Sofosbuvir for the Treatment of Hepatitis C and Evaluation of the 2014 American Association for the Study of Liver Diseases Treatment Guidelines

May 2014

Center for Evidence-based Policy
Oregon Health & Science University
3455 SW US Veterans Hospital Road
Mailstop SN-4N, Portland, OR 97239-2941
Phone: 503.494.2182
Fax: 503.494.3807
www.ohsu.edu/policycenter

About the Center for Evidence-based Policy

The Center for Evidence-based Policy (Center) is recognized as a national leader in evidence-based decision making and policy design. The Center understands the needs of policymakers and supports public organizations by providing reliable information to guide decisions, maximize existing resources, improve health outcomes, and reduce unnecessary costs. The Center specializes in ensuring diverse and relevant perspectives are considered, and appropriate resources are leveraged to strategically address complex policy issues with high-quality evidence and collaboration. The Center is based at Oregon Health & Science University in Portland, Oregon.

This report was prepared by:
Allison Leof, PhD
Martha Gerrity, MD, MPH, PhD
Aasta Thielke, MPH
Valerie King, MD, MPH

Center for Evidence-based Policy

Suggested citation:
Leof, A., Gerrity, M., Thielke, A., & King, V. (2014). *Sofosbuvir for the treatment of hepatitis C and evaluation of the 2014 American Association for the Study of Liver Diseases treatment guidelines.* Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University.

Table of Contents

List of Tables and Appendices

Introduction

Chronic hepatitis C virus (HCV) infection is a slowly progressive condition affecting between 2.7 million and 5.2 million United States (US) citizens (Chak 2011; Denniston 2014). Hepatitis C infection is associated with an increased risk of cirrhosis, liver failure, and hepatocellular carcinoma, and is the most common condition leading to liver transplant. Over a 20- to 30-year period, 5% to 20% of infected patients will develop cirrhosis and 1% to 5% will die of cirrhosis or liver cancer (Center for Disease Control and Prevention [CDC] 2010).

For HCV infected patients who develop liver disease, the most recently recommended standard of care is a combination of pegylated interferon therapy (PEG) and ribavirin (RBV), and, for patients with genotype 1 HCV infection, one of the protease inhibitors boceprevir (VICTRELIS®) or telaprevir (INCIVEK®). The standard interferon-based treatment regimens result in 45% to 75% of patients having no detectable virus at 24 weeks post treatment with results varying based on patient characteristics (US Department of Veterans Affairs 2013). These regimens can take up to a year to complete, place a high burden on patients by requiring weekly injections and complicated dosing schedules, and are associated with significant side effects leading patients to discontinue treatment. The ideal treatment for HCV would be highly effective, easy to take, have a low side effect profile, have a low patient burden, and be affordable.

Pharmaceutical companies have invested significant resources in finding alternative treatment regimens that would improve rates of sustained viral response while reducing patient burden for patients infected with HCV. More than 30 direct-acting anti-viral agents (DAAs) designed to treat HCV have entered clinical trials since 2011 (Tice 2014). In 2013, two new DAAs were approved: sofosbuvir (SOVALDI®) and simeprevir (OLYSIO™). At least two more DAAs are expected to be approved in 2014, including faldaprevir and daclatasvir. In addition, Gilead Sciences, Inc. (Gilead) is seeking approval for multi-drug combination pills including sofosbuvir, and AbbVie Inc. recently reported positive results from its investigational oral regimen (AbbVie 2014).

Of the recently developed DAAs, sofosbuvir has drawn the most attention, because it is the first new DAA the US Food and Drug Administration (FDA) approved for the treatment of HCV genotypes 1 to 4 (including an interferon-free regimen for genotypes 2 and 3). In addition, many reports of the initial sofosbuvir trials suggest that 80% to 90% of patients will not have detectable virus levels 12 weeks after completing treatment. In January 2014, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) released treatment guidance for hepatitis C and recommended sofosbuvir for all patients except those with severe renal impairment.

With the recent FDA approval of sofosbuvir, clinicians and purchasers will need to decide whether to include sofosbuvir in their treatment protocols for HCV infection. This report evaluates the evidence about the effectiveness and harms of sofosbuvir treatment for HCV, evaluates the AASLD guideline, and provides a compilation of the evidence to guide decisions on who and when to treat. With the approval of new HCV treatments and more drug approval applications currently at the FDA, it is clear that this is a rapidly evolving clinical and policy topic. Center for Evidence-based Policy staff will continue to place updated material on the Medicaid Evidence-based Decisions (MED) Project Clearinghouse website and will consider this report for updating as new evidence emerges.

Background

Clinical Overview

Between 2.7 million and 5.2 million Americans are infected with the HCV virus (Chak 2011; Denniston 2014). Prevalence of the HCV infection is greater in Medicaid and non-insured populations than in commercially insured groups, with one Florida study showing the Medicaid infection rate to be twice that of the commercially insured populations (663 per 100,000 beneficiaries compared to 302 per 100,000 over ten years) (Levin 2012). Because the early stages of the disease are often asymptomatic, up to half of infected individuals are unaware of their status. In June 2013, the United States Preventive Services Task Force (USPSTF) recommended that individuals at high risk of infection (i.e., intravenous drug users, individuals who received blood transfusions before 1992) and all adults born between 1945 and 1965 be screened for HCV (USPSTF 2013).

Progression of HCV is generally slow and varies significantly by individual. Approximately 15% to 25% of people infected with HCV will clear the virus during the acute stage without treatment. Seventy-five percent to 85% of infected individuals will develop a chronic HCV infection, and 60% to 70% of patients with chronic infection will develop chronic liver disease. Over 20 to 30 years, 5% to 20% of infected patients will develop cirrhosis and 1% to 5% will die of cirrhosis or liver cancer (CDC 2010).

Table 1. Progression of Hepatitis C Virus Infection (CDC 2014)

Condition	Percentage of Patients Who Develop Condition
Chronic HCV infection	75% to 85%
Chronic liver disease	60% to 70%
Cirrhosis over 20 to 30 years	5% to 20%
Death from cirrhosis or liver cancer	1% to 5%

Accelerated progression of the disease is associated with male gender, greater age, duration of the disease, steatosis, obesity, human immunodeficiency virus infection (HIV), hepatitis B infection (HBV), immunosuppression following solid organ transplant, insulin resistance and type 2 diabetes, and significant alcohol consumption (European Association for the Study of the Liver [EASL] 2013; Ghany 2009; Louie 2012). It is also important to note that neither spontaneous clearance nor successful treatment confers immunity and that reinfection can occur (Grebely 2012).

Common comorbid conditions with HCV infection include metabolic syndrome (approximately 27% of infected people), dyslipidemia (16% to 21%), peripheral vascular disease (19%), HIV (4%), and diabetes (5% to 15%) (Levin 2012). In a commercially insured population, alcohol and drug abuse were more common in HCV-infected patients than non-infected controls, with 7% versus less than 1% having an alcohol problem and 15% versus 3% abusing illegal drugs (Louie 2012).

There are six major genotypes of the HCV virus. Genotype 1 (HCV-1) is the most common form found in the US population accounting for approximately 73% of cases. Genotype 1 is further distinguished by subtypes 1a (HCV-1a) (39% of patients) and 1b (HCV-1b) (29%). Genotype 2 (HCV-2) is found in approximately 14% of US patients, genotype 3 (HCV-3) in 8%, a mixed-genotype in 4%, and genotypes 4 through 6 (HCV-4, -5, -6) in less than 1% of patients (Blatt 2000). Patients with genotype 1 have had a poorer response to treatment than patients with genotype 2 or 3, and subtype 1a has a poorer response than subtype 1b.

In addition, people have a gene that is related to HCV infection called the IL28B gene. The IL28B genotype can be of CC, CT or TT type. Patients with IL28B genotype CC are significantly more likely to clear the virus spontaneously and to respond to HCV treatment than patients with types CT or TT (EASL 2013).

Treatment

The goal of HCV treatment is to decrease the risk of virus-related conditions such as cirrhosis, hepatocellular carcinoma (HCC), decompensated liver disease, liver transplant, or death from other liver-related causes. Because of the slow progression of the disease, clinical trials have not evaluated these patient-important conditions as trial outcomes. Instead, a surrogate endpoint of sustained virologic response (SVR) has been used to measure success of treatment. The SVR is defined as undetectable HCV-ribonucleic acid (RNA) levels. The standard measure of treatment success has been SVR at 24 weeks post treatment (SVR24).

Several long-term studies of patients with chronic HCV infection have shown an association between achieving SVR24 and patient-important clinical outcomes. In a systematic review by the Agency for Healthcare Research and Quality (AHRQ), Chou (2012) found a moderate

strength of evidence that achievement of SVR24 post treatment was associated with lower risks of all-cause mortality, liver-related mortality, and HCC with hazard ratios ranging from 0.10 to 0.71. Chou (2012) also reviewed nine poor-quality studies which found a low strength of evidence that achieving SVR24 was associated with improvement in generic and disease-specific quality of life. Two additional studies were published since the AHRQ systematic review and corroborate its findings. Van der Meer (2012) found that among patients with HCV and advanced fibrosis or cirrhosis (Ishak scores between four and six) achievement of SVR24 was significantly associated with reduced mortality. The ten-year cumulative all-cause mortality rate in the 192 patients who achieved SVR24 was 8.9% (95% confidence interval [CI], 3.3% to 14.5%) compared to 26% (95% CI, 20.2% to 28.4%) ($p<0.001$) in the 338 patients who failed to achieve SVR24. A 2014 observational study of a VA population found that out of 128,769 patients infected with HCV, the 5,180 patients (4%) who were able to achieve an undetectable viral load with interferon-based treatment had a 45% reduction in the risk of death (hazard ratio [HR] 0.55, 95% CI 0.47 to 0.64) and a 27% reduction in the composite clinical endpoint (HR 0.73, 95% CI 0.66 to 0.82) of newly diagnosed cirrhosis, HCC, or a liver-related hospitalization (McCombs 2014).

The FDA recently accepted SVR at 12 weeks post treatment (SVR12) as an endpoint for FDA drug approval (FDA 2013a). This decision is based on a 2013 analysis of data from 13,599 adults (11,730 with genotype 1) treated with double (PEG+RBV) or triple therapy (PEG+RBV+PI) in phase II or III drug development trials. The analysis found an association between SVR12 and SVR24 as measured by a positive predictive value (PPV) of 98%. (Chen 2013). However, there is uncertainty about this result due to uncertainty about how the authors accounted for missing data. Although the authors state that they imputed missing data for some analyses, the data used to calculate their main measure of concordance (positive and negative predictive values) did not employ imputed values. The authors state that "missing viral load data were not used in calculating the tabularized relations between SVR24 and SVR12 or SVR4" (Chen 2013, p. 1451). There were 1,536 patients excluded with missing data. Ten-thousand one hundred-ninety-four (10,194/11,730 or 87%) genotype 1 patients were included in the analysis. If the 1,536 missing patients were added back into the calculations for PPV, making assumptions about the best case scenario (all patients with missing data achieved SVR24) and worst case scenario (all patients with missing data did not achieve SVR24), the range of potential values for the PPV is 77% to 99%. These calculations show that of a hundred patients, between 1 and 23 patients who achieved SVR12 will not achieve SVR24. In addition, these calculations are based on trial populations who generally have favorable treatment characteristics and may not reflect patient populations likely to be treated under Medicaid programs.

In contrast to Chen's findings (2013), Thorlund (2014) performed a meta-analysis of randomized controlled trials that treated HCV genotype 1 patients with PEG and RBV. Thorlund found that

SVR12 was 5% to 6% higher than SVR24 in these studies (2014). It may be that the association between SVR12 and SVR24 could vary depending on treatment regimen and concordance measures for one treatment cannot be extrapolated from data gathered from other regimens (Thorlund 2014). If this is true, the lack of data on both SVR12 and SVR24 for the new DAAs precludes certainty about long-term effectiveness of these drugs.

The sofosbuvir trial protocols registered in the ClinicalTrials.gov database include SVR24 as a secondary outcome, yet only two of these studies, ELECTRON (Gane 2013) and the NIH-funded study (Osinusi 2013), reported SVR24 data. Thorlund (2014) has called upon researchers in clinical trials to report both SVR12 and SVR24 "to allow for complete transparency and clarity in […] interpretation" (p. 49).

Standard Treatment Regimens

Since the early 2000s, standard treatment for HCV infection has been a combination of pegylated interferon (PEG-INF) in a weekly injection (either PEG-INF alfa-2a or alfa-2b) and ribavirin (RBV) daily (double therapy). In 2011, the FDA approved the protease inhibitors boceprevir (BOC) or telaprevir (TVR) in addition to PEG-INF and RBV to treat genotype 1 (triple therapy). Standard treatment protocols by genotype and the estimated SVR24 rates from treatment are described in Table 2 below.

Table 2. Standard of Care Treatment Regimens (US Department of Veterans Affairs 2013)

Genotype	Treatment	Approximate SVR24 Rate
HCV-1	<u>Double therapy</u> PEG-IFN alfa-2a or alfa-2b weekly + RBV daily for up to 48 weeks	45%
	<u>Triple therapy</u> PEG-INF alfa-2a OR alfa-2b weekly + RBV daily for up to 48 weeks depending on treatment response and either BOC or TVR. BOC is added during weeks 8 to 32 depending on treatment response and TVR is given with PEG-INF and RBV during first 12 weeks of treatment.	65% to 70%
HCV-2	PEG-INF weekly + RBV daily for up to 24 weeks	75%
HCV-3	PEG-INF weekly + RBV daily for up to 24 weeks	75%

Treatment effectiveness for HCV with double or triple therapy varies based on patient characteristics. Patients with genotype 1 are significantly less likely to achieve SVR24 than patients with genotypes 2 or 3. Patients with high pre-treatment viral loads (HCV-RNA greater than 600,000 IU/mL) are also less likely to achieve SVR. Other factors associated with lower

response to treatment include male sex, older age, being African American, obesity, diabetes, reduced alanine aminotransferase (ALT) levels, bridging fibrosis or cirrhosis, and a CT or TT polymorphism on the IL28B gene. In patients with genotype 1 treated with PEG-INF and RBV, SVR24 rates ranged from 69% in patients with the CC genotype, to 33% with CT, and 27% with TT (Ghany 2011). Differences in response rates by race may be related to African Americans being less likely to have the favorable CC polymorphism on the IL28B gene (Chou 2012; Ghany 2011).

Issues with Standard Treatment

Interferon-based treatments have high rates of side effects that affect quality of life. Patients report significant fatigue, headache, and flu-like symptoms as well as neuropsychiatric symptoms such as depression. The Veteran's Administration reports that approximately 10% of patients discontinue interferon-based treatment due to side effects (VA 2013). Interferon and RBV are also associated with anemia, neutropenia, thrombocytopenia, ophthalmologic disorders, thyroid dysfunction, and sarcoidosis.

Triple therapy with BOC or TVR involves a high burden on patients as the dosing schedule is complicated with multiple doses during the day and all medication must be consumed with fat. There are also significant drug-drug interactions with BOC and TVR (Ghany 2011). Adverse events associated with these drugs include increased hematological complications (BOC) and increased risk of anemia and severe rash (TVR) that may lead to discontinuation of treatment (Chou 2012).

Deciding to Initiate Treatment

In contrast to conditions where there is rapid progression and an immediate need for treatment (e.g., acute leukemia or serious bacterial infections), hepatitis C is a slowly progressing disease. Fifteen percent to 25% of infected persons clear the infection spontaneously. For those with ongoing infection, it is a disease where clinicians and patients have the option of delaying or forgoing treatment. Because of the slow progression of the disease as well as the moderate success rates and the side effects of current treatments, many patients have refused interferon-based treatments. Some physicians have also been recommending that patients wait until new treatment regimens are approved by the FDA. Earlier guidelines by the AASLD recommended that patients be monitored and treated if they show signs of liver involvement. Indications include a liver biopsy showing significant fibrosis (bridging or higher), compensated liver disease (defined as total serum bilirubin less than 1.5 g/dL; international normalized ratio [INR] of 1.5; serum albumin greater than 3.4, platelet count of 75,000 mm and no evidence of hepatic decompensation) and acceptable hematological and biochemical indices (hemoglobin 13 g/dL for men and 12 g/dL for women; neutrophil court of 1500/mm^3, serum creatinine less than 1.5 mg/dL). Interferon treatment is contraindicated for

patients with uncontrolled major depression, solid organ transplant, untreated thyroid disease, severe comorbid health conditions (e.g., hypertension, heart failure, coronary heart disease, diabetes, chronic obstructive pulmonary disease), or known hypersensitivity to medications (Ghany 2009).

Sofosbuvir (SOVALDI®)

Sofosbuvir (SOF), manufactured by Gilead, is a nucleotide analog NS5B polymerase inhibitor. In December 2013, the FDA approved SOF 400mg in a once daily pill for the treatment of hepatitis C genotypes 1, 2, 3 and 4, in combination with RBV and, for genotype 1, PEG-INF. The approval specifically includes patients who have the most urgent need for treatment due to advanced disease and increased risk of death including those with HCC, those awaiting liver transplantation, and patients with HIV-1 co-infection. Sofosbuvir is not approved for patients with severe renal impairment (estimated glomerular filtration rate less than or equal to 30 mL/min/1.73m^2) or end stage renal disease. The FDA approved sofosbuvir under a priority review process that allowed use of SVR12 as a study endpoint. Approved treatment regimens are described in Table 3 below.

Table 3. FDA Approved Sofosbuvir Treatment Regimens (FDA 2013b)

Patient Genotype	Treatment Regimen	Duration[1]
HCV-1 or -4	PEG-INF weekly + RBV + SOF daily	12 weeks
HCV-1	For interferon-ineligible: RBV + SOF	24 weeks
HCV-2	RBV + SOF	12 weeks
HCV-3	RBV + SOF	24 weeks

[1]All medications are taken for the full duration.

The FDA approved label for sofosbuvir does not identify any adverse reactions besides those that commonly occur with RBV treatment (fatigue and headache) or PEG-INF (fatigue, headache, nausea, insomnia, and anemia).

Sofosbuvir has attracted attention because of its potential improvement over previous standard of care. For genotypes 2 and 3, SOF plus RBV provides an interferon-free, all oral regimen with shorter duration. For genotype 1, SOF provides an alternative to BOC and TVR with their higher pill burden and side effect profile; it provides a shorter treatment period; and, for interferon-ineligible patients, it offers an alternative treatment protocol. Studies report SVR12 rates of 80% to 90% in patients treated with sofosbuvir regimens, and low rates of serious adverse events. If, indeed, the clinical research evidence supports these claims, the new SOF regimens would be a tremendous step forward for patients with HCV.

Gilead has set the wholesale acquisition cost of sofosbuvir at $1,000 per tablet in the US. With daily dosing, the cost of a course of treatment with sofosbuvir will range from $84,000 for 12 weeks of treatment to $168,000 for 24 weeks of treatment (Robison 2013). This price does not include the drug cost of RBV and/or PEG-INF in regimens that include those drugs. These costs also do not account for the medical care needed before, during and after treatment, or further treatment in the case of treatment failure or relapse.

Key Questions

This report will address the following Key Questions:

1. What is the evidence for the efficacy of sofosbuvir in treating hepatitis C?
2. What is the evidence for harms of sofosbuvir treatment?
3. Is there any evidence of subgroup differences in efficacy and harms (e.g., genotype, race, comorbidity)?
4. Are there studies in the research pipeline that will add significantly to the knowledge of sofosbuvir's effectiveness and harms?
5. What polices have private payers set around sofosbuvir coverage?
6. What is the quality and reliability of the AASLD treatment guideline?
7. What does the evidence say about whom to treat and when to treat?

