The Comparative Clinical Effectiveness and Value of Simeprevir and Sofosbuvir in the Treatment of Chronic Hepatitis C Infection

A Technology Assessment

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Table of Contents

Abbreviations used in this report

AEs:	Adverse events
BOC:	Boceprevir
CDC:	Centers for Disease Control and Prevention
CI:	Confidence Interval
CMS:	Centers for Medicare & Medicaid Services
CTAF:	California Technology Assessment Forum
DARE:	Database of Abstracts of Reviews of Effects
DAA:	Direct-acting antiviral agent
FDA:	US Food and Drug Administration
IFN	Interferon alfa
HCC:	Hepatocellular carcinoma
HCV:	Hepatitis C virus
HR:	Hazard ratio
NR:	Not reported
NS:	Not significant
OR:	Odds ratio
P:	Pegylated interferon alfa
PR:	Pegylated interferon alfa plus ribavirin
Q8:	Taken every 8 hours
R:	Ribavirin
RCT:	Randomized Controlled Trial
SIM:	Simeprevir
SOF:	Sofosbuvir
SVR:	Sustained virologic response
SVR12:	SVR at 12 weeks
TVR:	Telaprevir
US:	United States

Executive Summary

This assessment of the California Technology Assessment Forum (CTAF) evaluates the evidence on the comparative clinical effectiveness and value of two drugs recently approved by the FDA for the treatment of chronic hepatitis C: simeprevir and sofosbuvir. Chronic hepatitis C is a common infection that is a major cause of chronic liver disease, liver failure, and hepatocellular carcinoma, and is the leading indication for liver transplantation in the Western world.[1] Prior to 2011, the combination of pegylated interferon and ribavirin (PR) was the gold standard of therapy for the treatment of chronic hepatitis C. Approximately half of patients with genotype 1 disease, the most prevalent type of hepatitis C in the US, could expect to achieve sustained virologic response (SVR) with PR therapy. PR therapy can be difficult, however, as both interferon and ribavirin can produce bothersome side effects, and in some cases, dangerous levels of anemia, neutropenia, and/or thrombocytopenia.[2] The 2011 introduction of direct-acting antiviral (DAA) protease inhibitors boceprevir (Victrelis®, Merck & Co.) and telaprevir (Incivek®, Vertex Pharmaceuticals, Inc.) has resulted in substantially improved SVR rates in many patients when used with PR regimens. This improvement has come with new challenges, however, including significant additional side effects and drug-drug interactions as well as stringent dosing requirements and high pill burdens for patients.[3]

Novel DAA agents have been developed with the potential for simplified dosing, fewer side effects and drug-drug interactions, and in some patients, the promise of interferon- and/or ribavirin-free treatment, particularly for genotypes 2 and 3 (the other common genotypes in the US). These new agents include the recently-approved protease inhibitor simeprevir (Olysio®, Janssen Products, LP) and polymerase inhibitor sofosbuvir (Sovaldi™, Gilead Sciences, Inc.), as well as several other agents that are currently in late-stage clinical trials. Uncertainties remain with these new agents, however, as data on treatment-related side effects and their performance in particular patient populations are still emerging in the published literature. In addition, the costs of treatment are expected to increase substantially, as treatment regimens with the two new agents are expected to cost between $70,000 and $150,000 per course of therapy.[4,5] Accordingly, the California Technology Assessment Forum has chosen to review the evidence on the comparative clinical effectiveness and comparative value of new DAA agents for chronic hepatitis C in relation to the existing standard of care in multiple patient populations.

Genotype 1

Table ES1 below summarizes the key benefits and harms for the treatment options for genotype 1. Among treatment-naïve patients, the protease inhibitors increased the SVR at 12 weeks (SVR12) from the 40% range with PR to the 70% range. The improved SVR was somewhat offset by an increase in the complexity of the drug therapy. A large number of pills had to be taken about every 8 hours. In addition, there were burdensome new side effects added to the flu-like symptoms of interferon and the anemia and teratogenicity of ribavirin. These included a marked increase in anemia and nausea for both drugs, 20% more patients experiencing taste disturbance for boceprevir, and 20% more patients experiencing generalized pruritus with telaprevir. The drugs also have a large number of important drug interactions. Despite these problems, triple therapy with one of the two protease inhibitors is the standard of care for treatment of genotype 1.

Table ES1. Summary of Benefits and Harms for Genotype 1 by Prior Treatment Status and Interferon Eligibility.

Treatment Approach (weeks)	SVR12 (Percent)	Treatment Burden	Adverse effects	Interferon-ineligible
Genotype 1				
Treatment-Naive				
PR (48)	47	48 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (≤ 30%)	No
BOC(24) + PR(48)	73	Add Q8 hour pills	Anemia (≤ 50%), more nausea and dysguesia, drug interactions	No
TVR(12) + PR(48)	74	Add Q8 hour pills	Anemia (≤ 50%), more nausea and pruritus, drug interactions	No
SMV(12) + PR(24-48)	76	1 pill to PR	No increase in anemia.	No
SOF(12) + PR(12)	83	1 pill to PR Fewer weeks	No increase in anemia.	No
SMV(12) + SOF(12)	No data (?>90)	No P, maybe no R	Not reported yet	Maybe
Treatment-Experienced				No
PR (48)	22	48 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (up to 30%)	No
BOC(24) + PR(48)	64	Add Q8 hour pills	Anemia (≤ 50%), more nausea and dysguesia, drug interactions	No
TVR(12) + PR(48)	70	Add Q8 hour pills	Anemia (≤ 50%), more nausea and pruritus, drug interactions	No
SMV(12) + PR(24-48)	67	1 pill to PR	No increase in anemia.	No
SOF(12) + PR(12)	No data	1 pill to PR Fewer weeks	No increase in anemia.	Maybe
SMV(12) + SOF(12)	90	No P, maybe no R	Not reported yet	Yes

Abbreviations: Q8 = taken every 8 hours; P = pegylated interferon; R = ribavirin

Simeprevir does not appear to significantly improve the SVR12 compared with triple therapy. The primary benefits of simeprevir are the reduced incidence of anemia and the reduced pill burden: it only requires taking one pill a day. Adverse events (AEs) specifically associated with simeprevir include pruritus, photosensitivity-induced rashes, and hyperbilirubinemia, but these were generally not severe and were easily managed. The increase in pruritus compared to PR was less than that seen with telaprevir. One important finding specific to simeprevir is that its effectiveness is markedly diminished in patients with the Q80K genetic polymorphism in HCV genotype 1. If the Q80K polymorphism is present, simeprevir should not be used. Simeprevir requires PR and cannot be used to treat interferon-ineligible patients. The primary weakness in the data is the lack of head to head trials comparing simeprevir and one of the protease inhibitors. There is a large (n=766) randomized trial comparing simeprevir to telaprevir that should complete data collection for its primary outcome in March 2014. In addition, there are no data on the impact of treatment on long term outcomes such as the incidence of cirrhosis, liver decompensation, hepatocellular carcinoma, transplant or death.

Sofosbuvir plus PR also appears to cause less anemia and certainly represents a lower pill burden than standard triple therapy. It also requires only 12 weeks of PR rather than the 24 to 48 weeks with the protease inhibitors. There are less robust comparative data on sofosbuvir + PR compared to PR alone than for simeprevir, and there are no data comparing it to PR plus simeprevir, boceprevir or telaprevir. However in the network meta-analysis sofosbuvir + PR had nominally the highest SVR12. Because of the shorter course of PR, sofosbuvir + PR had fewer grade 3 and 4 AEs and less stopping treatment due to AEs, with no consistent pattern of an increase in AEs other than anemia (23% versus 14% for PR). As with simeprevir, this combination cannot be used in patients who are interferon-ineligible, and there are no long-term outcome data.

The preliminary data on simeprevir plus sofosbuvir with or without ribavirin are encouraging. The available SVR12 data from treatment-experienced patients averaged 90%; the SVR12 of treatment-naïve patients should be even better. It is interferon-free, so can be used in interferon-ineligible patients. Since it is interferon-free (and perhaps ribavirin-free), it should have markedly lower adverse event rates than PR based treatment. The data come from four different regimens in one small study without detailed published results and should be considered preliminary at this point.

