ritonavir/ombitasvir plus dasabuvir; d. Elbasvir/grazoprevir; or e. sofosbuvir/velpatasvir)? Note: Patients who failed treatment with sofosbuvir +/- ribavirin or pegylated interferon can be retreated (see table below).	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: If urgent retreatment is needed, resistance testing must be done to indicate susceptibility to prescribed regimen. Refer to medical director for review.	**No:** Go to #6
6. Which regimen is requested?	Document and go to #7	
7. Is the regimen prescribed by, or in consultation with, a hepatologist, gastroenterologist, or infectious disease specialist with experience in treatment of Hepatitis C?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness. Forward to DMAP for further manual review to determine appropriateness of prescriber.

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Approval Criteria		
8. Does the patient have: a. A biopsy, imaging test (transient elastography [FibroScan®], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE]) to indicate advanced fibrosis (METAVIR F3) or cirrhosis (METAVIR F4); or b. Clinical, radiologic or laboratory evidence of complications of advanced cirrhosis (ascites, portal hypertension, hepatic encephalopathy, hepatocellular carcinoma)**?**	**Yes:** Go to #12 Note: Other imaging and blood tests are not recommended based on insufficient evidence for high sensitivity and specificity compared to a liver biopsy	**No:** Go to #9
9. Does the patient have HIV coinfection AND: A biopsy, imaging test (transient elastography [FibroScan®], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE]), or serum test if the above are not available (enhanced liver fibrosis [ELF]; Fibrometer; FIBROSpect II) to indicate fibrosis (METAVIR F2) AND the patient is under treatment by a specialist with experience in HIV?	**Yes:** Go to #12 Note: Other imaging and blood tests are not recommended based on insufficient evidence for high sensitivity and specificity compared to a liver biopsy	**No:** Go to #10
10. 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)? a. Type 2 or 3 cryoglobulinemia with end-organ manifestations (i.e., leukocytoclastic vasculitis); or b. Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis; or c. Porphyria cutanea tarda	**Yes:** Go to #12	**No:** Go to #11

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Approval Criteria		
11. Is the patient in one of the following transplant settings: a. Listed for transplant and it is essential to prevent recurrent hepatitis C infection post-transplant; or b. Post solid organ transplant?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. In the previous 6 months: a. Has the patient actively abused alcohol (>14 drinks per week for men or >7 drinks per week for women or binge alcohol use (>4 drinks per occasion at least once a month); or b. Has the patient been diagnosed with a substance use disorder; or c. Is the prescriber aware of current alcohol abuse or illicit injectable drug use?	**Yes:** Go to #13	**No:** Go to #14
13. Is the patient enrolled in a treatment program under the care of an addiction/substance use treatment specialist?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness.
14. Will the patient and provider comply with all case management interventions and adhere to monitoring requirements required by the Oregon Health Authority, including measuring and reporting of a post-treatment viral load?	**Yes**: Go to #15	**No:** Pass to RPh. Deny; medical appropriateness.
15. Is the prescribed drug: a. Elbasvir/grazoprevir for GT 1a infection; or b. Daclatasvir + sofosbuvir for GT 3 infection?	**Yes**: Go to #16	**No:** Go to #17
16. Has the patient had a baseline NS5a resistance test showing a resistant variant to one of the agents in #16?	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #17

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Approval Criteria		
17. Is the prescribed drug regimen a recommended regimen based on the patient's genotype and cirrhosis status (see Table 1)?	**Yes:** Approve for 8-12 weeks based on duration of treatment indicated for approved regimen (Table 1).	**No:** Pass to RPh. Deny; medical appropriateness.

Table 1: Recommended Treatment Regimens for Chronic Hepatitis C.

Genotype	Cirrhosis Status	Approved Regimen^	Duration of Treatment
Genotype 1			
Treatment-naïve	Non-cirrhotic	• EBR/GZR • LDV/SOF	12 weeks except if LDV/SOF and *HCV RNA < 6 million IU/mL, give for 8 weeks*
	Compensated Cirrhosis	• EBR/GZR • LDV/SOF	12 weeks
	Decompensated Cirrhosis	• LDV/SOF + RBV	12 weeks
Treatment-experienced*	Non-cirrhotic	• EBR/GZR • LDV/SOF +/- RBV$^{\pm}$	12 weeks
	Compensated Cirrhosis	• EBR/GZR +/- RBV$^{\pm}$ • LDV/SOF + RBV	12 weeks
	Decompensated Cirrhosis	• LDV/SOF + RBV	24 weeks
Genotype 2			
Naïve or Experienced	Non-cirrhotic	• SOF/VEL+/- RBV$^{\pm}$	12 weeks
	Compensated Cirrhosis	• SOF/VEL+/- RBV$^{\pm}$	12 weeks
	Decompensated Cirrhosis	• SOF/VEL + RBV	12 weeks

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Genotype 3			
Naïve or Experienced	Non-cirrhotic	• LDV/SOF + RBV • SOF/VEL	12 weeks
	Compensated Cirrhosis	• SOF/VEL + RBV • DCV/SOF + RBV	12 weeks
	Decompensated Cirrhosis	• SOF/VEL + RBV • DCV/SOF + RBV	12 weeks
Genotype 4			
Naïve	Non-cirrhotic	• EBR/GZR • LDV/SOF	12 weeks
	Compensated Cirrhosis	• EBR/GZR • LDV/SOF	12 weeks
	Decompensated Cirrhosis	• LDV/SOF + RBV	12 weeks
Experienced	Non-cirrhotic	• EBR/GZR +/- RBV • LDV/SOF	12 weeks -16 weeks (patients with prior on-treatment failure while on PEG should be treated with 16 weeks and have RBV added to EBR/GZR regimen)
	Compensated Cirrhosis	• EBR/GZR +/- RBV • LDV/SOF + RBV	12 weeks-16 weeks (patients with prior on-treatment failure while on PEG should be treated with 16 weeks and have RBV added to EBR/GZR regimen)
	Decompensated Cirrhosis	• LDV/SOF + RBV	12 weeks
Genotypes 5 and 6			
Naïve or Experienced	With or Without Cirrhosis	• LDV/SOF	12 weeks

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Abbreviations: DCV = daclatasvir (Daklinza®); EBV/GZR = elbasvir/grazoprevir (Zepatier®) ; LDV/SOF = ledipasvir and sofosbuvir (Harvoni®); PEG = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir (Sovaldi®); SOF/VEL = sofosbuvir/velptasvir (Epclusa®)

*Treatment-experienced defined as previous treatment with PEG/RBV or SOF/RBV only.

± Weight based ribavirin recommended in whom prior treatment with sofosbuvir and ribavirin has failed

^ 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 limited. However, in these cases, a pangenotypic regimen is appropriate.
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.
Sofosbuvir-containing regimens should not be used in patients with severe renal impairment (GRF < 30 mL/min) or end stage renal disease requiring dialysis.
Elbasvir/grazoprevir or ombitasvir/paritaprevir/ritonavir + dasubuvir should not be used in patients with moderate to severe hepatic impairment (CTP and C)

P&T/DUR Review: *9/16 (MH); 1/16; 5/15; 3/15; 1/15; 9/14; 1/14*
Implementation: *TBD; 2/12/16; 4/15; 1/15*