Methods

Search Strategy

The FDA's website was searched for the summary review of evidence and the approved label for sofosbuvir. The website ClinicalTrials.gov was searched with the term "sofosbuvir" and all studies were reviewed for their design, treatment population, interventions and outcomes. Completed studies were reviewed to identify publications. A MEDLINE® search was conducted with the search term "sofosbuvir" and all studies examining efficacy and harms of sofosbuvir were included regardless of design. Editorials, letters, and commentaries were excluded. Studies were also initially excluded if they were unpublished or presented in abstracts or slides since details about study design and patient characteristics were not available. However, after peer review comments were received, additional studies available in abstract form only and unpublished studies from the information submitted by the manufacturer for FDA review were included. Due to insufficient information within these documents, formal methodological quality assessment was not performed on abstracts or unpublished trials.

The search for relevant clinical practice guidelines included the following sources: the United Kingdom National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), USPSTF, Institute for Clinical Systems Improvement (ICSI), and the

Australian Government National Health and Medical Research Council (NHMRC), Veterans Affairs guidelines, and gastroenterology and hepatology professional organizations.

Quality and Applicability Assessment

All identified published studies were included for review. Three reviewers rated the quality (risk of bias or internal validity) of each study as well as criteria to assess the risk for biased inferences from study results (external validity or applicability) due to factors such as inappropriate comparator or outcome for the Key Questions raised in this report. Several studies presented in abstracts and slides were later summarized, based on requests from external reviewers, but were not quality rated.

A checklist was adapted from those used by NICE, SIGN, and the Drug Effectiveness Review Project (DERP) for risk of bias (internal validity). Reviewers used a checklist based on criteria proposed by Montori (2004) to address potential biases in inferences made from study results for questions posed in this report (external validity). Finally, conflicts of interest and study funding were noted. Disagreements were resolved by discussion and studies received an overall quality rating that incorporated both risk of bias related to study results and applicability of study results to questions in this report (Appendix D).

Table 4. Critical Appraisal and Summary Judgment

Author, Year (Trial)	How well was the study done to minimize bias in study design? (Good, Fair, Poor)	How well did the study respond to the questions of this report? (Good, Fair, Poor)	Overall Study Quality (Good Fair, Poor)
Gane, 2013 (ELECTRON)	Poor	Poor	Poor
Jacobson, 2013a (Study 1) (POSITRON)	Poor	Poor	Poor
Jacobson, 2013a (Study 2) (FUSION)	Poor	Poor	Poor
Kowdley, 2013 (ATOMIC)	Poor	Poor	Poor
Lawitz, 2013 (Lancet)	Poor	Poor	Poor
Lawitz, 2013 (NEJM) (Study 1) (NEUTRINO)	Poor	Poor	Poor
Lawitz, 2013 (NEJM) (Study 2) (FISSION)	Poor	Poor	Poor
Osinusi, 2013	Poor	Poor	Poor

Author, Year (Trial)	How well was the study done to minimize bias in study design? (Good, Fair, Poor)	How well did the study respond to the questions of this report? (Good, Fair, Poor)	Overall Study Quality (Good Fair, Poor)
(Study 1)			
Osinusi, 2013 (Study 2)	Poor	Fair	Poor
Rodriguez-Torres, 2013	Poor	Poor	Poor

Two raters independently rated the quality of the guidelines using a checklist adapted Appraisal of Guidelines Research & Evaluation (AGREE) instrument. Disagreements were resolved by discussion. For guidelines to be considered evidence-based, the following criteria had to be met: systematic search for studies; study selection criteria clearly described; quality of individual studies and overall strength of evidence assessed; methods for formulating recommendation clearly described; benefits/side effects/risks considered; explicit link between evidence and recommendations; external review; funding source and member conflict of interest managed so as not to influence recommendations.

Peer Review

The draft report was peer reviewed by four experts representing the fields of pharmacology, hepatology, primary care, clinical epidemiology and health policy. Potential reviewers were asked to declare any significant financial or intellectual conflicts of interest. None of the experts who completed the standardized peer review form reported conflicts of interest. A table of de-identified peer reviewer comments, along with their disposition, was developed and a final version of this report was prepared by the authors.

Findings

Seven publications addressing the effectiveness and harms of sofosbuvir (Gane 2013; Jacobson 2013a; Kowdley 2013; Lawitz 2013a; Lawitz 2013b; Osinusi 2013; Rodriguez-Torres 2013) were identified. These seven publications described ten studies, with three articles (Jacobson 2013a; Lawitz 2013b; Osinusi 2013) describing two studies each. In addition, three studies cited in the FDA review which have not been published were reviewed and data from these trials was included in the appendices where appropriate (Mishra 2013). Three abstracts presented at two conferences on the unpublished COSMOS trial of a sofosbuvir and simeprevir treatment regimen were also reviewed and are described below (Jacobson 2013b; Lawitz 2014; Sulkowski 2014).

Full study descriptions are offered in Appendix C titled Evidence Tables. The evidence tables give detailed information about each study, including design, sample size, inclusion and

exclusion criteria, patient characteristics, the drug regimen and comparator employed, the primary outcomes reported, and study limitations. In addition, Appendix A presents response and relapse rates by study, and Appendix B breaks down study populations by important characteristics (i.e., HCV genotype, prior treatment experience, proportion of male and Caucasian subjects in study, and proportion of subjects with cirrhosis or bridging fibrosis). A table summarizing the findings from the detailed critical appraisal assessment conducted on each of these studies is presented in Appendix D. This report identified 53 studies registered on ClinicalTrials.gov, of which 15 were marked as completed. Of the 15 trials marked as completed, only four trials had results posted on ClinicalTrials.gov.

The only guideline that addressed the use of sofosbuvir is the 2014 AASLD publication.

Treatment Effectiveness

Overview – Published Studies

Of the ten published studies, there was one placebo controlled trial (Jacobson 2013a, POSITRON trial) and one study that compared SOF + weight-based RBV to PEG + low dose RBV (Lawitz 2013b, FISSION trial). Both of these studies included patients with HCV genotypes 2 and 3. All other studies were designed to refine drug dose, drug combination or duration of treatment. Nine studies enrolled patients with HCV-1 (total n=889), five included those with HCV-2 or HCV-3 (total n=1060), and two studies also included patients with HCV-4, -5, or -6 (total n=41).

Studies tended to include populations with favorable prognostic factors. About 10% of total enrolled populations were African or African American. Slightly over 13% had cirrhosis. No subjects with concurrent hepatitis B or HIV infections were included among the published studies. However, one study of HCV/HIV co-infected patients (Mishra 2013, PHOTON-1 trial) was included in the FDA review and available details of the study are described below.

All studies were rated as having a high risk of bias. No study was judged to have good applicability, and only the National Institutes of Health (NIH) sponsored study by Osinusi (2013) was rated as having fair applicability. The overall summary judgment for each of the published studies yielded a rating of poor. Only one of 10 published studies used a comparator that would answer the key clinical question raised in this report – do the new sofosbuvir drug regimens have better clinical outcomes and fewer harms than the current standard of care? In other words, do the sofosbuvir trials compare the current treatment (see Table 2) to the newly recommended sofosbuvir regimens (see Table 3)? These nine published studies, as well as the three unpublished trials included in the FDA review, were single arm non-comparative studies, placebo controlled, or dose or duration varying studies that did not have a meaningful comparator. The outcomes of these studies (e.g., SVR12, SVR24, harms) may be strongly

influenced by the characteristics of the patients in the studies, many of whom had characteristics associated with better outcomes (e.g., Caucasian, lower viral load at baseline, no active or excessive alcohol use, low rates of cirrhosis, other comorbid conditions such as cardiac disease). The one study which did compare the sofosbuvir regimen to the standard PEG and RBV treatment used a low dose of RBV (800mg) rather than weight-based RBV (1000 to 12000 mg depending on weight) which is the current standard of care. Neither this comparator nor the placebo controlled trial were appropriate study designs for answering the questions raised by this report.

No study of sofosbuvir in HCV-1 populations compared the drug to current standard of care, which is triple therapy including PEG-INF + RBV with boceprevir or telaprevir. Most studies were open label and all but one (Osinusi 2013) were funded and controlled by the drug's manufacturer. Most study arms included few patients, especially among subgroups of particular interest to public payers. Duration of follow-up was limited with no study reporting primary outcomes at more than 24 weeks after the end of treatment. Most studies were multi-centered, and eight studies enrolled 10 or fewer patients per site. None of these studies reported results by study center.

Response rates tended to vary by the underlying prognostic factors of the population (i.e., genotype, presence of cirrhosis, prior treatment status), sample size, and study characteristics. Response rates from the published studies, using SVR12 as the outcome measure, ranged from 10% to 89% for patients with HCV-1, 82% to 95% for HCV-2, and 30% to 84% for patients with HCV-3 (Appendix A and B). Few studies reported SVR24, and among the eight study arms reporting both SVR12 and SVR24, the differences in these response rates ranged from 0% to 7%.

Not all studies reported relapse rates and those that did used various measures of "relapse." Relapse is defined as a patient achieving HCV RNA less than the lower limit of quantitation (LLOQ) or the lower limit of detection (LLOD) at the last measurement on treatment but subsequently having a HCV RNA greater than or equal to LLOQ or LLOD post treatment. The FDA analysis (Mishra 2013) as well as the FISSION, NEUTRINIO, POSITRON, and FUSION studies (Jacobson 2013a; Lawitz 2013b) all defined the LLOQ as less than 25 IU/mL. The ELECTRON study (Gane 2013) used a measure of LLOD of less than 15 IU/mL while the NIH study (Osinusi 2013) measured both LLOQ and LLOD, but the thresholds varied based on the assay used. Osinusi (2013) specified that when using the Abbot Molecular assay, the LLOQ should be less than 12 IU/mL and the LLOD less than 3 IU/mL, but when using the COBAS TaqMan assay, the LLOQ should be less than 43 IU/mL and LLOD less than 12 IU/mL. The FDA review (Mishra 2013) did not specify which assay was used to determine LLOQ, but Gane (2013), Jacobson (2013a), and Lawitz (2013) all used the COBAS TaqMan assay.

In those studies that did report relapse rates, some reported only on the basis of per-protocol analysis (patients completing treatment only) and did not account for losses to follow-up. Relapse rates ranged from 5% in treatment naïve genotype 2 patients treated with SOF + RBV for 12 weeks, (Jacobson 2013a, POSITRON; Lawitz 2013b, FISSION) to 90% in treatment experienced genotype 1 patients treated with the interferon-free SOF + RBV 12 week regimen (Gane 2013). For the FDA approved treatment regimens, relapse rates were 4% to 8.6% for genotype 1 patients treated with SOF + PEG + RBV for 12 weeks (Lawitz 2013a; Lawitz 2013b) and 28% for genotype 1 patients treated with the interferon-free SOF + RBV for 24 weeks (Osinusi 2013). For genotype 2 patients treated with SOF + RBV for 12 weeks, relapse rates ranged from 5% to 18% (Jacobson 2013a; Lawitz 2013b) and for genotype 3 patients treated with SOF + RBV for 24 weeks, the relapse rates was 14% (Mishra 2013).

Overview – Unpublished Studies Included in FDA Review

Three additional unpublished studies were identified. These three studies, VALENCE, PHOTON-1 and an unnamed trial in pre-transplant patients, were all on-going trials at the time of FDA review but were included in the FDA's efficacy and safety assessment.

The original protocol for VALENCE was as a placebo controlled trial of SOF + RBV for 12 weeks in patients with HCV genotypes 2 or 3. Early results, primarily from the FUSION trial, however, indicated that SVR12 rates in genotype 3 patients improved with longer duration of treatment, and so the protocol for VALENCE was redesigned to treat all genotype 2 patients with SOF + RBV for 12 weeks, and offer genotype 3 patients SOF + RBV for 24 weeks. The SVR12 rate for genotype 3 patients in the trial who took 12 weeks of treatment was 56%, which increased to 93% with 24 weeks of treatment. The relapse rate decreased from 40% to 5%. The VALENCE trial led the FDA to approve a genotype 3 treatment regimen of SOF + RBV for 24 weeks (Mishra 2013).

The PHOTON-1 trial was an on-going, three arm trial of SOF + RBV therapy in patients co-infected with HIV. The first arm included treatment naïve patients with genotype 2 or 3 who received 12 weeks of therapy. The SVR12 rate for the genotype 2 patients was 88% (23/26) and 67% (28/42) for genotype 3. The second arm included treatment experienced patients with genotypes 2 and 3, and they received 24 weeks of treatment. The SVR12 rates were 93% for genotype 2 (14/15) and 92% (12/13) for genotype 3. The third arm included treatment naïve genotype 1 patients who received SOF + RBV for 24 weeks, and the SVR12 response was 76% (87/114). Genotype 1a responded better with 82% achieving SVR12 (74/90) compared to genotype 1b where only 54% (13/24) achieved SVR12 (Mishra 2013).

The FDA also included data from an unnamed, on-going, open-label trial evaluating whether administering SOF + RBV to pre-transplant patients would prevent HCV recurrence post-

transplant (trial number P7977-2025). The trial reported incomplete data on a total of 61 patients (Mishra 2013). The preliminary results are presented in Appendix C.

All three of these unpublished trials were incomplete at the time of FDA review and had not been published in a peer reviewed publication as of April 2014. Available details of the trials are included in report charts and tables, but the studies were not quality assessed or reviewed due to lack of information.

Summary of Evidence on FDA Approved Treatment Regimens

Of the 11 studies identified which evaluated sofosbuvir treatment in general populations (ten published studies and the unpublished VALENCE trial, excluding the HIV and pre-transplant studies), only six studies tested one of the four FDA approved treatment regimens. These studies are summarized in Table 5 below.

Table 5. FDA Approved Treatment Regimens and Response Rates

Genotype	Treatment	SVR12	Relapse	# of Studies (Study name)	Study N
HCV-1	SOF+PEG+RBV 12 w	89%	4% to 8.6%	2 (NEUTRINO, ATOMIC)	379
	SOF+RBV 24 w	68%	28%	1 (Osinusi, NIH Study)	60
HCV-2	SOF+RBV 12 w	82% to 95%	5% to 18%	4 (FISSION, FUSION, POSITRON, VALENCE)	1051
HCV-3	SOF+RBV 24 w	84%	14%	1 (VALENCE)	250

Note that for both genotype 3 and the interferon-free regimen for genotype 1, the evidence base consists of one study and the total number of patients with reported data is 60 (for genotype 1 patients treated with the interferon-free regimen) and 250 (genotype 3 regimen). The evidence for the genotype 1 SOF + PEG + RBV 12-week treatment is primarily based on the NEUTRINO study which tested the regimen on a total of 327 patients. Fifty-two additional patients also received that treatment regimen in the ATOMIC study that evaluated duration ranges. The genotype 2 regimen has the most documented evidence with the SOF + RBV 12-

week treatment being tested on 1051 patients in four trials, and the SVR12 rate varied from 82% to 95%.

Adverse Events

The FDA compiled reports of adverse events from four trials (FISSION, FUSION, NEUTRINO, POSITRON) compiling a data-set of 1305 patients treated with sofosbuvir and RBV, with or without PEG, or placebo. There were no treatment-related deaths reported.

Approximately 78% of patients receiving placebo, 88% of patients on SOF + RBV treatment and 95% of patients receiving PEG + SOF + RBV reported a side effect from treatment. The most common side effects were fatigue, anemia, nausea, rash, headache, insomnia, and pain (Mishra, 2013, p. 115).

Discontinuation of therapy due to adverse events was relatively low in these studies. In the combined safety analysis, the FDA reported withdrawal rates of approximately 1.4% in patients receiving SOF + RBV for 12 weeks (eight out of 566 patients). This compares to 4.2% of patients receiving placebo (three out of 71 patients), 1.5% of patients receiving SOF + PEG + RBV for 12 weeks (five out of 327 patients), and 10.7% of patients on PEG + RBV alone (26 out of 243 patients) (Mishra 2013, p. 109).

Fifty-one treatment-emergent, serious adverse events (SAE) occurred in 34 patients (2.6%). The events by treatment regimen are summarized in Table 6 below.

Table 6. Total Number of Patients with Serious Adverse Events

Regimen	Placebo 12 wks	SOF+RBV 12 wks	SOF+RBV 16 wks	PEG+SOF+RBV 12 wks	PEG+RBV 24 wks
N	71	566	98	327	243
Number of pts w/ SAE	2 (2.8%)	22 (3.9%)	3 (3.1%)	4 (1.2%)	3 (1.2%)
Number of SAEs	3	31	3	8	6
SAES (# of events)	Pancreatitis (1); bile duct stone (1); bronchitis (1);	Anemia (1); abdominal pain (1); non-cardiac chest pain (1); pyrexia (2); chest pain (1); drug withdrawal syndrome (1); edema peripheral (1); portal vein thrombosis (1); allergy	Non-cardiac chest pain (1); overdose (1); suicide attempt (1);	Anemia (1); leukopenia (1); abdominal pain (1); non-cardiac chest pain (1); pyrexia (1); cryoglobulinaemia (1); spinal compression	Atrioventricular block (1); infection (1); clavicle fracture (1); rib fracture (1); breast cancer in situ (1); pneumothorax

Regimen	Placebo 12 wks	SOF+RBV 12 wks	SOF+RBV 16 wks	PEG+SOF+RBV 12 wks	PEG+RBV 24 wks
		to arthropod sting (1); hypersensitivity (1); cellulitis (2); abdominal abscess (1); osteomyelitis chronic (1); urinary tract infection (1); overdose (1); spinal compression fracture (1); fall (1); injury (1); road traffic accident (1); toxicity to various agents (1); upper limb fracture (1); hypoglycemia (1); hepatic neoplasm malignant (3); basal cell carcinoma (1); abnormal behavior (1); COPD (1); eczema (1)		fracture (1); laryngeal cancer	(1)

Adapted from Mishra 2013, p.101.

The other studies reviewed reported similar high rates of mild to moderate side effects such as fatigue, nausea and headache. No significant patterns in serious adverse events were noted.

In assessing the risk of adverse events, it is important to note that the studies on sofosbuvir were small, included populations that were healthier than the general hepatitis C population, were of short duration and had limited follow-up. In many of the studies, the manufacturer was responsible for recording and reporting adverse events. In general, reporting of adverse events is often incomplete and discrepancies between clinical trial reports and publications are common (Hartung 2014). All of these factors would lead to a bias in under-representing the true nature of adverse events.

Long-range studies and expanded use may reveal a different harms profile as adverse events associated with new medications often appear only after general clinical use (Prasad 2013). When the protease inhibitors BOC and TVR were approved, studies showed 9% to 14% of patients experienced serious side effects. Post-approval studies in Europe found the rate of serious adverse events to be significantly higher, with 38% of patients treated with boceprevir

experiencing an adverse event and 48.6% of those receiving telaprevir developing a serious side effect (Hezode 2012).

While the studies reviewed here do not report significant adverse events associated with sofosbuvir treatment, larger and longer term studies would be needed to accurately describe the drug's harms profile.