Genotype 2

For genotype 2 the story is more straightforward (see Table ES2 below). The combination of sofosbuvir plus ribavirin is superior in clinical effectiveness to prior standard treatment options. Among treatment-naïve patients, there was a large increase in SVR12 seen in the randomized FISSION trial and supported by the non-randomized VALENCE trial. The SVR12 for treatment-experienced patients was 86% and 90% in the two uncontrolled studies, but high enough to assume at least non-inferiority to PR therapy. The sofosbuvir-based regimen is interferon-free, which decreases grade 3 and 4 adverse events, markedly decreases stopping therapy because of adverse events, and reduces interferon-associated adverse events such as fatigue, fever, myalgias, and headaches. Sofosbuvir therapy does not come with an increase in the anemia seen with the first generation protease inhibitors – in fact the incidence of anemia was lower in the sofosbuvir arms of the trials. The treatment course is also half as long (12 versus 24 weeks). Since the sofosbuvir-based regimen is interferon-free, the benefits should be even greater in those genotype 2 patients who are treatment-naïve but ineligible for interferon because of psychiatric or other co-morbidities. In the POSITRON trial, the SVR12 was 93% compared to 0% for treatment-naïve patients and 76% versus 0% for treatment-experienced patients.

Table ES2. Summary of Benefits and Harms for Genotype 2 by Prior Treatment Status and Interferon Eligibility.

Treatment Approach (weeks)	**SVR12 (Percent)**	**Treatment Burden**	**Adverse effects**	**Interferon-ineligible**
Genotype 2				
Treatment-Naive				
PR (24)	78	24 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (up to 30%)	No
SOF(12) + R(12)	97	Shorter, no P	Less fatigue, less anemia	Yes
Treatment-Experienced				
PR (24)	No data	24 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (up to 30%)	No
SOF(12) + R(12)	88	Shorter, no P	Less fatigue, less anemia	Yes

Abbreviations: P = pegylated interferon; R = ribavirin

Genotype 3

For genotype 3 the story is more complex (see Table ES3 below). The combination of sofosbuvir plus ribavirin for 12 weeks did not increase SVR12 compared to PR among treatment-naïve patients in the FISSION trial. However the SVR12 consistently increased with increasing lengths of therapy to 16 and 24 weeks (56% to 93% in the uncontrolled VALENCE trial). The SVR12 for treatment-experienced patients increased from 30% (12 weeks) to 62% (16 weeks) to 77% (24 weeks). As noted above, the sofosbuvir-based regimen is interferon-free, which decreases grade 3 and 4 adverse events, markedly decreases stopping therapy because of adverse events, and reduces interferon-associated adverse event such as fatigue, fever, myalgias, and headaches. Sofosbuvir therapy has a lower incidence of anemia than PR in the phase 3 trials. The treatment course is the same as PR, but without the injections and side effects of interferon. Since the sofosbuvir-based regimen is interferon-free, the benefits should be even greater in those genotype 3 patients who are treatment naïve, but ineligible for interferon because of psychiatric or other co-morbidities. In the POSITRON trial, the SVR12 was 61% compared to 0% for treatment naïve patients and 76% versus 0% for treatment-experienced patients.

Table ES3. Summary of Benefits and Harms for Genotype 3 by Prior Treatment Status and Interferon Eligibility.

Treatment Approach (weeks)	SVR12 (Percent)	Treatment Burden	Adverse effects	Interferon-ineligible
Genotype 3				
Treatment-Naive				
PR (24)	62	24 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (up to 30%)	No
SOF(12) + R(12)	93	Shorter, no P	Less fatigue, less anemia	Yes
Treatment-Experienced				
PR (24)	No data	24 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (up to 30%)	No
SOF(12) + R(12)	77	Shorter, no P	Less fatigue, less anemia	Yes

Abbreviations: P = pegylated interferon; R = ribavirin

Model Results Evaluating Clinical and Economic Outcomes of Hepatitis C Treatment Scenarios

Consistent with the findings of the systematic review and network meta-analysis, our model demonstrates that therapeutic regimens containing sofosbuvir have the potential to substantially increase the number of patients achieving SVR relative to previous therapeutic options, as well as to provide the first effective interferon-free option to patients ineligible or intolerant to interferon. These advantages are considerable. By contrast, use of simeprevir with pegylated interferon and ribavirin appear to provide limited benefit over the previous standard of care.

For many patient subpopulations, however, the benefits of sofosbuvir and simeprevir come at a substantially increased cost. The costs for initial treatment regimens including sofosbuvir or simeprevir are expected to range from a low of approximately $88,000 to a high exceeding $175,000 per patient, depending on the drug selected and the time course of initial treatment. Many patients who are treated with an initial course and who fail to achieve a prolonged SVR would be expected to be retreated, adding further to the estimated treatment costs over a one-year time frame.

For many comparisons with the historical standard of care, the incremental cost required to achieve one additional SVR with newer treatment regimens was greater than $300,000. While the "cost per additional SVR" is not a common measure of cost-effectiveness in the literature, the costs per SVR generated in this analysis are generally higher than those previously published for telaprevir ($189,000),[118] different regimens of PR ($17,000-$24,000),[119] and even highly active antiretroviral therapy in HIV patients ($1,000-$79,000).[120]

The clinical advantages of newer treatment regimens would therefore come with a substantial potential impact on health care budgets should a large number of patients be treated. As estimated by our model, we anticipate cumulative one-year treatment costs per 1,000 patients to be somewhere between $100-$200 million. For example, if a risk-bearing integrated provider group is responsible for the care of 500,000 patients, and one assumes an underlying infection rate of 1.7%, there would be approximately 8,500 patients in this population infected with Hepatitis C. If even 50% of this population comes forward for treatment, the immediate one-year budget impact for the provider group would be estimated to be well over $400 million. It would be impossible for this magnitude of immediate increased spending to be accommodated within the budgets established by current health care premium structures, provider risk-sharing contracts, and patient co-payments.

Using an estimate of the number of infected individuals in California who know of their infection and would be considered for treatment, we estimate that replacing current care with sofosbuvir-based regimens would raise drug expenditures by $18-$29 billion in a single year. We looked for potential cost offsets to these initial costs of drug treatment that could result from downstream reductions in liver-related complications following successful treatment of hepatitis C infection. At a 5-year time horizon, however, cost offsets would be estimated to represent less than 10-20% of upfront treatment costs. Even at a 20-year horizon, if all patients infected with hepatitis C are treated with new regimens, the cost offset will only cover approximately two-thirds of initial drug costs.

The budget impact and cost offset figures change substantially under a second treatment scenario in which only patients with advanced liver fibrosis are started on the new treatment regimens, with other patients treated with existing pre-DAA regimens. Treating this smaller group of patients is estimated to result in an increase in initial drug expenditures of “only” $6.3 billion for the population of California, one-third of the extra amount needed to treat all infected patients. At five years, costs saved by reducing liver-related complications in this subgroup would total only 15% of added drug costs, but at 20 years, estimated cost offsets would produce a net savings to the health care system of approximately $400 million.

We must emphasize several limitations of our budget impact analyses. First, while there were sufficient data to perform a network meta-analysis for patients with genotype 1 infection, estimates could not be generated for all stratifications of interest for the model, and we could not even attempt quantitative synthesis for patients with genotypes 2 or 3. We therefore often had to resort to basing the input to the model on point estimates from individual studies, which in some cases involved small numbers of patients. Our results are therefore quite sensitive to the estimates of drug effectiveness and should be viewed with caution.

In addition, as described previously, we modeled only the immediate clinical effects of treatment as well as the potential downstream benefits of preventing liver-related complications. While we presented pooled rates of discontinuation due to adverse events from available clinical trial data, we assumed equally across all drug regimens that all patients completed their course of therapy and were fully compliant while doing so. This assumption likely does not adequately reflect the benefits of better adherence to newer regimens with shortened courses of interferon or no interferon at all.

Finally, our analyses did not consider other possible benefits to patients from greater treatment success, such as improved quality of life and reduced absenteeism from work or school. Full analysis of all potential outcomes and costs of these new treatment options will only be possible through additional data collection and/or the development of complex simulation models that approximate the natural history of hepatitis C and its treatment.

Introduction

This assessment of the California Technology Assessment Forum (CTAF) evaluates the evidence on the comparative clinical effectiveness and value of two drugs recently approved by the FDA for the treatment of chronic hepatitis C: simeprevir and sofosbuvir.

Chronic hepatitis C is a common infection that is a major cause of chronic liver disease, liver failure, and hepatocellular carcinoma (HCC), and is the leading indication for liver transplantation in the Western world.[1] Prior to 2011, the combination of pegylated interferon and ribavirin (PR) was the gold standard of therapy for the treatment of chronic hepatitis C. Approximately half of patients with genotype 1 disease, the most prevalent type of hepatitis C in the US, could expect to achieve sustained virologic response (SVR) with PR therapy. PR therapy can be difficult, however, as both interferon and ribavirin can produce bothersome side effects, and in some cases, dangerous levels of anemia, neutropenia, and/or thrombocytopenia.[2] The 2011 introduction of direct-acting antiviral (DAA) protease inhibitors boceprevir (Victrelis®, Merck & Co.) and telaprevir (Incivek®, Vertex Pharmaceuticals, Inc.) has resulted in substantially improved SVR rates in many patients when used with PR regimens. This improvement has come with new challenges, however, including significant additional side effects and drug-drug interactions as well as stringent dosing requirements and high pill burdens for patients.[3]

Novel DAA agents have been developed with the potential for simplified dosing, fewer side effects and drug-drug interactions, and in some patients, the promise of interferon- and/or ribavirin-free treatment, particularly for genotypes 2 and 3 (the other common genotypes in the US). These new agents include the recently-approved protease inhibitor simeprevir (Olysio®, Janssen Products, LP) and polymerase inhibitor sofosbuvir (Sovaldi™, Gilead Sciences, Inc.), as well as several other agents that are currently in late-stage clinical trials. Uncertainties remain with these new agents, however, as data on treatment-related side effects and their performance in particular patient populations are still emerging in the published literature. In addition, the costs of treatment are expected to increase substantially, as treatment regimens with the two new agents are expected to cost between $70,000 and $150,000 per course of therapy.[4,5] Accordingly, the California Technology Assessment Forum has chosen to review the evidence on the comparative clinical effectiveness and comparative value of new DAA agents for chronic hepatitis C in relation to the existing standard of care in multiple patient populations.

This assessment will attempt to answer the key issues that patients, providers, and payers face. These include the following questions: 1) among patients with genotype 1, are treatment regimens incorporating the new DAAs (simeprevir, sofosbuvir) equivalent or superior to the current standard of care, pegylated interferon plus ribavirin and one of the protease inhibitors telaprevir or boceprevir; 2) among patients with genotypes 2 and 3, is the combination of sofosbuvir and ribavirin equivalent or superior to the current standard of care, pegylated interferon plus ribavirin; and 3) among interferon-ineligible or intolerant patients, is the combination of sofosbuvir plus ribavirin or sofosbuvir plus simeprevir equivalent or superior to no treatment. The purpose of this assessment is to help patients, providers, and payers address these important questions and to support dialogue needed for successful action to improve the quality and value of health care for these patients.

1. Background

1.1 Hepatitis C

The worldwide prevalence of hepatitis C infection is estimated to be between 120 and 170 million.[6] Estimates for the prevalence of hepatitis C in the United States range from 3.0 to 5.2 million people.[7-10] It is the leading cause of liver failure requiring liver transplant.[11]

There are six major genotypes of hepatitis C.[12] The most common genotype in the United States in genotype 1 (70-75%), followed by genotype 2 (13-17%) and genotype 3 (8-12%).[13-18] Genotypes 4 to 6 are uncommon in the United States (1% or less) and will not be considered further in this review. Knowledge of the viral genotype is important because response to therapy varies by genotype.

The acute phase of hepatitis C infection is asymptomatic for most patients. The Centers for Disease Control and Prevention (CDC) estimates that among 100 people infected with hepatitis C, only 20 to 30 will develop symptoms (see Table 1 below). The symptoms are primarily fatigue, decreased appetite, nausea, and jaundice. Of the 100 people infected with hepatitis C, 70 to 80 will not have any symptoms and 75 to 85 will remain chronically infected with hepatitis C. [19-21] Between 60 and 70 of these individuals will develop chronic liver disease and 5 to 20 will develop cirrhosis over 20 years.[22,23]

Table 1. Natural History of Hepatitis C Infection.

Condition	Number of individuals
Infection with hepatitis C	100
Develop symptoms	20-30
Remain asymptomatic	70-80
Develop chronic infection	75-85
Develop chronic liver disease	60-70
Develop cirrhosis over 20-30 years	5-20
Die from cirrhosis or liver cancer	1-5

The development of chronic hepatitis is partly dependent on an individual's genetics. Variants in interleukin 28 (IL28) predict clearance of the virus. Approximately half of patients with the IL28 CC variant spontaneously clear the virus while only 16 to 20% of those with the IL28 TT variant clear the virus.[24-26] This will be important to consider in treatment trials as patients carrying the IL28B CC virus are more likely to respond to treatment with interferon.[27,28]

Since most infections are asymptomatic, the majority of patients with chronic hepatitis C infections are unaware of their infections unless they have been screened. It is estimated that approximately half of patients infected with Hepatitis C in the United States are unaware of their infection and that less than 15% have received treatment.[9,29,30] The majority of Americans infected with the hepatitis C virus or HCV (~76%) were born between the years of 1945 and 1965.[30] Both the CDC and the U.S. Preventive Services Task Force (USPSTF) now recommend hepatitis C screening for all Americans born during that time frame.[31,32]

Chronic hepatitis C is a slowly progressive disease. Between 20 and 30% of patients develop cirrhosis over 20 to 30 years of infection.[22,23] The median time from infection to cirrhosis is estimated to be about 40 years, which means that approximately half of patients infected 40 years ago will have developed cirrhosis. Once bridging fibrosis or cirrhosis develops, patients with chronic HCV infection are at risk for the development of hepatocellular carcinoma. Factors associated with progression to cirrhosis include male sex, alcohol intake, aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio, elevated total bilirubin, low albumin, low platelets, and higher fibrosis scores.[22,23,33-36]

1.2 Definitions

- *Cirrhosis*: progressive scarring of liver tissue that may affect performance of chronic hepatitis C treatment. It is typically biopsy-proven in clinical trials of chronic hepatitis C therapies.
- *Decompensated cirrhosis:* The presence of cirrhosis plus one or more complications including esophageal varices, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, or hepatocellular carcinoma.
- *Genotype*: a classification of hepatitis C based on genetic material in the RNA strands of the virus. There are 6 main genotypes, which are further divided into subtypes in some cases.
- *Interferon-ineligible:* patients in whom interferon therapy is contraindicated due to such conditions as anemia, alcohol abuse, advanced or decompensated cirrhosis, or severe psychiatric disorder.
- *Interferon-intolerant:* patients who discontinue interferon therapy prematurely due to side effects.
- *Sustained virologic response (SVR)*: Absence of detectable HCV RNA, measured 12-24 weeks following the completion of treatment.
- *Relapse:* achieving an undetectable HCV viral load during treatment with recurrence of detectable viral RNA at some point thereafter.
- *Null response:* no reduction of at least 1 $\log_{10}$ in HCV RNA during prior treatment.

- *Partial response:* greater than a 1 log_{10} reduction in HCV RNA during prior treatment, but never achieving undetectable viral RNA.
- *Treatment-naïve:* Not previously treated for chronic hepatitis C infection.
- *Treatment-experienced:* One or more previous attempts at treatment of chronic hepatitis C infection. This group may contain a mix of patients who relapsed, those with a partial response, and those with a null response to prior treatment.

The **METAVIR score** is a standardized measure of fibrosis and inflammation seen on a liver biopsy. The fibrosis score ranges from 0 to 4, and the inflammation activity score is measured from 0 to 3.

Fibrosis score:
F0 = no fibrosis
F1 = portal fibrosis without septa
F2 = portal fibrosis with few septa
F3 = numerous septa without cirrhosis
F4 = cirrhosis

Activity score:
A0 = no activity
A1 = mild activity
A2 = moderate activity
A3 = severe activity

The fibrosis score is particularly useful because patients with higher fibrosis scores are more likely to progress to cirrhosis and HCC and may warrant earlier treatment.

The **Ishak scale** is a second commonly reported histologic grading system for liver fibrosis that ranges from 0 to 6.

Ishak Scale
1 = no fibrosis (normal)
2 = fibrous expansion of some portal areas ± short fibrous septa
3 = fibrous expansion of most portal areas ± short fibrous septa
4 = fibrous expansion of portal areas with marked bridging (portal to portal, portal to central)
5 = marked bridging with occasional nodules (incomplete cirrhosis)
6 = cirrhosis

A rough approximation of how the two scoring systems compare is as follows:

Ishak	METAVIR
0	0
1,2	1
3	2
4,5	3
6	4

1.3 Treatment of Chronic Hepatitis C Infection

The primary goal of HCV treatment is the prevention of cirrhosis and hepatocellular carcinoma. The combination of interferon alfa plus ribavirin has been the backbone of treatment for patients infected with HCV. Treatment is guided by genotype. Patients infected with genotype 1 tend to have a poor response to interferon plus ribavirin. The first direct-acting antiviral agents (DAAs) – the protease inhibitors boceprevir and telaprevir – were approved for treatment of genotype 1 in 2011. The cure rate with triple therapy with a DAA, pegylated interferon and ribavirin (commonly referred to using the acronym "PR") is approximately double the cure rate of the combination of interferon and ribavirin alone. Newer DAAs are available for some of the other genotypes and offer the promise of interferon-free therapy. Because the natural history for the development of cirrhosis and HCC is long, treatment success is usually measured by the maintenance of a sustained virologic response (SVR), defined as undetectable serum HCV RNA for at least 24 weeks (SVR24) after the completion of treatment. In recent trials, the FDA has allowed the SVR 12 weeks after the completion of treatment (SVR12) to be the primary outcome.