Subgroup Differences in Effectiveness and Harms

The 11 studies reviewed did not report effectiveness or harms data separately for many relevant subgroups (e.g., by race, gender, IL28B genotype). These studies did suggest that sofosbuvir treatment regimens are similar to interferon-based treatment regimens in that the treatment is more effective in patients with genotype 2 and 3 than in patients with genotype 1, patients with genotype 2 do better than patients with genotype 3, patients with the IL28B CC genotype fare better, and patients without cirrhosis are more likely to achieve SVR12 than those with cirrhosis.

Additional Studies

Due to the rapidly changing environment and information surrounding treatment options for HCV, several peer reviewers suggested including the COSMOS study which tests a treatment regimen of both simeprevir and sofosbuvir for HCV genotype 1 patients. The study remains unpublished.

COSMOS (Sofosbuvir [SOVALDI®] and Simeprevir [OLYSIO™])

Simeprevir (OLYSIO™) is a NS3/4A protease inhibitor jointly developed by Janssen Research & Development, LLC and Medivir AB. In October 2013, the FDA approved simeprevir for the treatment of HCV genotype 1 patients in combination with PEG and RBV.

In November 2013, preliminary results from the COSMOS trial were presented at the annual meeting of the American Association for the Study of Liver Diseases (AASLD). The COSMOS trial includes 167 patients divided into two cohorts, each with four study arms, and treats HCV genotype 1 patients with 400 mg SOF and 150 mg SMV with or without weight-based ribavirin for 12 or 24 weeks. The 2013 AASLD presentation reported data for the 80 patients in Cohort 1 who were all non-responders to prior treatment with PEG and RBV and who had Metavir fibrosis scores of F0 to F2. The preliminary results were published in *Hepatology* in December 2013 (Jacobson 2013b).

In April of 2014, during the European Association for the Study of the Liver (EASL) conference, two additional presentations on COSMOS trial data were made with the abstracts published on the conference website. The first abstract (Sulkowski 2014) was presented as a "subgroup analysis" of COSMOS, but essentially repackaged the data previously presented at the 2013

AASLD conference which was published in *Hepatology* (Jacobson 2013b). The data is from Cohort 1 (HCV genotype 1 patients with prior non-response to therapy) but the EASL presentation excludes "five patients withdrawn for non-virologic failure" and thus the reported SVR12 rates increase significantly in one treatment group (SMV + SOF + RBV for 24 weeks, see Table 7 below). The second abstract (Lawitz 2014) reported SVR12 results from Cohort 2 patients who were either treatment naïve or prior null responders with Metavir scores of F3 to F4. The SVR12 results are summarized in Table 7 below.

Table 7. COSMOS Trial – SVR12 Results

COSMOS SVR12 Results Presented at AASLD and EASL Conferences					
Cohort	**Citation**	**SOF + SMV 12 weeks**	**SOF+SMV+RBV 12 weeks**	**SOF + SMV 24 weeks**	**SOF+SMV+RBV 24 weeks**
1	AASLD 2013 (Jacobson 2013b)	92.9% (13/14)	96.3% (26/27)	100% (14/14)	79.2% (19/24)
	EASL 2014 (Sulkowski 2014)	92.9% (13/14)	96.3% (26/27)	100% (13/13)	90.5% (19/21)
2	EASL 2014 (Lawitz 2014)	92.9% (13/14)	92.6% (25/27)	100% (16/16)	93.3% (28/30)

Adverse events occurred in approximately 77% of individuals in both cohorts. For Cohort 1, Jacobson (2013b) reported that four patients (2.4%) discontinued treatment due to adverse events while Sulkowski (2014) reported two discontinuations due to adverse events. For Cohort 2, Lawitz (2014) reported two discontinuations (2.3%). Jacobson (2013b) reported three serious adverse events (1.8%) in Cohort 1. However, Sulkowski (2014) reported no serious adverse events. Lawitz (2014) reported four serious adverse events but did not provide details.

The abstracts do not present sufficient information to assess adverse events fully or to judge study quality.

No other published studies on the SOF and SMV combination treatment have been identified. In total, there is data on this treatment regimen in 58 genotype 1 patients, 28 of whom had a 12-week course of treatment and 30 who received the drugs for 24 weeks.

Drug Research Pipeline

As of March 7, 2014, there were 53 studies registered on ClinicalTrials.gov that include the drug sofosbuvir. The majority of the studies are similar to the studies reviewed in this report in that they compare different doses of sofosbuvir or vary duration of treatment in defined populations. No registered studies compare a sofosbuvir-based regimen with current standard

of care (e.g., interferon based double or triple therapy). All but four of the studies are sponsored by sofosbuvir's manufacturer, Gilead, and the other trials are sponsored by Bristol Myers (three trials combining sofosbuvir and daclatasvir) and the University of Florida with Vertex Pharmaceuticals (sofosbuvir combined with telaprevir).

Twenty-two of the registered studies test regimens that combine sofosbuvir with other new DAAs. Most significantly, the manufacturer has registered 15 trials of a sofosbuvir/ledipasvir fixed dose combination (FDC) pill with or without ribavirin in all genotypes. These trials do not include interferon. The manufacturer has also registered four trials combining sofosbuvir treatment with unnamed drugs identified as GS-9669, GS-9938, and GS-5816.

Several trials address specific populations, including HIV co-infection (one completed study, not yet published and two studies in progress), patients with renal insufficiency, pre and post-liver transplant, and cirrhosis. No trials examine sofosbuvir, interferon and ribavirin in genotype 1 patients who have previously failed treatment. There are four trials that administer the sofosbuvir/ledipasvir FDC with or without ribavirin to genotype 1 patients who have failed treatment. Those trials are scheduled for completion between July and December 2014.

In summary, there are no studies registered in ClinicalTrials.gov which compare sofosbuvir-based treatment to the current standard of care, there is no forthcoming evidence on sofosbuvir, interferon, and ribavirin treatment in genotype 1 patients who have failed previous treatment, and there are no registered studies being conducted by any parties other than pharmaceutical companies.

Private Payer Policies

A review of Center core policy sources and references from the California Technology Assessment Forum draft report (Tice 2014) identified six private payer policies on sofosbuvir: Aetna, Anthem/Express Scripts, Caremark/CVS, Cigna, Health Net, and Humana. Copies of these policies are included in Appendix E. Four of the policies cover sofosbuvir for all FDA approved indications, although three payers require evidence of compensated liver disease and Humana requires that patients with genotype 1 have previously failed treatment with triple therapy or have documented contraindications to interferon therapy. Cigna has published a prior authorization form but does not have coverage criteria publicly available. The private payer policies are summarized in Table 8 below.

Table 8. Private Payer Policies

Payer	Prior Authorization	Approved for all FDA Indications	Notes
Aetna	Yes	Yes	Allows for simeprevir and sofosbuvir

Payer	Prior Authorization	Approved for all FDA Indications	Notes
			combination treatment for genotype 1 PEG ineligible or non-responder
Anthem/Express Scripts	Yes	Yes	Requires compensated liver disease including cirrhosis
Caremark/CVS	Yes	Yes	Excludes ESRD, decompensated cirrhosis, post liver transplant, or significant or unstable cardiac disease
Cigna	Yes	Unclear	PA form requests information but does not list approval criteria
Health Net	Unclear	Yes	Requires liver biopsy showing fibrosis Metavir score ≥ 2 or Ishak score ≥ 3 Policy states that treatment is not authorized for "treatment regimen that patient who has failed therapy with an NS3/4A protease inhibitor (e.g., boceprevir, simeprevir, telaprevir)." Not authorized for post-liver transplant Explicitly excludes simeprevir and sofosbuvir combination treatment
Humana	Yes	No	Requires compensated liver disease Genotype 1 without HIV or HCC requires prior treatment failure with PI triple therapy Approved for all other FDA indications

Abbreviations: ESRD – end-stage renal disease; HIV – human immunodeficiency virus; HCC – hepatocellular carcinoma; PA – prior authorization; PI – protease inhibitors

Note: Private payer policies state coverage subject to individual member benefit contracts.

Guideline Assessment

The only identified guideline addressing the use of sofosbuvir is published by the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) Hepatitis C Guidance (AASLD 2014). The AASLD/IDSA hepatitis C guidance was published in January 2014 and includes 27 recommended treatment regimens based on HCV genotype, prior treatment, co-morbid conditions, and nine alternative treatment regimens. All 27 recommended regimens include sofosbuvir except in patients with severe renal impairment.

When the guideline was published, the authors noted that three sections would be “coming soon” including:

- In whom and when to initiate treatment;
- Monitoring patients who are on or have completed therapy; and
- Management of acute HCV infection.

As of May 1, 2014, the additional sections had not been published. The guideline is available on a dedicated website (http://www.hcvguidelines.org).

The overall methodologic quality of the guidance was poor (see Table 9 below). Two areas raised the greatest concern. First, there were no assessments of risk of bias (quality) for individual studies or of the overall strength of the evidence cited for each recommendation. The published studies cited in the AASLD/IDSA guidance as supporting the efficacy of sofosbuvir are described in other sections of this report. As noted above, all of the 10 published studies (Gane 2013; Jacobson 2013a; Kowdley 2013; Lawitz 2013a; Lawitz 2013b; Rodriguez-Torres 2013; Osinusi 2013) were given a poor quality summary rating. Second, there is substantial risk of conflict of interest influencing the recommendations from both individual panel members and funding sources. For example, four of the five panel chairs had financial relationships with Gilead, as did 15 of the 21 panel members. Although members were given the "opportunity" to divest and recuse themselves from discussions or be recused by the chair, there was no description of when or how this occurred. More important, the International Antiviral Society-USA (IAS-USA) was the collaborating partner for development of the guidance. It was "responsible for providing expertise and managing the [p]anel and the [g]uidance development process" (AASLD 2014, p. 3) and one of the five panel chairs was from this society. Funding for the IAS-USA is primarily from the pharmaceutical industry including Gilead.

Table 9. AASLD/IDSA Hepatitis C Guidance Quality Assessment*

Category	Rating
Primary Criteria	
Rigor of development: Evidence	Poor
Rigor of development: Recommendations	Poor
Editorial independence	Poor
Secondary Criteria	
Scope and purpose	Fair
Stakeholder involvement	Fair
Clarity and presentation	Fair
Applicability	Poor

Category	Rating
Overall rating	**Poor**

*Checklist adapted Appraisal of Guidelines Research & Evaluation (AGREE) instrument. Each category rated as good, fair or poor by two raters who were consistent in all ratings. To be considered evidence-based, none of the primary criteria should receive a poor rating.

In summary, the ASSLD/IDSA guidance was found to be of poor methodological quality, as its findings were based on poor-quality evidence and the authors and sponsors of the guidance had multiple and significant conflicts of interest.

Who to Treat and When to Treat

The primary goal of treating patients with chronic HCV infection is to prevent long-term complications including cirrhosis (compensated and decompensated), HCC, and mortality. Hepatitis C is a slowly progressive disease and current treatments have significant side effects making it difficult to determine who to treat and when (Davis 2010). The AASLD and others suggest using the following guiding principle in selecting patients for treatment – *antiviral treatment should be considered in patients who are at greatest risk of progressing to cirrhosis or serious hepatic complications from HCV (e.g., decompensated cirrhosis, HCC, death) or extra hepatic complications such as cryoglobunimia* (AASLD 2009; SIGN 2013; Veterans Health Administration Pharmacy Benefits Management 2014). Ongoing trials involving new direct acting agents may clarify treatment choices in the next one to two years.

In general, patients at greatest risk of progressing to cirrhosis have detectable HCV-RNA and liver histology demonstrating fibrosis as defined by Metavir fibrosis stage 2 or greater (portal fibrosis with few septa, see Table 10 below). In fact, the current AASLD-IDSA guidance states that "it may be advisable to delay treatment for some patients with documented early fibrosis state (F 0 to 2), because waiting for future highly effective, pangenotypic, DAA combinations in INF-free regimens may be prudent" (AASLD 2014, p.31). Other risk factors for progression are listed in Table 11 and mirror the factors predicting response to treatment (Table 12) (AASLD 2009; Chou 2012; Freeman 2001; Thein 2008; Yee 2012). These factors may play an additional role in identifying patients most likely to benefit from treatment. Patients with compensated cirrhosis (total serum bilirubin less than 1.5 g/dL, INR less than or equal to 1.5, serum albumin greater than 3.4 g/dL, platelet count greater than or equal to 75,000/mm^2, no evidence of ascites or hepatic encephalopathy) are at risk of progressing to decompensation, HCC, or death.

Table 10. Metavir Fibrosis Scores

Score	Description
F0	No fibrosis
F1	Portal fibrosis without septa

Score	Description
F2	Portal fibrosis with few septa
F3	Numerous septa without cirrhosis
F4	Cirrhosis

Table 11. Risk Factors for Progression of Hepatic Fibrosis

Risk Factor for Progression of Hepatic Fibrosis
Detectable HCV RNA
Hepatic fibrosis greater than stage 1*
Male sex
Obesity
Hepatic steatosis
Heavy alcohol use
Advanced age
Elevated serum alanine transaminase
Greater hepatic inflammation

*Metavir fibrosis score 1: portal fibrosis without septa formation

Table 12. Factors Predicting Response to Treatment for HCV

Major Predictors
Viral genotype other than genotype 1
Pretreatment viral load less than 600,000
Other Predictors
Female sex
Age less than 40 years
Non-Black race
Absence of bridging fibrosis or cirrhosis on liver biopsy
Body weight less than or equal to 75 kg
Absence of insulin resistance or metabolic syndrome
Elevated alanine aminotransferase (ALT) levels (3x higher than the upper limit of normal)
IL28B genotypes CC

Once the decision is made to treat patients with antiviral agents, the next step is to consider who to treat with the current standard treatment and who to treat with regimens containing sofosbuvir. The recent AASLD/IDSA guidance on simeprevir and sofosbuvir (AASLD/IDSA 2014)

and other organizations (i.e., Veterans Health Administration Pharmacy Benefits 2014) *recommend against using sofosbuvir as monotherapy*.

The inclusion and exclusion criteria from published studies (Gane 2013; Jacobson 2013a; Kowdley 2013; Lawitz 2013a; Lawitz 2013b; Osinusi 2013; Rodriguez-Torres 2013) may be useful in selecting patients who are more likely to have response rates closer to those reported in these studies. It is important to note that of the 10 currently published studies and the three trials added in FDA review, only two are comparative (Jacobson [NEJM] 2013a, Lawitz [NEJM] 2013). These two studies only enrolled *patients with genotype 2 and 3*. Table 13 lists the exclusion criteria from the published trials. Six of the 10 studies excluded patients with cirrhosis. The presence or absence of cirrhosis was usually based on liver biopsy within three years of trial entry, and liver biopsy is currently the standard for confirming the degree of fibrosis (Bain 2004; Imbert-Bismut 2001; Parkes 2006). In the four studies including patients with cirrhosis, 15% to 35% percent of patients had cirrhosis, and none had decompensated cirrhosis (Jacobson [NEJM] 2013a; Lawitz [NEJM] 2013).

Table 13. Patient Exclusion Criteria from Published Sofosbuvir Trials

Exclusion Criteria
Age less than 18 years
HIV or HBV co-infection
Significant alcohol or drug use within the past 12 months
Excessive current alcohol use
Significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, significant renal disease (estimated glomerular filtration rate less than 60mL/min)

Treatment Summary

Although the evidence base to support use of sofosbuvir presently is poor, some clinicians, policymakers, and payers may wish to develop interim treatment and coverage criteria. Potential criteria to guide the use of sofosbuvir that are consistent with current published studies are listed below with several factors to consider.

- Limit use to genotypes 2 and 3, until comparative trials are available for genotype 1.
- Do not use sofosbuvir as monotherapy.
- Limit use to patients who failed or did not tolerate current standard of care regimens or in whom PEG is contraindicated.
- Confirm degree of liver fibrosis or cirrhosis prior to authorizing treatment.
- Treat only patients at greatest risk of progressing to cirrhosis (e.g., Metavir fibrosis stage greater than or equal to 2 and additional factors increasing risk of progression to

cirrhosis [e.g., hepatic steatosis, men, older, elevated serum alanine transaminase, greater hepatic inflammation]).

- Consider use for patients with HIV or HBV co-infection or those post-liver transplant carefully until comparative trials are available.
- Exclude use in patients with alcohol or drug use within the past year, significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, renal disease (estimated glomerular filtration rate less than 60mL/min).
- Ensure that patients who start therapy are closely tracked to optimize full treatment and follow-up, including prevention of re-infection.

Overall Summary

Hepatitis C is estimated to affect between 1% and 2% of the US population. Although up to one-quarter of those infected can clear the virus spontaneously, in those remaining infected it can progress over the span of 10 to 30 years or more to cirrhosis, liver failure, HCC and death. The genotype HCV-1 accounts for about three-quarters of cases in the US. The current standard of care for HCV-1 involves treatment with PEG, RBV and a protease inhibitor (boceprevir and telaprevir are approved for this indication in the US) and treatment of HCV-2 and HCV-3 involves use of PEG and RBV only. These interferon-based regimens have success rates of 40% to 80%, depending of the underlying characteristics of the patient being treated, including factors such as genotype, progression of liver disease, adherence to therapy, and presence of other comorbidities.

Current therapy options present substantial treatment burdens to patients ranging from side effects of drugs and complicated dosing schedules. Treatment options for HCV have been changing quickly since 2011 when protease inhibitors were first approved in the US. In December 2013, the FDA approved two new agents, sofosbuvir and simeprevir, under expedited “breakthrough” status designation which allowed the use of an intermediate trial endpoint (SVR12 instead of the previously required SVR24). There are at least two more DAAs expected to be approved in 2014 and there are other newer drugs in the development pipeline.

Although improved treatments for HCV are certainly desirable, the long course of disease progression also makes it incumbent upon policymakers and clinicians to make sure that treatments will be effective. Most currently infected patients have time available to wait for conclusive data on the effectiveness and harm profile of sofosbuvir or other new drugs before deciding on an optimal treatment regimen.

This rapid evidence review located 10 studies published in seven articles, although the majority of the studies were non-comparative and all but one was at high risk of bias. There were two

comparative studies of sofosbuvir treatment for HCV-2 and HCV-3 infection, but no published comparative studies for the treatment of HCV-1. Based on the usual standards of comparative effectiveness research, currently available studies do not provide sufficient evidence for the routine use of sofosbuvir-containing regimens for the treatment of hepatitis C infection. While initial, uncontrolled, response rates appear to be relatively high among carefully selected populations, response rates in "real world" populations are likely to be lower. Furthermore, there is evidence that relapse rates may be substantial, ranging from 5% to 28% even among patients who are fully treated with these regimens. Similarly, adverse effects have not been studied in large numbers of patients and among those with substantial other risk factors for harms. When the first two protease inhibitors began to be used in clinical practice, the risks of adverse events approximately tripled and there could be a similar concern with these even newer drugs as they are used in widespread clinical practice.

The recently published HCV treatment guideline published by AASLD and IDSA is of poor methodologic quality and does not adhere to international or US standards for guideline development. In addition, guideline authors had substantial and multiple conflicts of interest.

Sofosbuvir may eventually be shown to be a valuable treatment for hepatitis C. However, due to the lack of well-designed comparative studies, there is not yet clear evidence that this drug should be used routinely to treat patients. While awaiting full disclosure of existing research and the production of more and better evidence on sofosbuvir, policymakers may decide to not allow use of, or to allow very limited use of this drug. If limited use is contemplated, this report details factors to consider, such as limiting use to carefully selected HCV-2 and -3 infected individuals who are at great risk of shortly progressing to cirrhosis, and only as part of a regimen including RBV. Policymakers, clinicians, and patients should remain aware of upcoming drug research and carefully examine the quality of new research as it is made available.