SVR is a reasonable, but imperfect measure of cure, and varies somewhat based on when it is measured. For example, the recent PILLAR trial,[37] a phase 2B trial of simeprevir, reported the number of participants who had undetectable RNA at the end of treatment and at 12, 24, and 72 weeks after treatment. The number of patients with undetectable HCV RNA declined from 336 at the end of treatment to 303 (12 weeks), 300 (24 weeks) and 293 (72 weeks), respectively. Thus SVR12 was a reasonably stable representation of SVR24 (only 3/303 or about 1% relapsed between those two time points). However, relapses did continue over time, with an additional 7/300 (2.3%) relapsing between 24 and 72 weeks of follow-up. In a meta-analysis of long-term outcomes following SVR24, the percentage of patients with long-term cure following SVR24 ranged from 98% to 100%.[38]

A number of factors have been identified that predict a poor response to treatment. As noted above, genotype 1 has a lower SVR24 than the other genotypes. Among patients infected with genotype 1, the subtype 1a has a lower response rate than subtype 1b. Patients with the IL28B CC genotype respond better than patients with the CT or TT genotype. Other poor prognostic factors include a higher HCV RNA viral load, higher levels of fibrosis of the liver, older age, Black race, obesity, and metabolic syndrome. Among patients who have been treated in the past, those who had a relapse after SVR respond better to new treatment than those with only a partial response to initial therapy, and patients with an initial null response to therapy are the least likely to respond to new treatment.

Treatment of Genotype 1

Pegylated interferon alfa plus ribavirin

Pegylated interferon alpha plus ribavirin (PR) was the primary treatment of HCV for more than 10 years. In clinical trials, the SVR24 for patients with genotype 1 treated with PR ranged from 40% to 50%, but was about 20% lower in real-world studies in part because of the poor tolerability of PR therapy and because of the special nature of patients willing to participate in clinical trials.[39-41] Interferon requires a weekly injection and commonly causes fatigue (50% to 60%), headache (50% to 60%), myalgias (40% to 55%), and fever (40% to 45%).[42] Other common side effects of PR include anemia (hemoglobin < 10 g/dL) in up to 30% of patients, generalized pruritis (25% to 30%), and psychiatric symptoms such as depression (up to 25%), insomnia, and anxiety (15% to 25%).[42] Ribavirin may cause birth defects, so women of child-bearing age must be on birth control.

For genotype 1, patients are treated for 48 weeks with once weekly subcutaneous injections of peginterferon alfa and twice daily oral ribavirin taken with food. Routine monitoring is performed with dose reductions recommended for neutropenia, thrombocytopenia, anemia, depression, and worsening renal function.

Boceprevir and Telaprevir

The protease inhibitors boceprevir and telaprevir were the first two DAAs approved by the FDA. Since their approval in 2011, the standard of care for the treatment of genotype 1 has been pegylated interferon and ribavirin in combination with either boceprevir or telaprevir.[43-45] Among treatment-naïve patients PR plus boceprevir or telaprevir has a SVR24 between 70% and 75%. Patients with the IL28B CC genotype respond well to interferon. In this group, the response to PR plus either boceprevir or telaprevir is between 80% and 90%.

The length of treatment is guided by the patient's liver histology, response to prior treatment, and the change in viral load during the first weeks of treatment. The treatment algorithm for boceprevir starts with four weeks of PR. Among treatment-naïve patients, this is followed by 24 weeks of PR plus boceprevir with no additional treatment if the patient has an undetectable HCV RNA during weeks 8 to 24 (so-called response guided therapy). Those with detectable RNA at week 8 receive an additional 8 weeks of PR + boceprevir (32 weeks total) followed by an additional 12 weeks of PR alone. Among treatment-experienced patients, the four weeks of PR is followed by 32 weeks of PR plus boceprevir with no additional treatment if the patient has an undetectable HCV RNA during weeks 8 to 24. Treatment-experienced patients with detectable RNA at week 8 receive an additional 12 weeks of PR alone. For both treatment-naïve and experienced patients, if the HCV RNA level is ≥ 100 IU per ml at week 12 or detectable at week 24, treatment is stopped. Patients with cirrhosis, a prior null response, or less than a one log decrease in HCV RNA during the 4 week

PR run in (i.e., a period of therapy with PR before initiating boceprevir) should also be considered for 48 weeks of treatment.

The treatment algorithm for telaprevir is somewhat simpler. Everyone starts with 12 weeks of PR plus telaprevir. Patients who are treatment-naïve or relapsed following prior SVR receive an additional 12 weeks of PR. Those who have HCV RNA > 1000 IU per ml at week 4 or 12 should stop therapy at that time. Prior partial responders and null responders and those who are treatment-naïve, but who have detectable CHV RNA at weeks 4 and / or 12 receive an additional 36 weeks of PR. All patients with cirrhosis should be considered for an additional 36 weeks of therapy rather than 12 weeks, even if their HCV RNA level is less than 25 IU per ml.

Challenges with boceprevir and telaprevir therapy

The marked improvement in SVR24 with the addition of boceprevir or telaprevir to PR comes with significant practical and clinical trade-offs. Patients must take either 6 or 12 pills per day spaced every 7 to 9 hours, and the pills must be taken with at least 20 grams of fat. Both medications increase the risk for severe anemia that is already common with PR treatment (increased from 30% with PR to 50% with either boceprevir or telaprevir).[42] Boceprevir causes a bitter or metallic taste (40% versus 20% with PR), and telaprevir causes rashes and pruritus (20% more than PR alone).[42] The combination of PR plus boceprevir or telaprevir is associated with serious adverse event rates between approximately 40% and 50%.[42,46,47] Neither can be used as monotherapy because resistance develops quickly.[48,49] Finally, boceprevir and telaprevir are strong inhibitors of the cytochrome P450 (CYP) 3A4 enzyme, leading to many potential drug interactions (statins, benzodiazepines, colchicine, St. John's wort, anticonvulsants, sulfonylureas, and some reverse transcriptase inhibitors).

Treatment of Genotypes 2 and 3

Pegylated interferon alfa plus ribavirin

Neither boceprevir nor telaprevir is approved for treatment of genotypes 2 and 3 and therefore the standard of care for these patients has been 24 weeks of PR. The duration of treatment is half that for genotype 1, but the response rate is significantly higher. The SVR24 of patients with genotypes 2 or 3 in clinical trials ranged from 75% to 85%, although the real world experience is again somewhat lower.

Newly-Approved Treatment Regimens

Boceprevir and telaprevir were the first two DAAs approved by the FDA. Since then, more than 30 additional DAAs have entered clinical trials. The new drugs attack different targets in the HCV life cycle including NS3/4A protease inhibitors, nucleoside and nucleotide polymerase inhibitors, non-nucleoside polymerase inhibitors, NS5A inhibitors, and cyclophilin inhibitors.

The goals of the new therapies include simpler dosing regimens (fewer pills, shorter duration), fewer side effects, fewer drug interactions, and higher cure rates. Two new DAAs were approved in late 2013: simeprevir and sofosbuvir. At least two additional DAAs, faldaprevir and daclatasvir, are likely to be approved in 2014.[50] Many physicians are keeping track of patients with chronic HCV infections, but not treating them while waiting for new medical therapies that will allow for high cure rates without the severe side effects of the current therapies, which require the use of interferon.

Simeprevir is a NS3/4A protease inhibitor that was approved for the treatment of HCV genotype 1 by the FDA in November 2013. It is considered a second-generation protease inhibitor (boceprevir and telaprevir were first generation protease inhibitors). A major improvement of simeprevir compared with earlier protease inhibitors is the dosing schedule. It may be taken once a day rather than six to twelve pills divided into doses taken every eight hours. A second major improvement is that it does not appear to increase the risk for anemia, which has been a major problem with the first generation protease inhibitors. Simeprevir must be used in combination with PR because viral resistance develops rapidly with monotherapy. Significant new adverse reactions associated with simeprevir include photosensitivity reactions, some of which have required hospitalization, and pruritus. The FDA indication for simeprevir is for genotypes 1 and 4 only: simeprevir 150 mg once daily with PR for 12 weeks followed by an additional 12 weeks of PR for treatment-naïve patients and patients who relapsed or by an additional 36 weeks of PR for prior partial and null responders (see Table 2 below).

Table 2. FDA Indications for Simeprevir and Sofosbuvir.

Drug	Genotype	Treatment
Simeprevir	1, 4	• 150 mg daily with PR x 12 weeks plus PR for an additional 12 to 36 weeks
Sofosbuvir	1, 4	• 400 mg daily with PR x 12 weeks • Alternate if interferon (IFN)-ineligible: 400 mg daily with R x 24 weeks
Sofosbuvir	2	• 400 mg daily with R x 12 weeks
Sofosbuvir	3	• 400 mg daily with R x 24 weeks

Sofosbuvir is the first drug in the class of HCV NS5B nucleotide analog polymerase inhibitors to be approved. Sofosbuvir is the third approved drug given breakthrough designation by the FDA. The goal of the breakthrough therapy program is to speed up the development and review of drugs for serious or life-threatening conditions that have substantial benefits over available therapy. The FDA requires substantially less evidence to support the approval of drugs with breakthrough designation. Like the other DAAs, sofosbuvir should not be prescribed as monotherapy. It has been studied in combination with PR, with ribavirin alone, with simeprevir, and in combination with other DAAs that have not yet received FDA approval. Like simeprevir, sofosbuvir only needs to be taken once daily. Unlike simeprevir, sofosbuvir is also approved to treat genotypes 2, 3, and 4 in addition to genotype 1. The details of therapy are guided by genotype, prior treatment status, interferon eligibility, and liver histology. The FDA indication for patients with genotype 1 is sofosbuvir 400 mg daily with PR for 12 weeks; patients who are interferon-ineligible may consider simeprevir 400 mg plus R alone for 24 weeks. The FDA indication for patients with genotype 2 is sofosbuvir 400 mg daily with R for 12 weeks. Finally, The FDA indication for patients with genotype 3 is sofosbuvir 400 mg daily with R for 24 weeks.

2. Clinical Guidelines

The American Association for the Study of Liver Diseases (AASLD) / Infectious Diseases Society of America (IDSA) / International Antiviral Society – USA (IAS USA)

http://www.hcvguidelines.org

On January 29, 2014, the AASLD, IDSA, and IAS-USA took the unusual step of jointly creating and updating an online guideline for the treatment of chronic hepatitis C because of the rapidly evolving treatment environment: the FDA is expected to approve an array of new drugs over the next few years. For genotype 1, they recommend sofosbuvir plus PR or sofosbuvir plus simeprevir (in interferon-intolerant patients) with simeprevir + PR as an alternative therapy for patients with genotype 1b without the Q80K polymorphism. For genotypes 2 and 3, they recommend sofosbuvir plus ribavirin.

The Department of Veterans Affairs (VA)

http://www.hepatitis.va.gov/provider/guidelines/2012HCV

The 2012 VA guidelines recommend PR plus either boceprevir or telaprevir for treating genotype 1 infections and PR alone for treating genotype 2 and 3 infections. An updated version of these guidelines following FDA approval of simeprevir and sofosbuvir has yet to appear.

National Institute for Health and Care Excellence (NICE)

http://cks.nice.org.uk/hepatitis-c

Current treatment guidelines at NICE recommend treatment with PR as the initial therapy for all genotypes. NICE is currently reviewing the new DAA drugs.

European Association for the Study of the Liver (EASL)

http://www.easl.eu/2013HCVguideline

In December 2013, EASL updated its HCV treatment guidelines. They recommend that treatment should not be deferred for patients with significant fibrosis (METAVIR F3 or F4). They recommend PR plus either boceprevir or telaprevir for treating genotype 1 infections and PR alone for treating genotype 2 and 3 infections.

The Canadian Association for the Study of the Liver (CASL)
http://www.hepatology.ca

Current CASL recommendations are to use PR plus either boceprevir or telaprevir for treating genotype 1 infections and PR alone for treating genotype 2 and 3 infections. No recommendations including the new DAA therapies have been made to date.

The Japan Society of Hepatology (JSH)
http://JSH2014HCVguidelines

In January 2014, the JSH updated their guidelines for the management of genotype 1. They recommend simeprevir plus PR as the primary therapy for most patients with telaprevir plus PR as an alternative. They do not comment on sofosbuvir as it is not approved for use in Japan.

3. Coverage Policies

3.1 Simeprevir

Medicare & Medicaid

No publicly-available coverage policies, prior authorization protocols, or formulary designations for simeprevir were available from the Centers for Medicare & Medicaid Services (CMS) or Medi-Cal, the state Medicaid agency.

Regional Private Payers

HealthNet

https://www.healthnet.com/static/general/unprotected/html/national/pa_guidelines/olysio_natl.html

HealthNet has published an interim prior authorization protocol that provides coverage for simeprevir+PR for chronic hepatitis C patients with genotype 1 but without the Q80K polymorphism. Coverage is *not* authorized for monotherapy with simeprevir, in patients who have failed prior treatment with any protease inhibitor (including simeprevir), or in patients with any known contraindication to interferon (e.g., decompensated liver disease, uncontrolled autoimmune hepatitis).

National Private Payers/Pharmacy Benefit Managers

Aetna

http://www.aetna.com/products/rxnonmedicare/data/2014/GI/hepatitis_c.html

Coverage is limited to patients with chronic hepatitis C virus genotype 1 with compensated liver disease who receive concurrent therapy with PR. Use of simeprevir is not covered in combination with any other protease inhibitor therapy (including sofosbuvir), in genotype 1 patients with the Q80K polymorphism, or in those who have failed previous therapy with protease inhibitors.

Anthem/Express Scripts

http://www.anthem.com/provider/noapplication/f0/s0/t0/pw_e210962.pdf?na=pharminfo

Simeprevir+PR is covered in adult genotype 1 patients with chronic hepatitis C *and* compensated liver disease who are negative for the Q80K polymorphism.

CVS-Caremark
http://www.caremark.com/portal/asset/FEP_Criteria_Olysio.pdf

CVS-Caremark has published prior authorization criteria stating that simeprevir+PR is approved for use in patients with genotype 1 chronic hepatitis C who have compensated liver disease, have not been previously treated with any protease inhibitor, have not had a liver transplant, and do not expect to reduce or interrupt simeprevir dosing. Monotherapy with simeprevir is not approved.

Humana
http://apps.humana.com/tad/tad_new/Search.aspx?criteria=simeprevir&searchtype=freetext&policyType=both

Humana limits coverage to adult patients who have a diagnosis of genotype 1 hepatitis C *with* evidence of compensated liver disease and concurrent therapy with PR. Simeprevir is not covered in combination with other protease inhibitors or sofosbuvir, in combination with medications that are either potent CYP3A4/5 inducers or CYP3A4/5 inhibitors, in patients with the Q80K polymorphism, or in those who have previously received a treatment with a protease inhibitor.

3.2 Sofosbuvir

Medicare & Medicaid

No publicly-available coverage policies, prior authorization protocols, or formulary designations for sofosbuvir were available from CMS or Medi-Cal, the state Medicaid agency.

Regional Private Payers

HealthNet
https://www.healthnet.com/static/general/unprotected/html/national/pa_guidelines/sovaldi_natl.html

HealthNet has published an interim prior authorization protocol that ties coverage for sofosbuvir to the FDA-approved indications and therapy durations. Monotherapy with sofosbuvir (i.e., without ribavirin) is not covered.

National Private Payers/Pharmacy Benefit Managers

Aetna:
http://www.aetna.com/products/rxnonmedicare/data/2014/GI/hepatitis_c.html

Aetna provides coverage for sofosbuvir+PR in patients with genotypes 1 or 4, and coverage for sofosbuvir+R in genotypes 2 and 3. Additionally, sofosbuvir+R may be used in genotype 1 patients who are ineligible for interferon, defined by Aetna as including: recent suicide attempt, severe depression, or previous interferon-related adverse events. Combination therapy with simeprevir is not covered.

Anthem/Express Scripts
http://www.anthem.com/provider/noapplication/f0/s0/t0/pw_e210963.pdf?na=pharminfo

Sofosbuvir is generally covered in adult patients with chronic hepatitis C who have evidence of compensated liver disease (including cirrhosis). Coverage is tied to FDA-approved indications and therapy durations. Sofosbuvir+R may be used in genotype 1 patients who are ineligible for interferon, defined by Anthem as including: autoimmune hepatitis, Child-Pugh liver function score >6, or known hypersensitivity to interferon.