In addition, the evidence gaps highlighted in this review may offer an opportunity for policymakers and clinicians to advocate for improved research and to contribute to a better evidence base for decision-making. Policymakers might consider the following activities:

- Require transparency about the research. Patients, clinicians, and policymakers need adequate information available in order to make good decisions about the safety, effectiveness, and place in treatment of sofosbuvir. True patient-centeredness requires the availability of all existing data in order for considered decisions to be made that respect patient autonomy. Public stewardship requires those same kind of data to make sure that patients are helped more than harmed and that the overall value of the treatment is worthwhile. As an example, most studies of sofosbuvir include SVR24 as a secondary outcome measure, but this information is not included in many publications.

Policymakers can encourage the FDA and ask the manufacturer directly to release this data.

- Policymakers can ask the NIH to fund and the FDA to demand truly comparative studies on this and other newer drugs for hepatitis C. Current trials do not answer the question of which therapy is best for which patient at which point in time during the disease course. Studies of these drugs should include populations that approximate the characteristics of publically insured patients including race, stage of disease, prior treatment history, and comorbid medical and behavioral health conditions.
- State policymakers may wish to cover sofosbuvir and other newer agents with the requirement of evidence development. Relatively simple data collection efforts may yield evidence more applicable to publically insured populations more rapidly than industry or federally funded research might. For example, if a state simply required submission of SVR24 as a condition of coverage, real-world data on this important outcome could be obtained in less than a year.

Appendix A. Treatment Response and Relapse Rates by Genotype and Specialized Studies

Genotype	Treatment	Response	Relapse[1]	Study
Treatment Response and Relapse Rates by Genotype				
Genotype 1	SOF + PEG + RBV 12 w	SVR12: 89% (260/291)	8.6% (28/326)[2]	NEUTRINO, Lawitz 2013, (NEJM)
	Interferon-free regimens			
	SOF + RBV 12 w (tx exp)	SVR12: 10% (1/10) SVR24: 10% (1/10)	90% (9/10)	ELECTRON, Gane 2013
	SOF + RBV 12 w (tx naïve)	SVR12: 84% (21/25) SVR24: 84% (21/25)	16% (4/25)	
	SOF + RBV 24 w	SVR12: 68% (17/25) SVR24: 68% (17/25)	28% (7/25)	NIH study, Osinusi 2013
	SOF + low-dose RBV (600mg) 24 w	SVR12: 48% (12/25) SVR24: 48% (12/25)	40% (10/25)	
Genotype 2	SOF + RBV 12 w	SVR12: 95% (69/73)	5% (4/73)	FISSION, Lawitz 2013, (NEJM)
		SVR12: 82% (33/39)	18% (7/39)	FUSION, Jacobson 2013a (NEJM)
		SVR12: 93% (101/109)	5% (5/107)	POSITRON, Jacobson 2013a (NEJM)
		SVR12: 93% (68/73)	7% (5/73)	VALENCE, Mishra (FDA) 2013 ***Unpublished study***
	SOF + RBV 16 w	SVR12: 89% (31/35)	11% (4/35)	FUSION, Jacobson 2013a

Genotype	Treatment	Response	Relapse[1]	Study
				(NEJM)
Genotype 3	SOF + RBV 12 w	SVR12: 56% (102/183)	40% (72/179)	FISSION, Lawitz 2013, (NEJM)
		SVR12: 30% (19/64)	66% (42/64)	FUSION, Jacobson 2013a (NEJM)
		SVR12: 61% (60/98)	38% (37/98)	POSITRON, Jacobson 2013a (NEJM)
	SOF + RBV 16 w	SVR12: 62% (39/63))	38% (24/63)	FUSION, Jacobson 2013a (NEJM)
	SOF + RBV 24 w	SVR12: 84% (210/250)	14% (34/249)	VALENCE, Mishra (FDA) 2013 ***Unpublished study***
Genotype 4	SOF + PEG + RBV 12 w	SVR12: 96% (27/28)	*Relapse rates were not separately reported by genotype. Overall relapse rate in study 8.6% (28/326)*	NEUTRINO, Lawitz 2013, (NEJM)
Treatment Response and Relapse Rates for HCV/HIV Co-infected Patients				
Genotype 1 (tx naïve)	SOF + RBV 24 w (***interferon-free regimen***)	SVR12: 76% (87/114)	22% (25/113)	PHOTON-1, Mishra (FDA) 2013 ***Unpublished study***
Genotype 2	SOF + RBV 12 w (tx naïve)	SVR12: 88% (23/26)	18% (12/67) (combines genotype 2/3)	
	SOF + RBV 24 w (tx exp)	SVR12: 93% (14/15)	7% (2/28) (combines genotype 2/3)	
Genotype 3	SOF + RBV 12 w (tx naïve)	SVR12: 67% (28/42)	18% (12/67) combines	

Genotype	Treatment	Response	Relapse[1]	Study
			genotype 2/3)	
	SOF + RBV 24 w (tx exp)	SVR12: 92% (12/13)	7% (2/28) (combines genotype 2/3)	
Treatment Response Sofosbuvir + Simeprevir Combination Study				
Genotype 1 **Cohort 1 (null response prior tx (PEG+RBV) Metavir score = F0-F2)**	SOF + SMV 12 w	SVR 12: 93% (13/14)	Relapse was unevenly reported in the abstracts Jacobson (2013b) reported that "3 pts in the C1/C2 12 w groups (± RBV) and 1 pt in the C1 24 w (+RBV) group" relapsed. Sulkowski (2014) reported that 3 pts in cohort 1 relapsed (tx regimen not specified) Lawitz (2014) reported that 3 pts relapsed in cohort 2 (tx regimen not specified)	COSMOS Jacobson 2013b Hepatology ***Published abstract only*** Sulkowski 2014 ***Conference presentation; excluded 5 pts included in Jacobson (2013b)***
	SOF + SMV + RBV 12 w	SVR12: 96% (26/27)		
	SOF + SMV 24 w	SVR12: 100% (14/14)		
	SOF + SMV + RBV 24 w	**SVR12: 79% (19/24)[3]**		
Genotype 1 **Cohort 2 – (null response to prior tx or tx naïve with Metavir Score F3-F4)**	SOF + SMV 12 w	SVR12: 92.9% (13/14)		Lawitz 2014 ***Conference presentation***
	SOF + SMV + RBV 12 w	SVR12: 92.9% (13/14)		
	SOF + SMV 24 w	SVR12: 92.9% (13/14)		
	SOF + SMV + RBV 24 w	SVR12: 92.9% (13/14)		

Abbreviations: Exp – experienced; NEJM – New England Journal of Medicine; NR – not reported; PEG – pegylated interferon therapy; RBV – ribavirin; unless otherwise specified, RBV refers to weight-based ribavirin, e.g. 1000 mg for weight < 75 kg and 1200 mg for weight ≥ 75 kg daily; SOF – sofosbuvir 400 mg daily; SMV – simeprevir 150 mg daily; SVR – sustained virologic response; tx – treatment; w – weeks

Notes

[1]Relapse is defined as a patient achieving HCV RNA < lower limit of quantitation (LLOQ) at the last measurement on treatment but subsequently having a HCV RNA ≥ LLOQ post treatment

[2]Relapse rate includes data on the 35 pts with HCV 4-6 as data was not separated out.

[3]A subsequent abstract presented at the April, 2014 European Association for the Study of the Liver (EASL) conference excluded "five patients withdrawn for non-virologic failure" and reported an SVR12 rate for this group of 90.5% (19/21) (Sulkowski 2014). No other SVR12 rates changed after excluding the patients.

Appendix B. Study Population Characteristics

Author, Year (Trial)	Study Design	HCV-1, Tx Naïve (n)	HCV-1, Prior Tx (n)	HCV-2 Tx Naïve (n)	HCV 2 , Prior Interferon Tx (n)	HCV-3, Tx Naïve (n)	HCV-3, Prior Interferon Tx (n)	HCV-2, Tx w/ Interferon Not an Option (n)	HCV-3, Tx w/ Interferon Not an Option (n)	HCV-4, 5 or 6 (n)	Male (n, %)	Caucasian (n, %)	C: Cirrhosis (n, %) F: Bridging fibrosis (n, %)
Gane, 2013 (ELECTRON)	Open label Largely a PEG regimen range study for HCV-2,3 and PEG sparing for HCV-1	25	10	18	---	42	---	---	---	---	58 (61%)	74 (78%)	---
Jacobson, 2013a (Study 1) (POSITRON)	Placebo control RCT INF tx contraindicated, unacceptable or prior discontinuation due to unacceptable AEs 12w SOF + RBV vs placebo	---	---	---	---	---	---	143	135	---	151 (54%)	254 (91%)	C: 68 (34%)
Jacobson, 2013a (Study 2) (FUSION)	Active control RCT No prior response to prior INF containing regimen Duration ranging study	---	---0	---	68	---	127	---	---	---	140 (70%)	174 (87%)	C: 44 (16%)

Author, Year (Trial)	Study Design	HCV-1, Tx Naïve (n)	HCV-1, Prior Tx (n)	HCV-2 Tx Naïve (n)	HCV 2 , Prior Interferon Tx (n)	HCV-3, Tx Naïve (n)	HCV-3, Prior Interferon Tx (n)	HCV-2, Tx w/ Interferon Not an Option (n)	HCV-3, Tx w/ Interferon Not an Option (n)	HCV-4, 5 or 6 (n)	Male (n, %)	Caucasian (n, %)	C: Cirrhosis (n, %) F: Bridging fibrosis (n, %)
Kowdley, 2013 (ATOMIC)	Open label RCT (Cohorts A and C) Duration ranging 12 vs 24w PEG + RBV	207	---	---	---	---	---	---	---	---	141 (68%)	[% black] 18 (9%)	F: 47 (14%)
Kowdley, 2013 (ATOMIC)	Open label NRS (Cohort B of ATOMIC with addition of NR HCV-4, 6 pts)	109	---	---	---	---	---	---	---	16	73 (58%)	[% black] 17 (14%)	See above: 23 of 47 pts with BF were in this group
Lawitz, 2013a (Lancet)	Dose finding placebo control RCT for HCV-1 and additional single group for HCV-2, 3; all tx naïve and non-cirrhotic	121	---	---	---	---	---	---	---	---	73 (60%)	97 (80%)	F: 5 (4%)
Lawitz, 2013a (Lancet)	Additional single group study with HCV-2,3	---	---	15	---	10	---	---	---	---	16 (64%)	20 (80%)	F: 0%
Lawitz, 201b3 (Study 1) (NEJM)	Open label, single group, tx naïve, predominantly HCV-1	291	---	---	---	---	---	---	---	35	209 (64%)	257 (79%)	C: 54 (17%)

Author, Year (Trial)	Study Design	HCV-1, Tx Naïve (n)	HCV-1, Prior Tx (n)	HCV-2 Tx Naïve (n)	HCV 2 , Prior Interferon Tx (n)	HCV-3, Tx Naïve (n)	HCV-3, Prior Interferon Tx (n)	HCV-2, Tx w/ Interferon Not an Option (n)	HCV-3, Tx w/ Interferon Not an Option (n)	HCV-4, 5 or 6 (n)	Male (n, %)	Caucasian (n, %)	C: Cirrhosis (n, %) F: Bridging fibrosis (n, %)
(NEUTRINO)													
Lawitz, 2013b (Study 2) (NEJM) (FISSION)	Open label non-inferiority RCT; tx naïve HCV-2, 3; 12w SOF + RBV vs PEG + RBV	3	---	137	---	359	---	---	---	---	327 (66%)	435 (88%)	100 (20%)
Osinusi, 2013 (Study 1)	Proof of concept(n=10) with HCV-1 and unfavorable tx characteristics	10	---	---	---	---	---	---	---	---	4 (40%)	1 (10%)	F: [Knodell HAI fibrosis score 3 to 4] 1 (10%)
Osinusi, 2013 (Study 2)	Open label RCT with HCV-1 and unfavorable tx characteristics	50	---	---	---	---	---	---	---	---	33 (66%)	7 (14%)	F: [Knodell HAI fibrosis score 3 to 4] 13 (26%)
Rodriguez-Torres, 2013	Blinded RCT; tx naïve with HCV-1; dose ranging	63	---	---	---	---	---	---	---	---	43 (68%)	57 (90%)	F: 4 (6 %)

Author, Year (Trial)	Study Design	HCV-1, Tx Naïve (n)	HCV-1, Prior Tx (n)	HCV-2 Tx Naïve (n)	HCV 2 , Prior Interferon Tx (n)	HCV-3, Tx Naïve (n)	HCV-3, Prior Interferon Tx (n)	HCV-2, Tx w/ Interferon Not an Option (n)	HCV-3, Tx w/ Interferon Not an Option (n)	HCV-4, 5 or 6 (n)	Male (n, %)	Caucasian (n, %)	C: Cirrhosis (n, %) F: Bridging fibrosis (n, %)
Unpublished Trial Included in FDA Review													
FDA (Mishra 2013) VALENCE	Open label trial; tx naïve with HCV 2 or 3 SOF + RBV for 12 w (HCV-2) SOF + RBV for 24 w (HCV 3)	---	---	91	---	317	---	---	---	---	250 (60%)	393 (94%)	C: 88 (21%)
TOTALS (from above trials)	n/a	879	10	261	68	728	127	143	135	51	n/a	n/a	n/a
Unpublished Trial Included in FDA Review on HCV and HIV Coinfected Patients													
FDA (Mishra 2013) PHOTON-1	Open label dose ranging study in patients **with HIV-1 diagnosis** Total n = Tx naïve HCV 2-3: SOF + RBV 12 w	114	---	26	24	42	17	---	---	---	185 (83%)	153 (69%)	C: 22 (10%)

Author, Year (Trial)	Study Design	HCV-1, Tx Naïve (n)	HCV-1, Prior Tx (n)	HCV-2 Tx Naïve (n)	HCV 2 , Prior Interferon Tx (n)	HCV-3, Tx Naïve (n)	HCV-3, Prior Interferon Tx (n)	HCV-2, Tx w/ Interferon Not an Option (n)	HCV-3, Tx w/ Interferon Not an Option (n)	HCV-4, 5 or 6 (n)	Male (n, %)	Caucasian (n, %)	C: Cirrhosis (n, %) F: Bridging fibrosis (n, %)
	Tx experienced HCV 2-3 or HCV 1 SOF + RBV 24 w												

Abbreviations: AEs – adverse events; HAI – histology activity index; HCV – hepatitis C virus; INT – interferon; n/a – not applicable; NR – not reported; NRS – not reported study; PEG – pegylated interferon therapy; RBV – ribavirin; unless otherwise specified, RBV refers to weight-based ribavirin, e.g. 1000 mg for weight < 75 kg and 1200 mg for weight ≥ 75 kg daily; RCT – randomized controlled trial; SOF – sofosbuvir 400 mg daily; tx – treatment; w – weeks

Appendix C. Evidence Tables

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
Gane, 2013	Open label Largely a PEG regimen range study for HCV-2, 3 and PEG sparing for HCV-1 N=95 *Group 1* n=10 *Group 2* n=9 *Group 3* n=10 *Group 4* n=11 *Group 5* n=10 *Group 6*	Inclusion • Age ≥ 19 • HCV RNA > 50,000 IU/mL • For groups 1 to 6, HCV-2 or 3 and tx naïve • For group 7, HCV-1, prior tx failure • For group 8, HCV-1, tx naïve Exclusion • Cirrhosis • HIV or HBV positive	*Group 1; Group 2; Group 3; Group 4; Group 5; Group 6; Group 7; Group 8* Male n (%) 8 (80) 5 (56) 5 (50) 9 (82) 4 (40) 5 (50) 7 (70) 15 (60) Race n (%) *White* 7 (70) 4 (44) 8 (80) 9 (82) 4 (40) 5 (50) 9 (90) 20 (80)	Intervention 8 arm trial, all pts rec'd SOF in different regimen Groups 1 to 6, all HCV-2 or 3 and tx naïve *Group 1* SOF 400 mg/d + weight based RBV/d for 12w *Group 2* SOF 400 mg/d + RBV for 12w + PEG 180µg/w for 4w *Group 3* SOF 400 mg/d + RBV for 12w + PEG 180µg/w	Outcomes • SVR 24 • Adverse events Findings **SVR 24** n (%, 95%CI) *Group 1* 10 (100, 69 to 100) *Group 2* 9 (100, 66 to 100) *Group 3* 10 (100, 69 to 100) *Group 4* 11 (100, 72 to 100) *Group 5* 6 (60, 26 to 88) *Group 6* 9 (90, 66 to 100)	Gilead sponsored, analyzed data and prepared final version of report Not a controlled trial as all pts rec'd SOF. 4 groups (2 HCV-2/3 and 2 HCV-1) did not also get PEG Small sample size, not designed to statistically test outcomes Race is reported only as percentage white with no

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	n=10 *Group 7* n=10 *Group 8* n=25		<u>Age</u> <u>mean (range)</u> 47 (36 to 53) 48 (29 to 66) 49 (30 to 62) 46 (37 to 57) 43 (22 to 58) 39 (19 to 54) 48 (30 to 58) 49 (22 to 69) <u>BMI</u> <u>mean (range)</u> 28 (24 to 36) 26 (21 to 32) 25 (18 to 33) 24 (21 to 28) 26 (18 to 39) 25 (21 to 35) 28 (20 to 36) 26 (19 to 38) <u>HCV RNA log_{10}IU/mL</u> <u>mean (range)</u> 6.7 (5.7 to 7.1) 6.6 (5.6 to 7.4)	for 8w *Group 4* SOF 400 mg/d + RBV for 12w + PEG 180µg/w for 12w *Group 5* SOF 400 mg/d for 12w *Group 6* SOF 400 mg/d + RBV + PEG for 8w *Group 7* HCV-1 with prior tx failure SOF 400 mg/d + RBV for 12w *Group 8* HCV-1 tx naïve SOF 400 mg/d + RBV for 12w	*Group 7* 1 (10, 0 to 45) *Group 8* 21 (84, 64 to 96) **Adverse events** n (%) *Grade 3 anemia* 17 (17.9%) *Grade 3 or 4 lymphopenia* 4 (4.2%) *Grade 3 or 4 neutropenia* 12 (12.6%) *Grade 3 leukopenia* 5 (5.3%) Authors state reduced hemoglobin levels more common in pts receiving PEG than those w/o,	further details

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			6.5 (5.5 to 7.2) 6.5 (5.2 to 7.3) 5.9 (4.6 to 7.4) 6.0 (4.3 to 7.3) 7.0 (5.6 to 7.5) 6.2 (4.4 to 7.2) HCV-2 (Groups 1 to 6) n (%) 4 (40) 3 (33) 4 (40) 4 (36) 3 (30) 0 HCV-3 (Groups 1 to 6) n (%) 6 (60) 6 (67) 6 (60) 7 (64) 7 (70) 10 (100)	Follow-up 24w post tx	but no statistical analysis	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			HCV-1a (Groups 7 to 8) n (%) 9 (90) 22 (88) HCV-1b (Groups 7 to 8) n (%) 1 (10) 3 (12) IL28B genotype n (%) *CC* 5 (50) 4 (44) 4 (40) 4 (36) 2 (20) 3 (30) 2 (20) 11 (44) *CT* 4 (40) 4 (44) 4 (40) 5 (45) 6 (60)			