CVS-Caremark
http://www.caremark.com/portal/asset/FEP_Criteria_Sovaldi.pdf

CVS-Caremark has published prior authorization criteria stating that sofosbuvir+PR (genotypes 1 and 4) or sofosbuvir+R (genotypes 2 and 3 as well as genotype 1 patients ineligible for interferon) must be used only in adults with chronic hepatitis C who do not have renal impairment, decompensated cirrhosis, liver cancer awaiting transplant, or significant or unstable cardiac disease. Sofosbuvir monotherapy is not allowed in any situation. The occurrence of liver transplant is a trigger for discontinuation of sofosbuvir.

Humana:
http://apps.humana.com/tad/tad_new/Search.aspx?criteria=sofosbuvir&searchtype=freetext&policyType=both

Humana limits coverage of sofosbuvir to adult patients who have a diagnosis of chronic hepatitis C *with* evidence of compensated liver disease. Additionally, coverage for genotype 1 patients is limited to those who have failed to achieve SVR with a prior regimen containing a protease inhibitor or who have documented contraindications to interferon therapy (e.g., hypersensitivity to interferon, hepatic decompensation, hemiglobinopathies). Coverage for genotypes 2, 3, and 4 is not restricted other than based on the general criteria above and FDA-approved treatment regimens. Use of sofosbuvir as monotherapy or in combination with any other protease inhibitor (including simeprevir) is not considered medically necessary and is not covered.

4. Previous Systematic Reviews and Technology Assessments

We were unable to identify any technology assessments of the new DAAs. Four systematic reviews evaluated the efficacy of boceprevir and telaprevir using network meta-analysis because there are no head-to-head comparisons of treatment regimens including the two drugs. There were no systematic reviews evaluating simeprevir or sofosbuvir.

4.1 Formal Health Technology Assessments

No formal health technology assessments were identified. However, the Canadian Agency for Drugs and Technologies in Health (CADTH) is currently undertaking a review of new DAA agents (among patients with genotype 1 chronic hepatitis C only), and NICE is undertaking individual technology assessments of sofosbuvir and simeprevir according to their labeled indications in Europe (i.e., all genotypes for sofosbuvir, genotypes 1 and 4 for simeprevir).

4.2 Systematic Reviews

Cure 2012

Cure S, Diels J, Gavart S, Bianic F, Jones E. Efficacy of telaprevir and boceprevir in treatment-naive and treatment-experienced genotype 1 chronic hepatitis C patients: an indirect comparison using Bayesian network meta-analysis. *Current medical research and opinion.* Nov 2012;28(11):1841-1856.

This systematic review and Bayesian network meta-analysis of 11 studies found that both boceprevir and telaprevir combined with PR were better than PR alone in treatment-naïve and treatment-experienced patients. The authors highlighted a trend towards better outcomes with telaprevir.

Cooper 2013

Cooper C, Lester R, Thorlund K, et al. Direct-acting antiviral therapies for hepatitis C genotype 1 infection: a multiple treatment comparison meta-analysis. *QJM : monthly journal of the Association of Physicians.* Feb 2013;106(2):153-163.

This systematic review and Bayesian network meta-analysis of 11 studies found that both boceprevir and telaprevir combined with PR were better than PR alone. In the treatment-naïve, telaprevir had lower rates of anemia and neutropenia, but higher rates of rash and pruritus. In the treatment-naïve, telaprevir had higher rates of all adverse events compared with boceprevir.

Kieran 2013

Kieran J, Schmitz S, O'Leary A, et al. The relative efficacy of boceprevir and telaprevir in the treatment of hepatitis C virus genotype 1. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Jan 2013;56(2):228-235.

This systematic review and Bayesian network meta-analysis of 10 studies found that both boceprevir and telaprevir combined with PR were better than PR alone. In the subgroup of patients who had relapsed following SVR, telaprevir based treatments were more effective than boceprevir based treatments.

Sitole 2013

Sitole M, Silva M, Spooner L, Comee MK, Malloy M. Telaprevir versus boceprevir in chronic hepatitis C: a meta-analysis of data from phase II and III trials. *Clinical therapeutics.* Feb 2013;35(2):190-197.

This systematic review and Bayesian network meta-analysis of eight studies found that both boceprevir and telaprevir combined with PR had higher SVR than PR alone, but with an increase in drug-related adverse events. They highlighted the lack of data on long-term outcomes such as hospitalization for liver disease, HCC, and mortality.

5. Ongoing Studies

We did not include studies focusing exclusively on the treatment of HCV genotypes 4, 5, or 6 nor did we include combinations with drugs that are not yet FDA approved.

Two of the ongoing studies of simeprevir stand out as likely to answer key open questions. The first (NCT01485991) is a randomized trial comparing simeprevir to telaprevir in treatment-experienced patients. This will be the first study to compare the new DAAs to the current standard of care for treating HCV genotype 1. The second (NCT01349465) is the three-year follow-up of patients in the phase 2 and 3 trials: this should give at least preliminary information on the impact of treatment on disease progression. The list of studies below does not include several ongoing studies of interferon-free combinations of simeprevir with DAAs that do not have FDA approval including daclatasvir, IDX-719, TMC-647055, and GSK-23336805.

None of the studies of sofosbuvir listed on clinicaltrials.gov have a PR or PR plus boceprevir or telaprevir control group. There are no trials with primary outcomes beyond SVR12. The list of studies below does not include several ongoing studies of interferon-free combinations of sofosbuvir with DAAs in development that do not yet have FDA approval including daclatasvir, ledipasvir, GS-5885, GS-0938, and GS-5816.

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Simeprevir or SMV (TMC435)					
An Efficacy, Safety and Tolerability Study for TMC435 vs Telaprevir in Combination With PegINFα-2a and Ribavirin in Chronic Hepatitis C Patients Who Were Null or Partial Responders to Prior PegINFα-2a and Ribavirin Therapy (ATTAIN) NCT01485991	RCT Double blind Placebo-controlled Non-inferiority N = 766	SMV 150 + PR TVR 750 mg every 8 hours + PR	• Genotype type (GT) 1 • Treatment-experienced	SVR12	March 2014
3-year Follow-up Study in Patients Previously Treated With a TMC435 for the Treatment of Hepatitis C Virus (HCV) Infection NCT01349465	Cohort N = 249	None	• Treated with simeprevir in a phase 2 or phase 3 study	SVR at 3 years	February 2016
An Efficacy, Pharmacokinetics, Safety and Tolerability Study of TMC435 as Part of a Treatment Regimen for Hepatitis C-Infected Patients (Phase 3) NCT01725529	RCT Double-blind Placebo (PBO) controlled N = 435	SMV 150 + PR SMV 100 + PR PBO + PR	• GT 1 • Treatment-naïve	SVR12	October 2014
A Study of TMC435 in Combination With Peginterferon Alfa-2A and Ribavirin for Hepatitis C Virus Genotype-1 Infected Patients Who Participated in a Control Group of a TMC435 Study NCT01323244	Cohort Open-label N = 270	SMV 150 + PR	• GT 1 • Did not achieve SVR in the placebo arm of prior trials of simeprevir	SVR12	January 2015

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
A Study of TMC435 in Combination With PSI-7977 (GS7977) in Chronic Hepatitis C Genotype 1-Infected Prior Null Responders To Peginterferon/Ribavirin Therapy or HCV Treatment-Naive Patients COSMOS Cohort B NCT01466790	RCT Open-label N = 168	SMV + sofosbuvir (SOF) 12 Weeks SMV + SOF + R 12 Weeks SMV + SOF 24 Weeks SMV + SOF + R 24 Weeks	• GT 1 • Naïve and Experienced • METAVIR F3 or F4	SVR12	January 2014
A Study to Evaluate the Efficacy, Safety and Tolerability of TMC435 in Combination With PegIFN Alfa-2a (Pegasys) and Ribavirin (Copegus) in Treatment-Naïve or Treatment-Experienced, Chronic Hepatitis C Virus Genotype-4 Infected Patients (RESTORE) Phase 3 NCT01567735	Cohort Open-label N = 107	SMV 150 + PR	• GT 4 • Naïve and Experienced	SVR12	March 2014
A Study to Assess the Safety, Tolerability and Efficacy of TMC435 Along With Pegylated Interferon Alpha-2a (Pegasys) and Ribavirin (Copegus) Triple Therapy in Chronic Hepatitis C Genotype-1 Infected Patients Co-infected With Human Immunodeficiency Virus (HIV)-Type 1 NCT01479868	Cohort Open-label	SMV 150 + PR	• GT 1 • HIV-1 infection	SVR24	August 2013
A Study of TMC435 Plus Pegylated Interferon Alfa-2a and Ribavirin in Participants With Chronic HCV Infection NCT01846832	Cohort Open label N = 225	SMV 150 + PR	• GT 1 or 4 • Naïve • METAVIR F0-F2	SVR12	October 2014