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			6 (60) 5 (50) 12 (18) *TT* 1 (10) 1 (11) 2 (20) 2 (18) 2 (20) 1 (10) 3 (30) 2 (8) <u>Loss to follow-up</u> 1 pt, group 6			
Jacobson , 2013a (study 1) POSITRON study	Placebo control RCT Interferon tx contraindicated, unacceptable or prior discontinuation due to unacceptable	<u>Inclusion</u> • Age ≥ 18 • HCV-2 or 3 • HCV RNA ≥ 104 IU/mL • BMI ≥ 18 kg/m2 • Discontinuation of previous interferon tx due to AE OR ineligible for interferon tx OR declined interferon tx • Up to 20% with	*Placebo; Intervention* <u>Age</u> <u>mean (range)</u> 52 (28 to 67) 52 (21 to 75) <u>BMI</u> <u>mean (range)</u> 28 (20 to 43) 28 (18 to 53)	<u>Intervention</u> SOF 400 mg/d and RBV 1000 to 12000 mg/d for 12w <u>Comparator</u> Placebo <u>Follow-up</u> 24w post tx	<u>Outcomes</u> • SVR 4 post tx • SVR 12 post tx • Relapse • Adverse events <u>Findings</u> n (%) **SVR 4 post tx** *Intervention* 172/207 (83%), 204 returned for	Gilead sponsored, analyzed data and prepared final version of report 63 sites in US, Canada, Australia, New

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	AEs N=278 *Intervention* n=207 *Comparator* n=71	compensated cirrhosis • ECG w/o abnormalities • AAT ≤ 10 x ULN • AST ≤ 10 x ULN • Hb ≥ 12 g/dL for men and ≥ 11 g/dL for women • Albumin ≥ 3 g/dL • Direct bilirubin ≤ 1.5 x ULN • HbA1c ≤ 10% • Creatine clearance ≥ 60mL/min • INR ≤ 1.5 x ULN • No investigational drug w/i 30d • Contraception <u>Exclusion</u> • Prior exposure to a direct-acting anti-viral targeting HCV NS5B polymerase • Pregnant/nursing/pregnant partner • Other clinically significant chronic liver disease • HIV or HBV positive	<u>Male n (%)</u> 34 (48%) 117 (57%) <u>Race n (%)</u> *White* 66 (93%) 188 (91%) *Black* 4 (6%) 9 (4%) *Hispanic* 11 (15%) 19 (9%) <u>HCV-2 n (%)</u> 34 (48%) 109 (53%) <u>HCV-3 n (%)</u> 37 (52%); 98 (47%) <u>IL28B genotype n (%)</u> *CC* 29 (41%)	6 pts (2.9%) did not complete tx, 2 pts lost to follow-up	visit *Placebo* 0/71 (0%), 71 returned for visit **SVR 12 post tx** n (%, 95% CI) *Intervention* 161/207 (78, 72 to 83) (only 171/207 pts returned for 12w post follow-up) **Factors significantly associated with SVR 12** *Sex (female vs male)* OR 2.668 (95% CI, 1.198 to 5.940) p=0.0163	Zealand Only reports SVR 12 Note that at the end of tx, all pts in intervention group showed HCV RNA < 25 IU/mL but by week 12 after tx had dropped to 78%. 22% had relapsed. What would happen by week 24?

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		• Contraindications to RBV therapy • Chronic use of immunosuppressive agents • Significant drug or alcohol abuse w/i 12m • Excessive alcohol consumption • Hx of malignancy, clinically significant hemoglobinopathy, solid organ transplantation, clinical hepatic decompensation, primary gastrointestinal disorder, significant pulmonary or cardiac disease or porphyria, or other serious clinical condition • Hx of difficulty with blood collection or venous access • Donation or loss of > 400mL of blood w/i 2m	97 (47%) *CT* 36 (51%) 84 (41%) *TT* 6 (8%) 26 (13%) Cirrhosis n (%) 13 (18%) 31 (15%) Baseline ALT > 1.5 x ULN 42 (59%) 117 (57%) INF tx classification *Unacceptable AE* 8 (11%) 17 (8%) *Contraindicated* 33 (46%) 88 (43%)		*HCV-2 vs HCV-3* OR 8.659 (95% CI, 3.616 to 20.732) p<0.0001 *Duration of prior HCV tx (>12w vs no tx)* OR 0.131 (95% CI 0.038 to 0.452) p<0.0013 **Relapse** 42 pts relapsed after stopping tx (42/207 = 20.3%)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Pts decision 30 (42%) 102 (49%) <u>Response to previous tx</u> *No response* 2 (3%) 2 (1%) *Relapse* 4 (6%) 11 (5%)			
Jacobson , 2013a (Study 2) FUSION study	Active control RCT No prior response to prior INF containing regimen N=201 *Group 1* n=103	<u>Inclusion</u> • Age ≥ 18 • HCV-2 or 3 • Prior tx failure with INF for ≥ 12w (non-response or relapse/breakthrough) • Up to 30% with compensated cirrhosis • HCV RNA ≥ 104 IU/mL • BMI ≥ 18 kg/m2 • ECG w/o abnormalities • Discontinuation of previous INF tx due to AE *or* ineligible	*Group 1, Group 2* <u>Age</u> <u>mean (range)</u> 54 (30 to 69) 54 (24 to 70) <u>BMI</u> <u>mean (range)</u> 28 (19 to 43) 29 (20 to 44) <u>Male n (%)</u> 73 (71%)	<u>Group 1</u> SOF 400 mg/d and RBV 1000 to 1200 mg/d for 12w then 4w of placebo <u>Group 2</u> SOF 400 mg/d and RBV 1000 to 1200 mg/d for 16w 1 pt in group 1	<u>Outcomes</u> • SVR 4w post tx • SVR 12w post tx • Relapse • Adverse events <u>Findings</u> n (%) **SVR 4 post tx** *Group 1* 56/100 (56%), 99 returned for visit	Gilead sponsored, analyzed data and prepared final version of report

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	Group 2 n=98	for interferon tx OR declined interferon tx • Up to 20% with compensated cirrhosis • AAT ≤ 10 x ULN • AST ≤ 10 x ULN • Hb ≥ 12 g/dL for men and ≥ 11 g/dL for women • Albumin ≥ 3 g/dL • Direct bilirubin ≤1.5 x ULN • HbA1c ≤ 10% • Creatine clearance ≥ 60mL/min • INR ≤ 1.5 x ULN • Platelets ≥ 50,000 µL • No investigational drug w/i 30 days • Contraception <u>Exclusion</u> • Prior exposure to direct-acting anti-viral targeting HCV NS5B polymerase • Pregnant/nursing/pregnant partner	67 (68%) <u>Race n (%)</u> *White* 88 (85%) 86 (88%) *Black* 5 (5%) 1 (1%) *Hispanic* 10 (10%) 8 (8%) <u>HCV-1 n (%)</u> 3 (3%) 3 (3%) <u>HCV- 2 n (%)</u> 36 (35%) 32 (33%) <u>HCV-3 n (%)</u> 64 (62%) 63 (64%)	discontinued tx due to AE, 2 pts in group 1 lost to follow-up	*Group 2* 73/95 (77%), 95 returned for visit **SVR 12 post tx** *Group 1* 50/100 (50%), 54 returned for visit *Group 2* 69/95 (73%), 73 returned for visit **Factors associated with SVR 12 for Group 1** *HCV- 2 vs HCV- 3* OR 21.486 (95% CI, 6.144 to 75.142) p<0.0001 *Baseline weight-based RBV dose* OR 1.469 (95% CI, 1.089 to 1.983) p=0.0119	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		• Other clinically significant chronic liver disease • HIV or HBV positive • Contraindication to RBV tx • Chronic use of immunosuppressive agents • Significant drug or alcohol abuse w/i 12m • Hx of malignancy, clinically significant hemoglobinopathy, solid organ transplantation, clinical hepatic decompensation, primary gastrointestinal disorder, significant pulmonary or cardiac disease or porphyria, or other serious clinical condition • Excessive alcohol consumption • Hx of difficulty with blood collection or venous access • Donation or loss of > 400mL of blood w/i 2m	<u>IL28B genotype n (%)</u> *CC* 31 (30%) 30 (31%) *CT* 53 (51%) 56 (57%) *TT* 19 (18%) 12 (12%) <u>Cirrhosis n (%)</u> 36 (35%) 32 (33%) <u>Response to previous tx</u> <u>n (%)</u> *No response* 25 (24%) 25 (26%) *Relapse* 78 (76%) 73 (74%)		*Cirrhosis (no vs yes)* OR 3.117 (95% CI 1.019 to 9.537) p=0.0463 **Factors associated with SVR 12 for Group 2** *HCV- 2 vs HCV-3* OR 10.522 (95% CI 2.251 vs. 49.174) p=0.0028 *Female vs male* OR 3.978 (95% CI, 1.169 to 13.539) p=0.0271 **Relapse** 73 pts relapsed after stopping tx (73/201, 36.3%), *no details provided*	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
Kowdley, 2013	Open label Duration ranging 12w vs 24w PEG + RBV N=332 *Cohort A* n=52 (HCV-1) *Cohort B* n=125 (HCV-1 = 109; HCV-4 = 11; HCV-6 = 5) *Cohort C* n=155 (HCV-1)	Inclusion • Age ≥ 18 • HCV-1, 4, 5 or 6 • Tx naïve • HCV RNA ≥ 50,000 IU/mL Exclusion • Cirrhosis or other chronic liver disease • BMI ≤ 18 kg/m2 • HIV or HBV positive	*Cohort A; Cohort B; Cohort C except where noted* Age (mean ± sd) 51 ± 9.8 50 ± 11 50 ± 10.8 Male n (%) 35 (67%) 73 (58%) 106 (68%) Race n (%) *Black* 2 (4%) 17 (14%) 16 (10%) *Non-black* 50 (96%) 108 (86%) 139 (10%)	Intervention *Cohort A* SOF 400 mg/d + weight based RBV/d + PEG 180µg/w for 12w *Cohort B* SOF 400 mg/d + RBV/d + PEG/w for 24w *Cohort C* SOF 400 mg/d + RBV/d + PEG for 12w then 50% rec'd SOF mono tx for 12w; 50% rec'd SOF + RBV for 12w Follow-up 24w	Outcome • SVR 24 • Adverse events Findings **SVR 24 for HCV-1** n (%, 95% CI) *Cohort A* 46/52 (89, 77 to 96) *Cohort B* 97/109 (89, 82 to 94) *Cohort C* 135/155 (87, 81 to 92) **SVR 24 for HCV-4** n (%, 95% CI) *Cohort B* 9/11 (82, 48 to 98) **SVR 24 for HCV-6** n (%, 95% CI) *Cohort B*	Gilead sponsored, analyzed data and prepared final version of report Pooled efficacy data for Cohort C's 2 extended tx arms Per-protocol analysis also included in article

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Hispanic 10 (19%) 26 (21%) 31 (20%) <u>BMI</u> <u>(mean ± sd)</u> 27.2 ± 4.6 27.6 ± 5.0 28.4 ± 4.6 <u>HCV RNA log_{10} IU/mL</u> <u>(mean ± sd)</u> 6.5 ± 0.7 6.3 ± 0.7 6.4 ± 0.8 <u>HCV-1a, 1b, 4, 6</u> <u>n (%)</u> *Cohort A* 40 (77%) 12 (23%) 0 0 *Cohort B* 85 (68%)		5/5 (100, 48 to 100) **Difference in SVR 24 for HCV-1 by regime** A to B: p=0.94 A to C: p=0.78 **Relapse** *Cohort A* 2 (4%) *Cohort B* 1 (1%) *Cohort C* 4 (3%) **Adverse events** 13 serious AEs in 12 pts *9 adverse events reported t as "non-tx related"* arrythemia, ischaemic colitis,	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			24 (19%) 11 (19%) 5 (4%) *Cohort C* 116 (75%) 39 (25%) 0 0 <u>IL28B genotype n (%)</u> *CC* 13 (25%) 36 (29%) 39 (25%) *CT* 33 (64%) 63 (50%) 88 (57%) *TT* 6 (12%) 26 (21%) 28 (18%)		chest pain, acute cholecystitis, cholelithiasis, alcohol poisoning, road traffic accident, costochondritis, hip arthroplasty *4 adverse events reported as related to PEG and RBV but not SOF* anemia, auto-immune hepatitis, pyelonephritis, pancytopenia	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			<u>No/minimal fibrosis n (%)</u> 9 (17%) 14 (11%) 20 (13%) <u>Portal fibrosis n (%)</u> 36 (69%) 93 (74%) 99 (64%) <u>Bridging fibrosis n (%)</u> 7 (14%) 17 (14%) 23 (15%) <u>Loss to f/u n (%)</u> 26 (7.8%) *Cohort A* 4 (7.7%) *Cohort B* 13 (10.4%) *Cohort C* 9 (5.8%)			

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
Lawitz , 2013a (Lancet)	Dose finding placebo control RCT for HCV-1 and additional single group for HCV-2, 3; all tx naïve and non-cirrhotic N=147 *Cohort A* n=122 Group 1 n=48 Group n=48 Group 3 n=26 *Cohort B* n=25	Inclusion • Age ≥ 18 • HCV-1, 2 or 3 • Tx naïve • HCV RNA ≥ 50,000 IU/mL • Neutrophil count 1-5 x 109/L or ≥ 1-25 x 109/L for black patients • Hb ≥ 11 g/dL for women or ≥ 12 g/dL for men • Platelets ≥ 90x109/L • Total bilirubin ≤ 2xULN • Albumin ≤ 30 g/L Exclusion • Cirrhosis • HIV or HBV positive • Hx of psychiatric illness, pulmonary or cardiac disease, seizure disorder or other serious comorbid condition	*Cohort A (Group 1, Group 2, Group 3)* Age (mean ± sd) 48.4 ± 11.5 51.4 ± 9.4 48.6 ± 9.4 Male n (%) 33 (69%) 21 (45%) 19 (73%) Race n (%) *White* 39 (81%) 37 (78%) 21 (80%) *Black* 6 (13%) 7 (15%) 5 (19%) *Hispanic* 5 (10%)	Intervention *Cohort A* HCV-1 randomized 2:2:1 to 3 protocols in 2 steps. 1st step for 12w *Group 1* SOF 200 mg/d + weight based RBV/d + 180µg PEG weekly *Group 2* SOF 400 mg/d + RBV/d + PEG weekly *Group 3* Placebo + RBV + PEG If pts achieved eRVR (HCV RNA ≤ 15	Outcomes • Primary outcome – safety and tolerability • "study was not designed to statistically test efficacy" (p.403) • Secondary outcomes ○ RVR 4 ○ SVR 12 ○ SVR 24 Findings **Adverse Events** (Cohorts A & B) *Common side effects* Fatigue, headache, nausea, chills, pain, insomnia Fatigue, rash,	Gilead sponsored, analyzed data and prepared final version of report Placebo group (Cohort A, PEG-INF + RBV + placebo) very small (n=26)

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			6 (13%) 1 (4%) <u>BMI</u> <u>(mean ± sd)</u> 26.6 ± 3.4 26.8 ± 4.5 28.6 ± 4.1 <u>HCV RNA IU/mL</u> <u>(mean ± sd)</u> 6.5 ± 0.6 6.4 ± 0.8 6.5 ± 0.8 <u>HCV-1a n (%)</u> 37 (77%) 35 (74%) 20 (77%) <u>HCV-1b n (%)</u> 11 (23%) 12 (26%) 6 (23%) <u>IL28B genotype n (%)</u> *CC*	IU/mL) in weeks 4 to 12, pts rec'd 12w of PEG + RBV If placebo or failure to achieve eRVR, pts rec'd 36w PEG + RBV *Cohort B* HCV-2 or -3 SOF 400 mg + RBV + PEG for 12w	fever, diarrhea "more common" in SOF groups than placebo (no p value) Headache more common in placebo group (no p-value) 3 pts in SOF regimens developed level 3 increase in AST levels 8 pts in Cohort A discontinued tx due to AE *Group 1* 2 pts – neutropenia, folliculitis *Group 2* 3 pts – aphthous	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			21 (44%) 18 (38%) 11 (42%) *CT* 24 (50%) 19 (40%) 11 (42%) *TT* 3 (6%) 10 (21%) 4 (15%) <u>No/minimal fibrosis n (%)</u> 12 (25%) 7 (15%) 3 (12%) <u>Portal fibrosis n (%)</u> 35 (73%) 38 (81%) 21 (81%)		ulcer; MI; depression & suicidal ideation Post SOF, 3 pts with severe AE: retinal vein occlusion; lymphangitis; chest pain & ECG ST segment elevation **RVR 4** n (%, 95% CI) *Cohort A* Group 1 47 (98, 89 to 100) Group 2 46 (98, 89 to 100) Group 3 5 (19, 7 to 39) *Cohort B* 24 (96, 80 to 100)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Bridging fibrosis n (%) 1 (2%) 2 (4%) 2 (8%) Loss to follow-up 2 *Cohort B* Age (mean ± sd) 47.2 ± 11.1 Male n (%) 16 (64%) Race n (%) *White* 20 (80%) *Black* 4 (16%) *Hispanic* 1 (4%) BMI (mean ± sd)		**SVR 12** n(%, 95% CI) *Cohort A* Group 1 43 (90, 77 to 97) Group 2 43 (91, 80 to 98) Group 3 15 (58, 40 to 77) *Cohort B* 23 (92, 74 to 99) **SVR 24** n (%, 95% CI) *Cohort A* Group 1 41 (85, 72 to 94) Group 2 42 (89, 77 to 96) Group 3 15 (58, 40 to 77)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			28.6 ± 4.8 <u>HCV RNA IU/mL (mean ± sd)</u> 6.1 ± 0.8 <u>HCV-2 n (%)</u> 15 (60%) <u>HCV-3 n (%)</u> 10 (40%) <u>IL28B genotype n (%)</u> *CC* 7 (28%) *CT* 17 (68%) *TT* 1 (4%) <u>No/minimal fibrosis n (%)</u> 7 (28%) <u>Portal fibrosis n (%)</u> 18 (72%)		*Cohort B* 23 (92, 74 to 99)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Loss to follow-up 1			
Lawitz, 2013b (NEJM) (Study 1) NEUTRINO study	Open label; single group; tx naïve; 89% HCV-1 (11% HCV-4, 5, 6); 17% cirrhotic N=327	Inclusion • Age ≥ 18 • HCV-1,4,5, or 6 • HCV RNA ≥ 10,000 IU/mL • HCV tx naïve • Up to 20% of pts could have evidence of cirrhosis • BMI ≥ 18 kgm2 • ALT ≤ 10x ULN • AST ≤ 10 x ULN • Hb ≥ 12 g/dL for males, ≥ 11 g/dL for females • White blood cell count ≥2500/µL • Absolute neutrophil count ≥1500/µL (or≥ 1000/µL if considered a physiologic variant in a subject of African descent) • Platelets ≥ 90,000/µL • INR ≤ 1.5 x ULN unless subject has known hemophilia or is stable on an	Age mean (range) 52 (19 to 70) Male n (%) 209 (64%) Race n (%) *White* 257 (79%) *Black* 54 (17%) *Hispanic* 46 (14%) HCV-1a n (%) 225 (69%) HCV-1b n (%) 66 (20%) HCV-4 n (%) 28 (9%)	Intervention SOF 400 mg/d, weight based RBV daily (1000mg < 75kg or 1200mg ≥ 75kg), and PEG alfa 2a 180 µg weekly for 12w Comparator *None* Follow up 12w post tx	Outcomes • SVR 12 post tx Findings n (%, 95% CI) **SVR 12** *Overall* 295/327 (90.2, 87 to 93) No significant difference in SVR by genotype or race *Cirrhosis* 43/54 (79.6, 67 to 89) *No cirrhosis* 252/273 (92.3, 88.5 to 5.2) (no p value)	Gilead sponsored, analyzed data and prepared final version of report

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		anticoagulant regimen affecting INR • Albumin ≥ 3 g/dL • Direct bilirubin ≤ 1.5 x ULN • Thyroid-stimulating hormone (TSH) ≤ ULN • HgbA1c ≤ 10% • Creatinine clearance ≥ 60 mL/min, as calculated by the Cockcroft-Gault equation • No investigational study participation w/i 30 days • Contraception <u>Exclusion</u> • Prior tx for HCV with an INF or RBV • Prior exposure to a direct-acting antiviral targeting the HCV NS5B polymerase • Pregnant/nursing/pregnant partner • Chronic liver disease of a non-HCV etiology (e.g., hemochromatosis, Wilson's disease, α1 antitrypsin	<u>HCV-5 n (%)</u> 1 (<1%) <u>HCV-6 n (%)</u> 6 (2%) <u>BMI</u> <u>Mean (range)</u> 29 (18 to 56) <u>Mean HCV RNA log_{10} UL/mL</u> <u>(mean ± sd)</u> 6.4 ± 0.7 <u>HCV RNA ≥ 800,000 IU/mL</u> <u>n (%)</u> 267 (82% <u>IL28B genotype</u> <u>n (%)</u> *CC* 95 (29%) *CT* 181 (55%)		*IL28B GT CC* 93/95 (97.9, 92.6 to 99.7) *IL28B GT non-CC* 202/232 (87.%,82.1 to 91.1) (no p value) **Adverse events** *Any AE* 310/327 (95%) 5 pts (2%) discontinued due to AE 4 pts (1%) serious AE (not specified)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		deficiency, cholangitis) • HIV or HBV positive • Contraindications for PEG or RBV therapy • Pre-existing significant psychiatric conditions including severe depression, severe bipolar disorder, and schizophrenia. Other psychiatric disorders are permitted if the condition is well controlled with a stable tx regimen for ≥ 1 yr from screening • Hx of autoimmune disorders, severe chronic obstructive pulmonary disease, significant cardiac disease, clinically significant retinal disease, clinically significant malignancy diagnosed or treated w/i 5 yrs, solid organ transplantation, hepatic decompensation, gastrointestinal disorder,	*TT* 51 (16%) Cirrhosis n (%) 54 (17%) AAT ≥ 1.5xUL n (%) 166 (51%) Loss to follow-up n (%) 2 (0.6%)			

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		porphyria, or other major illness. • Chronic use of systemically administered immunosuppressive agents • Clinically relevant drug or alcohol abuse w/i 12m of screening • Excessive alcohol ingestion • Hx of difficulty with blood collection and/or poor venous access for the purposes of phlebotomy • Donation or loss of >400 mL of blood w/i 2m prior to baseline/day 1 • Use of any prohibited concomitant medications w/i 28d of the baseline/day 1 visit • Known hypersensitivity to PEG, RBV, the study investigational medicinal product, the metabolites, or formulation excipients				

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
Lawitz , 2013b (NEJM) (Study 2) FISSION study	Open label RCT tx naïve; HCV-2, 3; 20% cirrhotic N=499 *Intervention* n=256 *Comparator* n=243	Inclusion • Age ≥ 18 • HCV-2 or 3 • HCV RNA ≥ 10,000 IU/mL • HCV tx naïve • Up to 20% of pts can have evidence of cirrhosis • BMI ≥ 18 kg m2 • Contraception Exclusion • HIV or HBV positive • Hx of clinically significant chronic liver disease, consistent decompensated liver disease, psychiatric illness, immunologic disorder, hemoglobinopathy, pulmonary disease (including pneumonia or pneumonitis), cardiac disease, seizure disorder or anticonvulsant use, poorly controlled diabetes, or cancer, malignancy, acute	*Intervention; comparator* Age mean (range) 48 (20 to 72) 48 (19 to 77) Male n (%) 171 (67%) 156 (64%) Race n (%) *White* 223 (87%) 212 (87%) *Black* 12 (5%) 5 (2%) *Hispanic* 41 (16%) 31 (13%) Genotype n (%) *HCV-2* 70 (27%)	Intervention SOF 400mg/d and weight based RBV for 12w Comparator PEG alfa2a 180 µg weekly and 800 mg/d RBV for 24w Follow-up 12w post tx	Outcomes • SVR 12 post tx Findings **SVR 12 post tx** 67% (170/253) vs 67% (162/243) **Relapse pts who completed tx** 29% (71/242) vs 20% (37/188) **Relapse pts who did not complete tx** 43% (3/7) vs 31% (9/29) **Total relapse** 74/249 (29.7%) vs 46/217 (21.2%) **SVR 12 by genotype** *Intervention* 97% of pts with	Gilead sponsored, analyzed data and prepared final version of report Comparator group rec'd a lower dose of RBV than SOC (800mg vs weight-based dose)

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		pancreatitis with elevated lipase, uncontrolled thyroid disease or abnormal TSH levels or solid organ transplantation • Clinically significant ECG • Active substance abuse, • Abnormal hematologic and biochemical parameters, including: a) neutrophil count < 1500 cells/mm3 (or < 1250 cells/mm^3 for African-American/black subjects or cirrhotic patients); b) Hb < 11 g/dL in females or <12 g/dL in males; c) Platelet count ≤ 90,000 cells/mm^3 (noncirrhotic) or ≤ 75,000 cells/mm^3 (cirrhotic); d) creatinine ≥ 1.5 x ULN; e) estimated glomerular filtration rate, calculated by the Chronic Kidney Disease-Epidemiology Collaboration equation, < 60 mL/min/1.73	67 (28%) *HCV-3* 183 (71%) 176 (72%) BMI mean (range) 28 (17 to 51) 28 (19 to 52) HCV RNA log_{10} UL/mL (mean ± sd) 6.0 ± 0.8 6.0 ± 0.8 HCV RNA ≥ 800,000 IU/mL n (%) 145 (57%) 157 (65%) IL28B genotype n (%) *CC* 108 (42%) 106 (44%)		HCV-2, 56% of pts with HCV-3 *Comparator* 78% of HCV-2, 63% of HCV-3 (*no p-values or CIs reported*) **SVR 12 by pts with cirrhosis at baseline n=50 both groups:** 47% vs 38% (*no p-values or CIs reported*) **Adverse Events** *Any AE* 220/256 (86%) vs 233/243 (96%) *Discontinuation due to AE* 3 (1%) vs 26 (11%)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		m^2;f) ALT or AST ≥ 10 x ULN; g) total bilirubin ≥ 1.5 x ULN (except patients with Gilbert's syndrome); h) albumin ≤ 3.2 g/dL 11 • Donation or loss of >400 mL of blood w/i 2m prior to first dose administration • Hx of clinically significant drug allergy to nucleoside/nucleotide analogs • Systemic antineoplastic or radiation therapy w/i 6m prior to the first dose of study drug or the expectation that such tx will be needed at any time during the study • Subjects receiving oral or intravenous strong p-glycoprotein inhibitors (including cyclosporine, quinidine, dronedarone, itraconazole, verapamil, or ritonavir) w/i 28d of dosing	*CT* 121 (47%) 98 (40%) *TT* 25 (10%) 38 (16%) <u>Cirrhosis n (%)</u> 50 (20%) 50 (21%) <u>AAT ≥ 1.5xULN n (%)</u> 138 (54%) 146 (60%) <u>Loss to follow-up n (%)</u> 1 (0.3%) 1 (0.03%)		*Serious AEs (not specified)* 7 (3%) vs 3 (1%) *Specific AEs* Influenza/fever 3 % vs 16 to 18%% Depression 5% vs 14% Hemoglobin < 10g/dcl 9% vs 14% Neutrophil count 500 to 700 mm^3 0% vs 12% Neutrophil count < 500 0% vs 2% Decreased lymphocyte, platelet, white cell counts 0% vs 1 to 7%	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		• Participation in a clinical study with an investigational drug, biologic, or device w/i 3m prior to first dose administration • Pregnant/nursing/pregnant partner • Poor venous access making the pt unable to complete the required laboratory testing schedule				
Osinusi, 2013 (Study 1)	Proof of concept with HCV-1 and unfavorable tx characteristics N=10	Inclusion "pts with unfavorable tx characteristics" • HCV-1 • Tx naïve • Neutrophil count ≥ 750 cells µL • Platelet count ≥ 50,000 cells/µL • Hb ≥ 11 g/dL (women) or ≥ 12 g/dL (men) • HIV negative • HBV negative	Age median (range) 54 (50 to 57) Men n (%) 4 (40%) BMI median (range) 26 (26 to 34) Race n (%) *Black* 9 (90%)	Intervention SOF 400 mg/d and weight based RBV daily (<75 kg= 400 mg RBV am and 600 mg pm; >75 kg = 600 mg RBV both am and p.m.) for 24w Follow-up 24w post tx	Findings **SVR 24** 9/10 (90%)	None

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			White 1 (10%) *Hispanic* 0 <u>IL28B genotype</u> <u>n (%)</u> *CC* 3(33%) *CT/TT* 6(67%) <u>Knodell HAI fibrosis</u> <u>score n (%)</u> *0 to 1* 9 (90%) *3 to 4* 1 (10%) <u>HCV-1a n (%)</u> 6/10 (60%) <u>HCV-1b n (%)</u> 4/10 (40%)			

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
Osinusi, 2013 (Study 2)	Open label RCT with HCV-1 and unfavorable tx characteristics N=50 *Group 1* n=25 *Group 2* n=25	Inclusion "pts with unfavorable tx characteristics" • HCV-1 • Tx naïve • Neutrophil count ≥ 750 cells µL • Platelet count ≥ 50,000 cells/µL • Hemoglobin ≥ 11 g/dL (women) or ≥ 12 g/dL (men) • HIV negative • HBV negative	*Group1, Group2* Age median (range) 54 (51 to 56) 55 (48 to 59) Men n (%) 19 (76%) 14 (56%) BMI median (range) 28 (25 to 31) 30 (27 to 37) Race n (%) *Black* 18 (72%) 23 (92%) *White* 5 (20%) 2(8%) *Hispanic* 2(8%)	Intervention *Group 1* SOF 400mg/d and weight based RBV for 24w *Group 2* SOF 400 mg/d and RBV 600 mg/d for 24w Follow-up 24w post tx	Outcomes • SVR 24 post tx • HCV RNA < level of quantification • Safety and tolerability Findings n (%, 95% CI) **SVR 24 post tx** *Group 1* NR (68, 46 to 85) *Group 2* NR (48, 28 to 69) **HCV RNA level < level of quantification** *Group 1* Week 24 24 (96, 80 to 100) 24w post tx 17 (68, 46 to 85)	5/33 authors report relationship to Gilead, including three Gilead employees

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			0 <u>IL28B genotype</u> <u>n (%)</u> *CC* 4(16%) 4(16%) *CT/TT* 21(84%) 21(84%) <u>Knodell HAI fibrosis score</u> <u>n (%)</u> *0 to 1* 19 (76%) 18 (72%) *3 to 4* 6 (24%) 7 (28%) <u>HCV-1a n (%)</u> 20 (80%) 16 (64%)		*Group 2* Week 24 22 (88, 69 to 97) 24w post tx 12 (48, 28 to 69) **Characteristics associated with relapse** *Male* OR 6.09, 95% CI 1.17 to 31.6, p=0.03 *Advanced fibrosis* OR 4.27, 95% CI 1.10 to 16.54, p=0.04 *Baseline HCV RNA ≥ 800,000 IU/mL* OR 5.74, 95% CI 1.35 to 24.38, p=0.02	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			HCV-1b n (%) 5 (20%) 9 (36%)		**Adverse Events** *Common* Headache, anemia, fatigue, nausea *Grade 3 events* 6 total Group 1 Hyperbilirubinemia 1 (4%) Group 2 Anemia 1 (4%) Hypophosphatemia 2 (8%) Neutropenia 1 (4%) Nausea 1 (4%)	
Rodriguez, 2013	Randomized, placebo controlled, double-blind	Inclusion • Age 18 to 65 • HCV-1 • Tx naïve	*Group 1, Group 2, Group 3, Group 4*	*Stage 1* Four groups first stage for 28d	Outcomes • Change in circulating HCV RNA over first	Authors report significant relationships with

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	dose ranging study N= 64 *Group 1* n=16 *Group 2* n=18 *Group 3* n=15 *Group 4* n=14	• HCV RNA levels ≥10,000 IU/ml at screening • BMI 18 to 36 kg/m^2 <u>Exclusion</u> • Cirrhosis • Significant comorbidity • Positive for HBsAg, anti-HBc IgM Ab, or anti-HIV A	<u>Age</u> <u>mean (range)</u> 44.4 (23 to 57) 44.4 (30 to 57) 44.9 (29 to 62) 46.6 (27 to 62) <u>Male (%)</u> 11 (69%) 10 (56%) 11 (73%) 11 (19%) <u>Race n (%)</u> *White* 15 (94%) 16 (89%) 12 (80%) 14 (100%) *Other races not provided* <u>HCV -1a/1b (n/n)</u> 14/2 15/2 12/3	1. SOF 100 mg daily + PEG/RBV 2. SOF 200 mg daily + PEG/RBV 3. SOF 400 mg daily + PEG/RBV 4. Placebo + PEG/RBV **Stage 2** All pts continue with PEG/RBV alone for 44w Used response guided protocol & allowed early stopping Not all pts followed 48w <u>Follow-up</u> 24w post tx	28d • Rates of rapid virologic response (RVR = HCV RNA < limit of detection at week 4) • SVR 12 and 24 post tx • Viral breakthrough <u>Findings</u> **Change from baseline HCV RNA at Day 28** *Group 1* -5.3 log_{10}IU/ml *Group 2* -5.1 log_{10}IU/ml *Group 3* -5.3 log_{10}IU/ml	pharmaceutical companies Three authors are employed by and hold stock in Gilead Outcomes not reported for substantial minority of pts due to loss to follow-up and study withdrawal

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			10/4 Mean baseline HCV RNA (log_{10} IU/mL) (n) 6.64 6.28 6.49 6.48 IL28B genotype n (%) *CC* 4 (25%) 5 (28%) 4 (27%) 4 (29%) HOMA-IR ≤ 3 n (%) 10 (63%) 13 (72%) 7 (47%) 7 (50%) No/minimal fibrosis F0-1 n (%) 5 (31%)		*Group 4* -2.8 log_{10}IU/ml (*no p values provided*) **RVR at 28 days** *Group 1* 14 (88%) *Group 2* 17 (94%) *Group 3* 14 (93%) *Group 4* 3 (21%) (no p values provided) **SVR 12 post tx** n (%, 95% CI) *Group 1* 9 (56%, 30 to 80) *Group 2* 13 (72%, 47 to 90)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			6 (33%) 5 (33%) 4 (29%) <u>Portal fibrosis – F1-2 n (%)</u> 11(69%) 10(56%) 9(60%) 9(64%) <u>Bridging fibrosis – F3 n (%)</u> 0 2(11%) 1(7%) 1(7%) <u>Loss to follow-up</u> Stage 1 1 pt Stage 2 16 pts		*Group 3* 13 (87%), 60 to 98) *Group 4* 7 (50%, 23 to 77) **SVR 24 post tx** n (%, 95% CI) *Group 1* 9 (56%, 30 to 80) *Group 2* 15 (83%, 59 to 96) *Group 3* 12 (80%, 52 to 96) *Group 4* 6 (43%, 18 to 71) **Viral breakthrough** *Phase I* No viral breakthrough *Phase II* 4 pts in Group 1; 2 pts in Group 3; 2	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
					pts in Group 4 **Relapse** *Not reported* **Adverse Events** 54/63 pts reported "mild" or "moderate" AEs during 28d initial tx phase No pts discontinued therapy during 1st phase Most common AEs = fatigue, nausea, chills, headache, and arthralgia No difference between SOF groups and placebo group in 1st phase AEs	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
					In 2nd phase, 5 serious AEs occurred > 50 days after ending SOF tx: peripheral ischemia, acute pancreatitis, anemia, depression, abdominal pain	
Non-published Studies Used in FDA Approval						
GS-US-334-0133 VALENCE study	Open-label N= 323 *Group 1 (genotype 2)* n=73 *Group 2 (genotype 3)* n=250 Trial originally planned as a randomized placebo-	Inclusion • Age > 18 • HCV genotype 2 or 3 • Tx naïve or tx experienced • HCV RNA levels ≥10,000 IU/ml at screening • Cirrhosis screening • Otherwise healthy • Contraception Exclusion • Hx of other significant chronic liver disease • Decompensated liver disease	*Group 1, Group 2;* Age mean (SD) 58 (10) 48 (10) Male (%) 40 (55%) 155 (62%) Race n (%) *White* 65 (89%) 236 (94%)	Intervention *Group 1* SOF 400mg/d and weight based RBV for 12w *Group 2* SOF 400 mg/d and weight based RBV for 24w Follow-up 24w post tx	Outcomes • SVR 12 post tx • Safety and tolerability Findings n (%) **Overall SVR 12 post tx** *Group 1* 68/73 (93%) *Group 2* 210/250 (84%)	Trial was on-going at time of FDA approval and results were preliminary. No final results have been published on ClinicalTrials.gov or in the literature. Trial sponsored by Gilead. No

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	controlled trial with intervention group to receive SOF + RBV for 12 weeks. Altered in course to direct all genotype 3 pts to receive SOF + RBV for 24 w, and genotype 2 pts to SOF + RBV for 12 w; placebo group discontinued. Safety analysis includes discontinued pts – n = 419	• HIV, HBV, HCC, or other malignancy • Any condition, therapy or laboratory abnormality that might interfere with study • Chronic use of immunosuppressive agents or immunomodulatory agents	*Black* 5 (7%) 0 (0%) *Asian* 1 (1%) 9 (4%) *Hispanic* 6 (8%) 36 (14%) <u>Tx naïve</u> 32 (44%) 105 (42%) <u>Tx experienced</u> 41 (56%) 145 (58%) *IFN Intolerant* 3 (4%) 10 (4%) *Non-Response* 10 (14%) 41 (16%)		**SVR 12 (Tx Naïve)** *Group 1* 31/32 (97%) *Group 2* 98/105 (93%) **SVR 12 (tx experienced)** *Group 1* 37/41 (90%) *Group 2* 112/145 (77%) **Overall relapse rate** *Group 1* 5/73 (7%) *Group 2* 32/249 (14%) **Relapse(tx naïve)** *Group 1* 1/32 (3%) *Group 2*	COI information available Study conducted in 10 countries in Europe

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Relapse/Breakthrough 28 (38%) 94 (38% <u>Baseline BMI (Kg/m^2)</u> <u>Mean (SD)</u> 26 (4) 25 (4) <u>Mean baseline HCV RNA (log_{10} IU/mL) (n)</u> 6.5 (0.7) 6.3 (0.7) <u>IL28B genotype n (%)</u> *CC* 24 (33%) 86 (34%) <u>Baseline cirrhosis</u> *No* 63 (86%) 192 (77%) *Yes* 10 (14%) 58 (23%0		5/105 (5%) **Relapse (tx experienced)** *Group 1* 4/41 (10%) *Group 2* 29/144 (20%) **Adverse events** N= 419 Group 1 (placebo) n=85 Group 2 (12wks) n=84 Group 3 (24 w) n=250 *Group 1, group 2, group 3* <u>Any AE n (%)</u> 61 (72%) 72 (86%)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Baseline ALT *≤ 1.5 x ULN* 39 (53%) 64 (26%) *1.5 x ULN* 34 (47%) 186 (74% Lost to follow-up 0 1 (< 1%)		228 (91%) Common AEs Fatigue, headache, pruritus, asthenia, insomnia, nasopharyngitis, nausea, dry skin, diarrhea, dyspnea, cough, irritability Serious AE n (%) *Group 1* 2 (2.4%) one each of adenocarcinoma of colon, gastroenteritis *Group 2* 0 *Group 3* 10 (4%), one each of: arrhythmia, haemorrhoidal haemorrhage, biliary colic, road	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
					traffic accident, amylase increased, lipase increased, hyperglyacemia, HCC, invasive ductal breast carcinoma, complex regional pain syndrome, suicide attempt <u>Grade 3 or 4 AE</u> 4 (5%) 3 (4%) 17 (7%)	
GS-US-334-0123 PHOTON-1 study	Open label study N= 223 N for efficacy analysis = 210 (13 group 2 pts had not completed trial at FDA review)	<u>Inclusion</u> • Age ≥ 18 • HCV genotype 1, 2 or 3 • HIV-1 infection • HCV RNA levels ≥10,000 IU/ml at screening • Cirrhosis screening • HIV antiretroviral therapy (ARV) criteria: ○ ARV untreated, CD4 T-cell count > 500	*Group 1, Group 2, Group 3* <u>Age</u> <u>mean (SD)</u> 49 (10) 54 (6) 48 (8) <u>Male (%)</u> 55 (81%) 37 (90%)	<u>Intervention</u> *Group 1* SOF 400mg/d and weight based RBV for 12w *Group 2* SOF 400 mg/d and weight based RBV for	<u>Outcomes</u> • SVR 12 post tx • Safety and tolerability <u>Findings</u> *Group 1, Group 2, Group 3* **Overall SVR 12 Post Tx** **n (%, 95% CI)**	Trial not completed at FDA review. 13 pts in group 2 not included in efficacy data set.