Sofosbuvir (GS-7977, PSI-7977)					
Sofosbuvir+R for 16 or 24 Weeks and Sofosbuvir+PR for 12 Weeks in Subjects With Genotype 2 or 3 Chronic HCV Infection NCT01962441	RCT Open label N= 600	SOF 400 + R 16 Weeks SOF 400 + R 24 Weeks SOF 400 + PR 12 Weeks	• GT 2 with cirrhosis or GT 3 • Naïve or experienced	SVR12	December 2014
Open-Label Safety Study of Telaprevir and Sofosbuvir in Chronic Hepatitis C Genotype 1 (STEADFAST) NCT01994486	Cohort Open label N = 20	SOF + TVR 12 Weeks	• GT 1 • Naïve	SVR12	July 2014
Safety and Efficacy Study of Sofosbuvir Plus Ribavirin in Treatment-Naive Adults With Genotype 1 and 3 Chronic HCV Infection. NCT01896193	RCT Open label N= 120	SOF 400 + R 16 Weeks SOF 400 + R 24 Weeks	• GT 1 or 3 • Naïve	SVR12	April 2014
Sofosbuvir Plus Ribavirin in Subjects With HCV Infection and Renal Insufficiency NCT01958281	Non-randomized Open label N = 40	SOF 200 + R 200 24 Weeks SOF 400 + R 200 24 Weeks	• GT 1 or 3 • Naïve • Renal insufficiency	SVR12	July 2016
A Phase 3b, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir Plus Ribavirin in Treatment-Naïve and Treatment-Experienced Japanese Subjects With Chronic Genotype 2 HCV Infection NCT01910636	Cohort Open label N = 134	SOF 400 + R 12 Weeks	• GT 2 • Naïve or experienced	SVR12	April 2014
Efficacy and Safety of Sofosbuvir Plus Ribavirin in Subjects With Chronic HCV Infection NCT02021643	RCT Open label N=450	SOF 400 + R 12 Weeks SOF 400 + R 16 Weeks SOF 400 + R 24 Weeks	• Naïve with GT 1, 2, 3, or 6 • Experienced with GT 2	SVR12	May 2015

Expanded Access Program of Sofosbuvir With Ribavirin and With or Without Pegylated Interferon-in Aggressive Post-transplant Hepatitis C NCT01779518	Cohort Open label	SOF 400 + R or PR 24 Weeks	• Post-liver transplant • Aggressive HCV infection	-	-
A Phase 3, Open-label Study to Investigate the Efficacy and Safety of Sofosbuvir Plus Ribavirin in Chronic Genotype 1, 2 and 3 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Co-infected Subjects NCT01667731	Cohort Open label N = 230	SOF 400 + R 12-24 Weeks	• GT 1, 2, or 3 • HIV-1 infection	SVR12	November 2013
Sofosbuvir (GS-7977) in Combination With P and Ribavirin for 12 Weeks in Treatment-experienced Subjects With Chronic HCV Infection Genotype 2 or 3 NCT01808248	Cohort Open label N = 47	SOF 400 + PR 12 Weeks	• GT 2 or 3 • Experienced	SVR12	September 2013
An Open-Label Study to Explore the Clinical Efficacy of Sofosbuvir With Ribavirin Administered Pre-Transplant in Preventing Hepatitis C Virus (HCV) Recurrence Post-Transplant NCT01559844	Cohort Open label N= 50	SOF 400 + R	• HCV Infection • HCC awaiting liver transplant	Post-transplant virologic response	September 2013
A Phase 3, Open-label Study to Investigate the Efficacy and Safety of Sofosbuvir Plus Ribavirin in Chronic Genotype 1, 2, 3 and 4 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Co-infected Subjects NCT01783678	Non-randomized Open label N = 270	SOF 400 + R 12 Weeks SOF 400 + R 24 Weeks	• GT 1, 2, 3, or 4 • HIV-1 infection • Naïve or experienced	SVR12	April 2014
Open-Label Study of Sofusbuvir+Ribavirin With or Without Peginterferon Alfa-2a in Subjects With Chronic HCV Infection Who Participated in Prior Gilead HCV Studies NCT01625338	Non-randomized Open label N = 600	SOF 400 + R 12 Weeks SOF 400 + R 24 Weeks SOF 400 + PR 12 Weeks	• Enrolled in prior sponsored studies of sofosbuvir	SVR12	July 2014

GS-7977 and Ribavirin in Patients With Chronic HCV With Cirrhosis and Portal Hypertension With or Without Liver Decompensation NCT01687257	RCT Open label N = 50	SOF 400 + R 48 Weeks Observe x 24 Weeks then SOF 400 + R 48 Weeks	• HCV infection, any genotype • Cirrhosis with Child-Pugh score < 10 • Esophageal or gastric varices	SVR12	August 2014
Safety of Efficacy of GS-7977 and Ribavirin in Subjects With Recurrent Chronic Hepatitis C Virus (HCV) Post Liver Transplant NCT01687270	Non-randomized Open label N = 40	SOF 400 + R 24 Weeks	• HCV infection, any genotype • Liver transplant 0.5 to 12 years prior to treatment	SVR12	January 2014

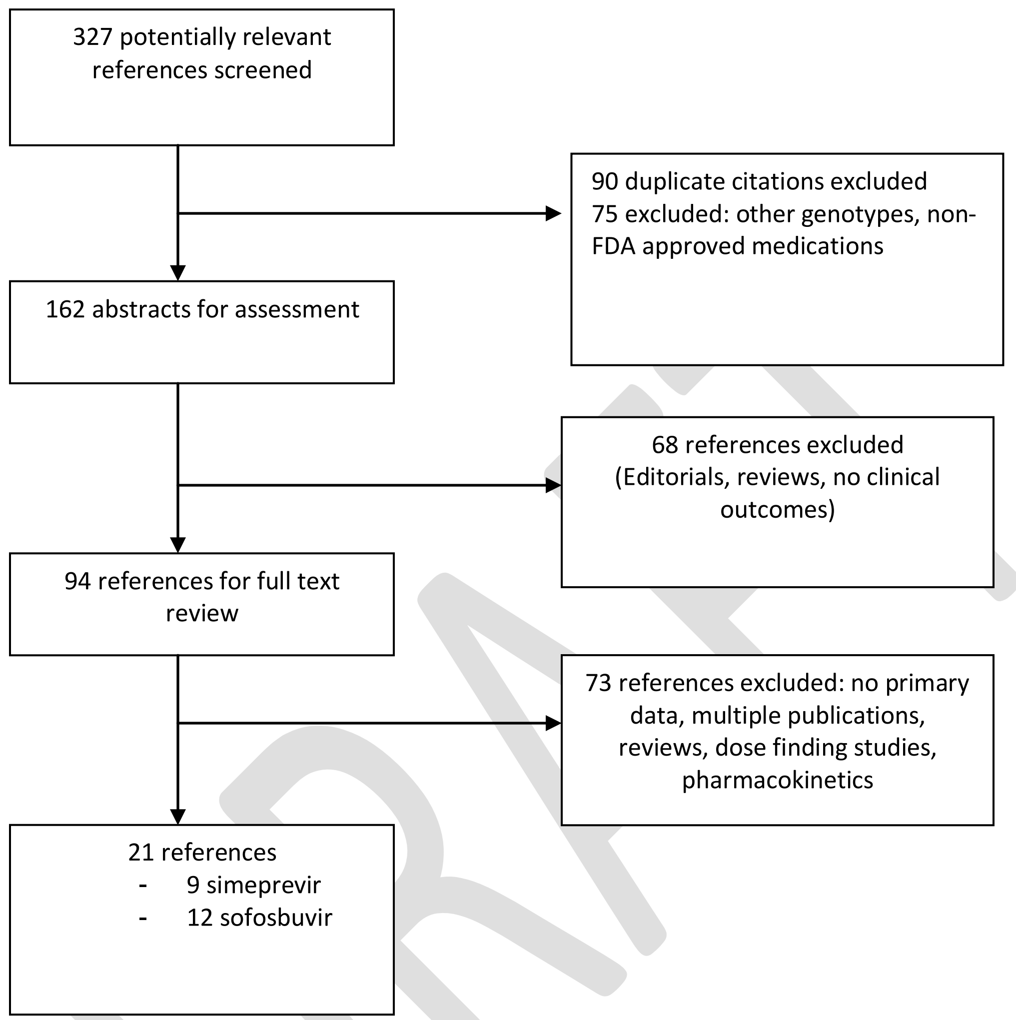
6. Evidence Review (Methods & Results)

The goal of this technology assessment is to evaluate the comparative effectiveness and value of the new DAAs simeprevir and sofosbuvir in the treatment of chronic hepatitis C infection. There were no randomized or other studies that directly compared therapies based on simeprevir to those based on sofosbuvir or to the two protease inhibitors boceprevir and telaprevir. We therefore performed a network meta-analysis to provide indirect evidence about the relative efficacy of the drug combinations available using currently FDA approved therapies.