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	Group 1 (genotype 2/3 tx naive) n=68 *Group 2 (genotype 2/3 tx experienced)* n=28 (completed trial, 41 enrolled in group) *Group 3 (genotype 1 tx naïve)* n=114	cells/mm3 ○ Stable, protocol approved ARV regimen > 8 w, CD4 T-cell count > 200 cells/mm2, undetectable plasma HIV-1 RNA level for ≥ 8 w • Approved ARV regimen • No investigational drug use within 30 days • Otherwise healthy • Contraception <u>Exclusion</u> • Prior tx for genotype 1 pts • Other chronic liver disease • Decompensated liver disease • HBV • Hx solid organ transplant • Contradiction to RBV tx • Serious infection requiring parenteral antibiotics, antivirals or antifungals within 30 days • Chronic use of	93 (82%) <u>Race n (%)</u> *White* 52 (76%) 32 (78%) 69 (61%) *Black* 8 (12%) 7 (17%) 37 (32%) *Asian* 1 (1%) 1 (2%) 6 (5%) *Hispanic* 19 (28%) 10 (24%) 25 (22%) <u>HCV genotype</u> *HCV-1a* 0 0	24w *Group 3* SOF 400 mg/d and weight based RBV for 24w <u>Comparator</u> *None* <u>Follow-up</u> 24w post tx	51/68 (75, 63-85) 26/28 (93, 77-99) 87/114 (76, 67-84) **SVR 12 Genotype HCV-1a** *(Group 3)* 74/90 (82, 73-89) **SVR 12 Genotype HCV-1b** *(Group 3)* 13/24 (54, 33-74) **SVR 12 Genotype HCV-2** *(Group1, Group 2)* 23/26 (88, 70-98) 14/15 (93, 68-99.8) **SVR 12 Genotype HCV-3** *(Group 1, Group2)* 28/42 (67, 50-80) 12/13 (92, 64-99.8) **Overall Relapse Rate n (%)** 12/67 (18%)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		immunosuppressive agents or immunomoedulatory agents	90 (79%) *HCV-1b* 0 0 24 (21%) *HCV-2* 26 (38%) 24 (59%) 0 *HCV-3* 42 (62%) 17 (41%) 0 <u>Group 2 Tx experienced</u> *IFN intolerant* 9 (22%) *Partial/null-response* 7 (17%) *Relapse/Breakthrough* 25 (61%)		2/28 (7%) 25/113 (22%) **Adverse Events (Safety Analysis n=223)** *Group 1, Group 2, Group 3* <u>Any AE n (%)</u> 57 (84%) 37 (90%) 106 (93%) <u>Common AEs</u> Fatigue, insomnia, nausea, headache, upper respiratory tract infection, diarrhea, irritability anemia, cough, dizziness <u>Serious AE n (%)</u> *Group 1* 5 pts (7.4%), 14 events - one each	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Cirrhosis *No* 61 (90%) 31 (76%) 109 (96%) *Yes* 7 (10%) 10 (24%) 5 (4%) Baseline BMI (Kg/m^2) mean (SD) 27 (4) 27 (5) 27 (5) Mean baseline HCV RNA *< 6 log_{10} IU/mL* 21 (31%) 7 (17%) 22 (19%) *≥ 6 log_{10} IU/mL* 47 (69%) 34 (83%)		of acute MI, pneumonia, incision site infection, septic shock, staphylococcal bacteremia, intentional overdose, fracture, encephalopathy, completed suicide, drug abuse, suicide attempt, acute renal failure, pulmonary embolism, respiratory failure *Group 2* 1 pt (2.4%), 3 events: pneumonia, COPD, leukocytoclastic vasculitis	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			92 (81%) <u>IL28B genotype n (%)</u> *CC* 25 (37%) 20 (49%) 30 (26%) *CT* 37 (54%) 17 (41%) 57 (50%) *TT* 6 (9%) 4 (10%) 26 (23%) <u>ARV Tx at Enrollment</u> *No* 7 (10%) 2 (5%) 2 (2%) <u>Baseline HIV-1 RNA</u> *< 50 copies/mL* 60 (88%)		*Group 3* 8 pts (7%), 18 events: one each (unless noted) of anemia, leukocytosis, atrial fibrillation, atrial flutter, abdominal pain, colitis, enteritis, chest pain, cellulitis (2), gastroenteritis salmonella, respiratory tract infection, intentional overdose, diabetic ketoacidosis, altered state of consciousness, bi-polar disorder, acute renal failure (2) <u>Grade 3 or 4 AE</u> 7 (10.3%)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			40 (98%) 108 (95%) *≥ 50 copies/mL* 8 (12%) 1 (2%) 6 (5%) Baseline CD4 (cells/mm^3)[3] mean (SD) 585 (246) 658 (333) 636 (251) Lost to follow-up 5 (7%) 1 (2%) 1 (2%)		3 (7.3%) 15 (3.2%)	
P7977-2025 Pre-transplant study	Open-label trial On-going N=61 (protocol on clinical trials.gov states 50, FDA analysis	Inclusion • Age ≥ 18 years • Patients meeting the MILAN criteria for liver transplantation for HCC secondary to HCV with a MELD < 22 and a HCC weighted MELD of ≥ 22	Status of pts at time of FDA analysis (n=61) n (%) In tx/pre transplant 9 (14.8%) Had liver transplant while on tx	Intervention SOF 400mg/d and weight based RBV for up to 48 weeks prior to transplantation or until	Outcomes • Post transplant reinfection as defined by SVR at 12 w post transplant (pTVR12) and 24 w post	Trial is not completed. FDA presentation of data is incomplete, does not include n's for many measures and

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
	reports 61 patients received at least one dose of drug) Study was originally designed to test SOF + RBV for 24 w prior to transplant. FDA reports that 11/15 pts (73%) who completed 24 w tx relapsed in the pre-transplant phase, so tx time was extended to 48w for pts who had not been transplanted	• Child-Pugh Score ≤ 7 • HCV RNA levels ≥10,000 IU/ml at screening • No investigational drug use within 30 days • Contraception Exclusion • Pregnant, nursing, pregnant partner • Other chronic liver disease • Post transplant immunosuppressive regimen not consistent with protocol • Decompensated cirrhosis • HBV • Hx or previous solid organ transplant • Evidence of renal impairment • Hx or current psychiatric illness, immunologic disorder, hemoglobinopathy, pulmonary or cardiac	29 (47.5%) Completed 24 w tx and then had transplant 8 (13.1%) Completed 24 w tx and terminated from trial due to disease progression 2 (3.3%) Completed 24 w tx, relapsed in post tx and currently being tx again in re-tx sub-study 7 (11.5%) Prematurely discontinued tx 6 (9.8%) for • Adverse event 2 (3.3%) • Efficacy failure	transplantation Mean exposure to SOF+RBV prior to transplantation 17.7 w (no n) Follow-up 48 w post transplant	transplant (pTVR24) • SVR 12 w post treatment • Safety and tolerability Findings n (%) **Virological response** 41 pts who had tx underwent transplant. Only 38 of those had HCV RNA < LLOQ at time of transplantation and were considered for further analysis. One of those 38 pts was transplanted with an HCV infected liver and excluded from analysis. Of the 37	does not provide clear information on tx failure/relapse. FDA reviewer notes that study population limited to patients with HCV related HCC and may not be applicable to all transplant candidates.

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
		disease, porphyria, poorly controlled diabetes, cancer other than HCC, acute pancreatitis • Hx of receiving systemic antineoplastic or immunomodulatory treatment (including radiation) w/I 6 months • Tx with transcatheter arterial chemoembolization (TACE) or radio frequency ablation (RFA) w/I 30 days • Participation in a clinical trial w/i 3 months • Contradiction to RBV tx • Chronic use of immunosuppressive agents prior to tx	4 (6.6%) Age mean (range) 59 (46 to 73) Male (%) 80.3% (*no n reported*) Race n (%) *White* 90.2% (*no n reported*) HCV genotype *HCV-1a* 39.3% (*no n reported*) *HCV-1b* 34.4% (*no n reported*) *HCV-2* 13.1% (*no n reported*) *HCV-3* 11.5% (*no n reported*) *HCV-4* 1.6% (*no n reported*)		included patients, 35 had been followed to 12 w post transplant and 24 patients to 24 w post transplant. Post-transplant virological response n (%, 95% CI) **pTVR 12** 23/35 (65.7, 50.4-78.9) **pTVR 24** 17/24 (70.8, 52.1-85.4) ***Inadequate information to identify relapse rates*** **Adverse Events** (n=61 for safety	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			Tx experienced *75.4%* (*no n reported*) Mean baseline HCV RNA *≥ 6 log_{10} IU/mL* 67.2% (*no n reported*) IL28B genotype n (%) *Non-CC* 78.3% (*no n reported*) ARV tx at enrollment *No* 7 (10%) 2 (5%) 2 (2%) Baseline Child-Pugh Turcotte Score *5* 42.6% (no n) *6* 29.5% (no n) *7*		analysis) Any adverse event 52/61 (85.2%) Common AEs Fatigue (36.1%), anemia (23.0%), headache (21.3%) Significant AEs 11/61 (18%), not considered related to study drug Grade 4 laboratory abnormality 6 (9.8%) • Decreased lymphocyte count 4 (6.6%) • Increased aspartate aminotransferase 1 (1.6%)	

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
			23.0% (no n) *8* 4.9% (no n) <u>Baseline MELD Score = 7 or 8</u> 49.2%		• Total bilirubin 1 (1.6%) <u>Grade 3 laboratory abnormality</u> 21 (31.4%) • Decreased hemoglobin 9 (14.8%) • Increased non-fasting glucose 7 (11.5%) • Increased total bilirubin 5 (8.2%)	
Non-published Study on Sofosbuvir and Simeprevir Combination Treatment						
COSMOS trial NCT01466790 Completed January 2014 ***Preliminary results***	Randomized open-label trial N=167 (in published abstract; n=168 in clinical trials.gov)	<u>Inclusion</u> • Age 18 to 70 • HCV genotype 1 • HCV RNA levels ≥10,000 IU/ml at screening • Cohort inclusion: ○ Cohort 1: previous tx with PEG+RBV for at least 12 w with a null response and	*No patient characteristic information available*	<u>Intervention</u> Divided into two cohorts, enrolled sequentially, and each cohort divided into four groups.	<u>Outcomes</u> • SVR 12 post tx • Safety and tolerability ***<u>NOTE:</u> The published abstract only reports SVR12 data on***	VERY small N Allocation to treatment weighted such that nearly twice as many subjects received SOF + SME + RBV as

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
presented at the American Association for the Study of Liver Diseased Conference and abstract published in *Hepatology* December, 2013. (Jacobson 2013b) full article not available.	<u>Cohort 1</u> *Group 1* n=14 *Group 2* n=27 *Group 3* n=15 *Group 4* n=24 <u>Cohort 2</u> *Group 1* n=14 *Group 2* n=27 *Group 3* n=16 *Group 4* n=30	Metavir score F0-F2 ○ Cohort 2: Tx naïve or previous tx with PEG+RBV for at least 12 w with a null response and Meativr score F3-F4 ○ Null response defined as < 2log10 IU/mL reduction in HCV RNA from baseline at week 12 of tx • Liver biopsy • Contraception <u>Exclusion</u> • Hepatic decompensation • Other significant liver disease • HIV, HBV, or non-genotype 1 HCV • Hx of malignancy w/I 5 yrs		*Group 1* SOF 400 mg/d + simeprevir (SME) 150 mg/d for 12 w *Group 2* SOF 400 mg/d + simeprevir (SME) 150 mg/d + weight based RBV for 12 w *Group 3* SOF 400 mg/d + simeprevir (SME) 150 mg/d for 24 w *Group 4* SOF 400 mg/d + simeprevir (SME) 150 mg/d + weight based RBV for	***Cohort 1*** ***The total number of patients reported on who received SOF + SME alone = 28*** <u>Findings n (%)</u> **SVR 12 – Cohort 1** *Group 1* 13/14 (92.9%) *Group 2* 26/27 (96.3%) *Group 3* 14/14 (100%) *Group 4* 19/24 (79.2%)	SOR + SME alone.

Reference	Study Design Sample Size	Inclusion Exclusion	Patient Characteristics	Intervention Comparator Follow-up	Outcomes Assessed Main Findings Adverse Events	Quality Comments
				24 w <u>Follow-up</u> 24 w post tx		

Abbreviations

AAT – alpha1-antitrypsin; AEs – adverse events; ALT =Alanine aminotransferase; AST – aspartate aminotransferase; BMI – body mass index; d – day; ECG – electrocardiogram; eRVR – extended rapid virologic response; f/u – follow-up; HAI = histology activity index; Hb – hemoglobin; HbA1c – glycated hemoglobin; HBV – hepatitis B virus; HCV – hepatitis C virus; HCV-1 – HCV genotype 1 (and equivalents for genotypes 2, 3, 4, 5, 6);HIV – human immunodeficiency virus; HOMA-IR – homeostasis model assessment of insulin resistance; Hx – history; INF – interferon; INR – international normalized ratio; m – months; mg – milligrams; pt – patient; PEG – pegylated interferon alpha; pTVR – post-transplant virological response; rec'd – received; RNA – ribonucleic acid; RBV – ribavirin; RCT – randomized controlled trial; RVR = rapid virologic response or HCV RNA below levels of detection; SOF – sofosbuvir; tx – treatment; SVR – sustained virologic response; ULN – upper limit of normal; w – weeks; w/I – within; w/o – without

Appendix D. Critical Appraisal Summary

Table 1. Internal Validity (Risk of Bias) Criteria

Author, Year (Trial)	Internal Validity (Risk of Bias) Criteria											
	Randomization adequate?	Allocation concealment adequate?	Groups comparable at baseline?	Masking of investigator to treatment assignment?	Masking of treatment team to treatment assignment?	Masking of patient to treatment assignment?	All treatment groups received same care aside from intervention(s)?	Appropriate length of follow-up? (follow-up length)	Groups followed for equal amount of time or analysis adjusted for time?	Intention-to-treat analysis performed or possible with data provided?	Outcomes measured in valid and reliable way?	Outcome assessors masked to treatment assignment?
Gane, 2013 (ELECTRON)	U	U-NR	N	N	N	N	U-NR	Y (≥ 24w)	Y	Y	Y	N
Jacobson, 2013a (Study 1) (POSITRON)	U	U-NR	Y	U	U	U	U	N (12w)	Y	Y (modified)	Y	U
Jacobson, 2013a (Study 2) (FUSION)	U	U-NR	Y	U	U	U	U-NR	N (12w)	Y	Y (modified)	Y	U
Kowdley, 2013 (ATOMIC)	N	Y	N	N	N	N	U-NR	Y (≥ 24w)	Y	Y (modified)	Y	N
Lawitz, 2013 (Lancet) (Study 1)	Y (Cohort A)	Y (Cohort A)	U (Cohort A)	Y (Cohort A to 12 w)	U-NR	Y (Cohort A to 12 w)	U	Y (≥ 24w)	Y	Y	Y	U-NR

Author, Year (Trial)	Internal Validity (Risk of Bias) Criteria											
	Randomization adequate?	Allocation concealment adequate?	Groups comparable at baseline?	Masking of investigator to treatment assignment?	Masking of treatment team to treatment assignment?	Masking of patient to treatment assignment?	All treatment groups received same care aside from intervention(s)?	Appropriate length of follow-up? (follow-up length)	Groups followed for equal amount of time or analysis adjusted for time?	Intention-to-treat analysis performed or possible with data provided?	Outcomes measured in valid and reliable way?	Outcome assessors masked to treatment assignment?
Lawitz, 2013 (NEJM) (Study 1) (NEUTRINO)	N	NA	NA	N	N	N	NA	N (12w)	NA	NA	Y	N
Lawitz, 2013 (NEJM) (Study 2) (FISSION)	U	U-NR	Y	N	N	N	U-NR	Y (≥ 24w)	Y	U	Y	N
Osinusi, 2013 (Study 1)	NA	NA	NA	N	N	N	NA	Y (≥ 24w)	NA	NA	Y	N
Osinusi, 2013 (Study 2)	U	U-NR	U	N	N	N	U-NR	Y (≥ 24w)	Y	Y	Y	N
Rodriguez-Torres, 2013	Y	U-NR	U	Y	U	Y	Y	Y (≥ 24w)	N	N	Y	U

Key: Y – Yes; N – No; U – Unclear; NA – Not applicable; NR – Not reported

Table 2. External Validity (Risk of Bias) Criteria

Author, Year (Trial)	External Validity (Applicability) Criteria					
	Study reports on important end outcomes? (or adequate rationale if surrogate used)	Single primary outcome used? (or adequate rationale if composite outcome used)	Author(s) have financial or other substantive conflicts of interest?	Sponsor(s) have financial or other substantive conflicts of interest?	Study population similar to population to whom intervention will be applied?	Control group received standard of care (adequate comparator)?
Gane, 2013 (ELECTRON)	Y (SVR 24)	Y	Y	Y	U (no HCV-1 enrolled)	N (HCV-1; various regimens with SOF + RBV, but no PEG, bocep or telap) N (HCV-2,3; various regimens & duration of SOF +/- RBV +/- PEG, but all grps rec'd SOF)
Jacobson, 2013a (Study 1) (POSITRON)	N (SVR 12)	Y	Y	Y	U (no HCV-1 enrolled)	N (placebo)
Jacobson, 2013a (study 2) (FUSION)	N (SVR 12)	Y	Y	Y	U (no HCV-1 enrolled)	N (HCV 2,3 w/o PEG)
Kowdley, 2013 (ATOMIC)	Y (SVR 24)	Y	Y	Y	U (no HCV-2,3 enrolled)	N (HCV-1 w/o bocep or telap)
Lawitz, 2013 (Lancet)	Y (SVR 24)	Y	Y	Y	U (no HCV-2,3 enrolled in RCT portion)	N (HCV-1 w/o bocep or telap)

Author, Year (Trial)	External Validity (Applicability) Criteria					
	Study reports on important end outcomes? (or adequate rationale if surrogate used)	Single primary outcome used? (or adequate rationale if composite outcome used)	Author(s) have financial or other substantive conflicts of interest?	Sponsor(s) have financial or other substantive conflicts of interest?	Study population similar to population to whom intervention will be applied?	Control group received standard of care (adequate comparator)?
Lawitz, 2013 (NEJM) (Study 1) (NEUTRINO)	N (SVR 12)	Y	Y	Y	U (largely HCV-1)	NA
Lawitz, 2013 (NEJM) (Study 2) (FISSION)	N (SVR 12)	Y	Y	Y	U (HCV-2,3)	Y (HCV-2,3 24w RBV + PEG)
Osinusi, 2013 (Study 1)	Y (SVR 24)	Y	Y	N	U (HCV-1 w/unfavorable characteristics)	NA
Osinusi, 2013 (Study 2)	Y (SVR 24)	Y	Y	N	U (HCV-1 w/unfavorable characteristics)	N (RBV 600mg rather than 1000 or 1200mg)
Rodriguez-Torres, 2013	Y (SVR 24)	Y	Y	Y	U (no HCV-2,3 enrolled)	N (HCV-1 w/o bocep or telap)

Key: Y – Yes; N – No; U – Unclear; NA – Not applicable

Abbreviations: bocep – boceprevir; grps – groups; HCV – hepatitis C virus; PEG – pegylated interferon alpha; RBV – ribavirin; SVR – sustained virologic response; telap – telaprevir

Table 3. Overall Quality Summary

Overall Quality Summary				
Author, Year (Trial)	How well was the study done to minimize bias in study design? (Good, Fair, Poor)	How well did the study respond to the questions of this report? (Good, Fair, Poor)	Overall Study Quality (Good, Fair, Poor)	Comments
Gane, 2013 (ELECTRON)	Poor	Poor	**Poor**	Open label study; largely a PEG regimen ranging study for HCV-2,3 and PEG-sparing for HCV-1
Jacobson, 2013a (Study 1) (POSITRON)	Poor	Poor	**Poor**	Placebo control RCT; interferon treatment contraindicated, unacceptable or prior discontinuation due to unacceptable AEs
Jacobson, 2013a (Study 2) (FUSION)	Poor	Poor	**Poor**	Active control RCT; no response to prior interferon containing regimen; duration ranging length of RBV tx (12w vs 16w)
Kowdley, 2013 (ATOMIC)	Poor	Poor	**Poor**	Open label study; duration ranging 12w vs 24w PEG + RBV
Lawitz, 2013 (Lancet)	Poor	Poor	**Poor**	Dose finding placebo control RCT for HCV-1 and additional single group for HCV-2, 3; all tx naïve and non-cirrhotic
Lawitz, 2013 (NEJM) (Study 1) (NEUTRINO)	Poor	Poor	**Poor**	Open label, single group study; tx naïve; 89% HCV-1 (11% HCV-4, 5, 6); 17% cirrhotic
Lawitz, 2013 (NEJM) (Study 2) (FISSION)	Poor	Poor	**Poor**	Open label non-inferiority RCT; tx naïve; HCV-2, 3; 20% cirrhotic

Overall Quality Summary				
Author, Year (Trial)	How well was the study done to minimize bias in study design? (Good, Fair, Poor)	How well did the study respond to the questions of this report? (Good, Fair, Poor)	Overall Study Quality (Good, Fair, Poor)	Comments
Osinusi, 2013 (Study 1)	Poor	Poor	**Poor**	Proof of concept study (n=10) with HCV-1 and unfavorable tx characteristics
Osinusi, 2013 (Study 2)	Poor	Fair	**Poor**	Open label RCT with HCV-1 and unfavorable tx characteristics
Rodriguez-Torres, 2013	Poor	Poor	**Poor**	Open label RCT; tx naïve; with HCV-1; dose ranging

Abbreviations: AEs – adverse events; HCV – hepatitis C virus; HCV-1 – HCV genotype 1 (and equivalents for genotypes 2, 3, 4, 5, 6); mg – milligrams; PEG – pegylated interferon alpha; RBV – ribavirin; RCT – randomized controlled trial; rec'd – received; tx – treatment; w – weeks

Definitions Used for Domains with Unique Features for Condition

Masking: If study was open label did not consider masking/blinding adequate for investigators, clinicians, patients or outcome assessors

Length of follow-up: Considered inadequate if greater than 24 weeks post-treatment

Important outcomes/surrogates: Accepted any important clinical outcomes such as development of end-state liver disease and considered SVR 24 to represent an adequate surrogate measure because strongly linked to clinical outcomes; considered inadequate if measure reported was SVR 12.

Comparability of study population to likely use population: Rated as uncertain if study restricted population to those likely to need treatment in real world situations, including representative populations of those with poor prognostic factors such as male sex, black race, and cirrhosis or advanced hepatic fibrosis, as well as those who are HBV or HIV positive, actively misusing alcohol and other drugs, and those who are unable to use interferon.

Standard of care: Current standard of care regimen for HCV-1 includes triple therapy with PEG, RBV, and a polymerase inhibitor (boceprevir or telaprevir) using response guided therapy; for HCV-2 or -3 standard of care is 24 weeks of treatment with PEG and RBV.

References

AbbVie Inc. (2014). AbbVie to present late-breaker Pearl-III study in patients with chronic hepatitis C at the 21st conference on retroviruses and opportunistic infections. March 3, 2014. Boston, MA: AbbVie Inc. Retrieved March 6, 2014, from http://abbvie.mediaroom.com/2014-03-03-AbbVie-to-Present-Late-breaker-PEARL-III-Study-in-Patients-with-Chronic-Hepatitis-C-at-the-21st-Conference-on-Retroviruses-and-Opportunistic-Infections

American Association for the Study of Liver Diseases (AASLD). (2009). *Diagnosis, management and treatment of hepatitis C: An update*. Retrieved March 9, 2014, from http://www.aasld.org/practiceguidelines/documents/bookmarked%20practice%20guidelines/diagnosis_of_hep_c_update.aug%20_09pdf.pdf

American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA). (2014). *Recommendations for testing, managing and treating hepatitis C.* Retrieved March 9, 2014, from http://www.hcvguidelines.org/sites/default/files/full_report.pdf

Bain, V.G., Bonacini, M., Govindarajan, S., Ma, M., Sherman, M., Gibas, A., et al. (2004). A multicentre study of the usefulness of liver biopsy in hepatitis C. *Journal of Viral Hepatitis, 11*(4), 375-82.

Blatt, L., Mutchnick, M., Tong, M., Klion, F., Lebovics, E., Freilich, B., et al. (2000). Assessment of hepatitis C virus RNA and genotype from 6807 patients with chronic hepatitis C in the United States. *Journal of Viral Hepatitis, 7*(3), 196-202.

Centers for Disease Control (CDC). (2010). Hepatitis C: General information. Retrieved February 19, 2014, from http://www.cdc.gov/hepatitis/hcv/pdfs/hepcgeneralfactsheet.pdf

Centers for Disease Control (CDC). (2014). Hepatitis C FAQs for health professionals. Retrieved April 29, 2014, from http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm#section1

Chak, E., Talal, A., Sherman, K., Schiff, E., & Saab, S. (2011). Hepatitis C virus infection in USA: An estimate of true prevalence. *Liver International, 31*(8), 1090-1101.

Chen, J., Florian, J., Carter, W., Fleischer, R., Hammerstrom, T, Jadhav, P., et al. (2013). Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. *Gasteroenterology, 144*(7), 1450-1455.

Chou, R., Hartung, D., Rahman, B., Wasson, N., Cottrell, E., & Fu, R. (2012). *Treatment for hepatitis C virus infection in adults. Comparative effectiveness review No. 76*. Prepared

by the Oregon Evidence-based Practice Center. Rockville, MD: Agency for Healthcare Research and Quality.

Davis, G.L., Alter, M.J., El-Serag, H., Poynard, T., & Jennings, L.W. (2010). Aging of hepatitis C virus (HCV)-infected persons in the United States: A multiple cohort model of HCV prevalence and disease progression. *Gastroenterology, 138*(2), 513-521.

Denniston, M., Jiles, R., Drobeniuc, J., Klevens, M., Ward, J., McQuillan, G., et al. (2014). Chronic hepatitis C virus infection in the United States: National Health and Nutrition Examination Survey 2003 to 2010. *Annals of Internal Medicine, 160*(5), 293-300.

European Association for the Study of the Liver (EASL). (2013). EASL clinical practice guidelines: Management of hepatitis C infection. *Journal of Hepatology, 60*(5), 392-420.

Food and Drug Administration (FDA). (2013a). *Guidance for industry: Chronic hepatitis C virus infection: Developing direct-acting antiviral drugs for treatment. Draft Guidance.* Baltimore, MD: US Department of Health and Human Services, Food and Drug Administration.

Food and Drug Administration (FDA). (2013b). *SOVALDI™ (sofosbuvir) tablets, for oral use*. Retrieved February 21, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204671s000lbl.pdf

Freeman, A.J., Dore, G.J., Law, M.G., Thorpe, M., Von Overbeck, J., Lloyd, A.R., et al. (2001). Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology*, *34*(4 Pt 1), 809-816.

Gane, E., Stedman, C., Hyland, R., Ding, X., Svarovskaia, E., & Symonds, W. (2013). Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *New England Journal of Medicine, 368*(1), 36-44.

Ghany, M., Strader, D., Thomas, D., & Seeff, B. (2009). AASLD practice guidelines: Diagnosis, management and treatment of hepatitis C: An update. *Hepatology, 49*(4), 1336-1374.

Ghany, M., Nelson, D., Strader, D., Thomas, D., & Seeff, L. (2011). An update on treatment of genotype 1 chronic hepatitis c virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology, 54*(4), 1433-1444.

Grebely, J., Prins, M., Helard, M., Cox, A., Osburn, W., Lauer, G., et al. (2012). Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: Towards a vaccine. *Lancet Infectious Diseases, 12* (5), 408-414.

Hartung, D., Zarin, D., Guise, J., McDonagh, M., Paynter, R., & Helfand, M. (2014). Reporting discrepancies between the ClinicalTrials.gov results database and peer-reviewed publications. *Annals of Internal Medicine, 160*(7), 477-484.

Hezode, C., Dorival, C., Zoulim, F., Poynard, T., Mathurin, P., Pol, S. et al. (2012). Safety of telaprevir or boceprevir in combination with peginterferon alfa/ribavirin in cirrhotic non responders: First results of the French early access program. Presented at The International Liver Congress, Barcelona, Spain, April 18-22, 2012. Retrieved March 9, 2014, from http://mobile.ilcapp.eu/EASL_161/poster_23756/program.aspx

Imbert-Bismut, F., Ratziu, V., Pieroni, L., Charlotte, F., Benhamou, Y., Poynard, T., et al. (2001). Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: A prospective study. *Lancet, 357*(9262), 1069-75.

Jacobson, I., Gordon, S., Kowdley, K., Yoshida, E., Rodriguez-Torres, M., Sulkowski, M., et al. (2013a). Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *The New England Journal of Medicine, 368*(20), 1867-1877.

Jacobson, I.M., Ghalib, R.H., Rodriguez-Torres, M., Younossi, Z.M., Corregidor, A., Sulkowski, M.S., et al. (2013b). SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naïve and prior null responder patients: The COSMOS study. [Abstract]. *Hepatology, 58*(6 Suppl), 1379A.

Kowdley, K., Lawitz, E., Crespo, I., Hassanein, T., Davis, M., & DeMicco, M. (2013). Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naïve patients with hepatitis C genotype 1 infection (ATOMIC): An open-label, randomized, multicenter phase II trial. *The Lancet, 381*(9883), 2100-2107.

Lawitz, E., Lalezari, J., Hassanein, T., Kowdley, K., Poordad, F., Sheikh, A., et al. (2013a). Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naïve patients with genotype 1, 2 and 3 hepatitis c infection: A randomized, double-blind, phase 2 trial. *The Lancet, 13*(5), 401-408.

Lawitz, E., Mangia, A., Wyles, D., Rodriguez-Torres, M., Hassanein, T., Gordon, S., et al. (2013b). Sofosbuvir for previously untreated chronic hepatitis C infection. *The New England Journal of Medicine*, *368*(20), 1878-1887.

Lawitz, E., Ghalib, R., Rodriguez-Torres, M., Younossi, Z., Corregidor, A., Sulkowski, M., et. al. (2014, April). Simeprevir plus sofosbuvir with/without ribavirin in HCV genotype 1 prior null-responders/treatment-naïve patients (COSMOS study): Primary endpoint (SVR12)

results in patients with Metavir F3-4 (Cohort 2). Paper presented at the conference of the European Association for the Study of the Liver. Retrieved April 24, 2014 from http://www.professionalabstracts.com/ilc2014/planner/index.php?go=abstract&action=abstract_show&absno=3655&

Levin, J. (2012). Prevalence, treatment, and comorbidities of hepatitis C infection (HCV) among patients with commercial and Medicaid insurance. *National AIDS Treatment Advocacy Project Digestive Disease Week*, May 18-21, 2013. Retrieved February 20, 2014, from http://www.natap.org/2013/DDW/DDW_03.htm

Louie, K., Laurent, S., Forssen, U., Mundy, L., & Pimenta, J. (2012). The high comorbidity burden of the hepatitis c virus infected population in the United States. *BMC Infectious Diseases, 12*(86), 1-11.

McCombs, J., Matsuda, T., Tonnu-Mihara, I., Saab, S., Hines, P., L'Italien, G., et al. (2014). The risk of long-term morbidity and mortality in patients with chronic hepatitis C: Results from an analysis of data from a Department of Veterans Affairs clinical registry. *Journal of the American Medical Association Internal Medicine, 174*(2), 204-212.

Mishra, P. (2013). *New drug application medical review: Sofosbuvir (GS-7977*). Washington, D.C.: US Food and Drug Administration. Retrieved March 5 from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204671Orig1s000MedR.pdf

Montori, V.M., Jaexchke, R., Schunermann, H.J., Bhandari, M, Brozek, J.L., Devereaux, P.J., et al. (2004). Users' guide to detecting misleading claims in clinical research reports. *British Medical Journal, 329*(6), 1093-1096.

Osinusi, A., Meissner, E., Lee, Y., Bon, D., Heytens, L., Nelson, A., et al. (2013). Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: A randomized clinical trial. *Journal of the American Medical Association, 310*(8), 804-811.

Parkes, J., Guha, I.N., Roderick, .P, & Rosenberg, W. (2006). Performance of serum marker panels for liver fibrosis in chronic hepatitis C. *Journal of Hepatology, 44*(3), 462-74.

Prasad, V., Vandross, A., Toomey, C., Cheung, M., Rho, J., Quinn, S., et al. (2013). A decade of reversal: An analysis of 146 contraindicated medical practices. *Mayo Clinic Proceedings, 88*(8), 790-798.

Robison, J. (2013). Gilead Sciences $1,000 per day Solvaldi pills ready to launch. *The Motley Fool*, 13 December 2013. Retrieved February 21, 2014, from

http://www.fool.com/investing/general/2013/12/13/gilead-sciences-1000-per-day-sovaldi-pills-ready-t.aspx

Rodriguez-Torres, M., Lawitz, E., Kowdley, K., Nelson, D., DeJesus, E., et al. (2013). Sofosbuvir (GS-7977) plus peginterferon/ribavirin in treatment naïve patients with HCV genotype 1: A randomized, 28-day, dose-ranging trial. *Journal of Hepatology, 58*(4), 663-668.

Scottish Intercollegiate Guidelines Network (SIGN). (2013). *Management of hepatitis C*. Edinburgh: (SIGN publication no. 133). Retrieved February 21, 2014 from http://www.sign.ac.uk/pdf/sign133.pdf

Sulkowski, M., Jacobson, I., Ghalib R., Rodriguez-Torres, M. Younossi, Z., Corredidor, A., et. al. (2014, April). *Once-daily simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in HCV genotype 1 prior null responders with Metavir F0-2: COSMOS study subgroup analysis.* Paper presented at the conference of the European Association for the Study of the Liver. Retrieved April 24, 2014 from http://www.professionalabstracts.com/ilc2014/planner/index.php?go=abstract&action=abstract_show&absno=2733&

Thein, H.H., Yi, Q., Dore, G.J., & Krahn, M.D. (2008). Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: A meta-analysis and meta-regression. *Hepatology,* 48(2), 418-431.

Thorlund, K., Druyts, E., & Mills, E. (2014). SVR 12 is higher than SVR24 in treatment-naïve hepatitis C genotype 1 patients treated with peginterferon plus ribavirin. *Clinical Epidemiology, 6*, 49-58.

Tice, J., Ollendorf, D., & Pearson, S. (2014). *The comparative clinical effectiveness and value of simeprevir and sofosbuvir in the treatment of chronic hepatitis C infection*. Draft report. Boston, MA: The Institute for Clinical & Economic Review (ICER) completed for the California Technology Assessment Forum (CTAF). Retrieved February 12, 2014, from http://ctaf.org/sites/default/files/assessments/CTAF_Hep_C_Apr14_final.pdf

United States Department of Veterans Affairs. (2013). Viral hepatitis. Retrieved February 21, 2014, from http://www.hepatitis.va.gov/patient/faqs/treatment-success.asp

United States Preventive Services Task Force (USPSTF). (2013). Screening for hepatitis C virus infection in adults. Retrieved April 29, 2014, from http://www.uspreventiveservicestaskforce.org/uspstf12/hepc/hepcfact.pdf

Van der Meer, A., Veldt, B., Feld, J., Wedemeyer, H., Dufour, J., Lammert, F., et al. (2012). Association between sustained virological response and all-cause mortality among

patients with chronic hepatitis C and advanced hepatic fibrosis. *Journal of the American Medical Association, 308*(24), 2584-2593.

Veterans Health Administration (VHA) Pharmacy Benefits Management Services, the Medical Advisory Panel, VISN Pharmacist Executives, and the Office of Public Health. (2014). *Interim considerations for use: simeprevir in combination with peginterferon alfa and ribavirin, sofosbuvir in combination with peginterferon alfa and ribavirin, sofosbuvir in combination with ribavirin.* Retrieved March 8, 2014, from www.pbm.va.gov/clinicalguidance/clinicalrecommendations/interim_considerations_simeprevir_sofosbuvir_2.doc

Yee, H.S., Chang, M.F., Pocha, C., Lim, J., Ross, D., Morgan, T.R., et al. (2012.) Update on the management and treatment of hepatitis C virus infection: Recommendation from the Department of Veterans Affairs Hepatitis Resource Center Program and the National Hepatitis C Program Office. *American Journal of Gastroenterology, 107*(5), 669-89.