The Medline database, Embase, Cochrane clinical trials database, Cochrane reviews database, the Database of Abstracts of Reviews of Effects (DARE), the Web of Science, and BIOSIS previews were searched using the key words “simeprevir” OR “sofosbuvir.” The search was performed for the period from 1945 through January 8, 2014. Full details of the search are in the Appendix. The bibliographies of systematic reviews and key articles were manually searched for additional references. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full. Because of the paucity of published data, we included meeting abstracts, FDA documents, and press releases as sources of information. There were peer-reviewed publications for 11 of the 26 studies identified. We included all studies of simeprevir or sofosbuvir for genotypes 1, 2, and / or 3 that reported SVR12 or SVR24 as an outcome in at least one study arm. In order for the results of a study to be included in the network meta-analysis, at least one study group must have received a treatment regimen with dosing similar to the final FDA indications. For example, we did not include data from the Japanese studies of simeprevir that used 100 mg rather than 150 mg daily in our analysis, though we have included the studies in our tables. We did not treat the data from study abstracts or FDA documents differently from that abstracted from published studies. If both were available, we preferentially used data from the published study. The major phase 3 trials of telaprevir and boceprevir were included for the network meta-analysis.[51-58]

The search identified 327 potentially relevant studies (see Figure 1 on the next page). After elimination of duplicate and non-relevant references, the search identified 21 publications and abstracts describing clinical trials of simeprevir[37,59-68] or sofosbuvir.[62,69-79] The primary reasons for study exclusion were (a) early dose finding studies, (b) lack of SVR or other clinical outcomes, or (c) reviews and commentaries.

Figure 1. Selection of Studies for Inclusion in Review.



The four most important outcomes in chronic HCV infection are the development of decompensated liver cirrhosis, hepatocellular carcinoma, liver transplantation, or death from liver-related causes. Because HCV has such a long natural history (20-40 years before the development of cirrhosis), large randomized trials with long follow-up are needed to demonstrate improvement in these outcomes. None of the studies identified in the search evaluated these four outcomes. For new drug evaluation, the primary outcome has been the sustained absence of HCV viral RNA for at least 24 weeks after the end of therapy (SVR24). The FDA has accepted recent studies with a primary outcome of SVR 12 weeks after the end of therapy, and SVR12 was the primary outcome for all of the phase 3 studies of simeprevir and sofosbuvir.

The vast majority of patients with SVR at 24 weeks (SVR24) remain HCV free during long-term follow-up. In several studies with five or more years of follow-up, 91% to 100% of patients remained virus free.[80-83] Additionally, patients with SVR24 have marked improvements or normalization of their ALT as well as improvements in liver histology.[80-85] More importantly, SVR24 has been associated with improvements in quality of life and a reduction in fatigue within months of treatment.[86,87] Recent studies have demonstrated that SVR24 is associated with decreases in decompensated liver disease, hepatocellular carcinoma, liver transplant, and all-cause mortality.[80,88-92] For example, in the HALT-C trial, the investigators prospectively followed 549 patients with advanced fibrosis who received treatment with interferon and ribavirin (140 patients with SVR; 309 patients with non-response to therapy) for a median of approximately 7 years.[89] The primary outcomes were death, liver transplant, death from liver-related causes, and decompensated liver failure. There was more than an 80% reduction in all clinically important outcomes including death or liver transplantation (HR=0.17, 95% CI: 0.06–0.46), decompensated liver disease or death from liver-related causes (HR=0.15, 95% CI: 0.06–0.38), and incident HCC (HR=0.19, 95% CI: 0.04–0.80).

In a much larger observational study of VA patients using data from their electronic medical record, the benefits of achieving SVR were somewhat lower. Over six years of follow-up, there was a 27% reduction in liver-related complications (HR 0.73, 95% CI 0.66 to 0.82) and a 45% reduction in all-cause mortality (HR 0.55, 95% CI 0.47to 0.64). The VA study compared patients with an undetectable viral load at one point in time following therapy to those with no documentation of an undetectable viral load.[92] Confounding by indication (sicker patients may be more likely to receive treatment) in the VA study may explain some of the difference between it and studies like HALT-C, which compared responders to non-responders in a population of treated patients.

All of the studies linking SVR to clinical outcomes are observational and thus may be subject to residual confounding. In addition, it is important to note that among patients with SVR, those with cirrhosis prior to treatment were still at risk for HCC during follow-up.[80,81,83,88,89,93] Thus achieving an SVR24 will not prevent the complications of chronic HCV infection for all patients.

6.1 Overview of the Key Studies of Simeprevir and Sofosbuvir

There are data available from seven trials of simeprevir (see Table 3 on next page). For completeness, an ongoing trial in HIV co-infected patients is also listed in the table. There are two published phase 2 trials (PILLAR, ASPIRE), three unpublished phase 3 trials (QUEST-1, QUEST-2, PROMISE), and one published Japanese trial (DRAGON). There are also data presented at conferences on a trial combining simeprevir with sofosbuvir (COSMOS). All seven trials enrolled only patients with genotype 1 HCV infections who were eligible to receive interferon. Four of the trials enrolled treatment-naïve patients and three enrolled treatment-experienced patients. The six trials of simeprevir plus PR all were randomized trials with PR control arms. None of the trials compared simeprevir to PR plus either boceprevir or telaprevir.

Table 3. Overview of the Clinical Trials of Simeprevir (aka TMC435).

Study	Publication	Treatment	Control	Genotypes	Treatment	IFN Eligible	Cirrhosis
Phase 2							
PILLAR	Fried 2013	SMV + PR	PR	1	Naïve	Yes	0
ASPIRE	Zeuzem 2014	SMV + PR	PR	1	Experienced	Yes	18
Phase 3							
QUEST 1		SMV + PR	PR	1	Naïve	Yes	12
QUEST 2		SMV + PR	PR	1	Naïve	Yes	9
PROMISE		SMV + PR	PR	1	Experienced	Yes	15
Japan							
CONCERTO-1		SMV + PR	PR	1	Naïve	Yes	
CONCERTO-2		SMV + PR		1	Experienced	Yes	
CONCERTO-3		SMV + PR		1	Experienced	Yes	
CONCERTO-4		SMV + PR		1	Naïve/Exp	Yes	
DRAGON	Hayashi 2013	SMV + PR	PR	1	Naïve	Yes	0
Other							
COSMOS	Cohort 1	SOF + SIM ± R	None	1	Experienced	Yes	0
HIV co-infected							
C212		SMV	TVR		Experienced		

The clinical trial data for sofosbuvir are more complex (see Table 4 on the next page). There are data available from 12 trials of sofosbuvir plus one ongoing trial in HIV co-infected patients and one trial in patients awaiting transplant for HCC. There are three published phase 2 trials (PROTON, ELECTRON, ATOMIC), two unpublished phase two trials (P7977-0221, QUANTUM), four published phase 3 trials (FISSION, POSITRON, FUSION, NEUTRINO), one unpublished phase 3 trial (VALENCE), and one published NIH trial (SPARE). The same trial that combines simeprevir with sofosbuvir (COSMOS) is also included in the table. The trials of sofosbuvir enrolled a mix of patients with genotypes 1 through 6 and a mix of treatment-naïve and experienced patients, although they primarily focused on genotypes 2 and 3. One study focused on patients with genotypes 2 and 3 who were unwilling or unable to take interferon or were intolerant of interferon (POSITRON). Three of the 12 trials were randomized trials with PR control groups (P7977-0221, PROTON, FISSION) and one randomized trial had a placebo only control group (POSITRON). The remaining eight trials had no control group that did not include sofosbuvir. None of the trials compared sofosbuvir to PR plus either boceprevir or telaprevir.

Table 4. Overview of the Clinical Trials of Sofosbuvir (GS-7977).

Study	Publication	Treatment	Control	Genotypes	Treatment	IFN Eligible	Cirrhosis
Phase 2							
P7977-O221	-	SOF + PR	PR	1	Naïve	Yes	0%
PROTON	Lawitz 2013b	SOF + PR	PR	1, 2, 3	Naïve	Yes	0%
ELECTRON	Gane 2013	SOF + PR	None	1, 2, 3	Naïve/Exp	Yes	0%
ATOMIC	Kowdley 2013	SOF + PR	None	1, 4, 5, 6	Naïve	Yes	0%
QUANTUM	-	SOF + R	None	1, 2, 3, 4, 5, 6	Naïve	Yes	6%
Phase 3							
FISSION	Lawitz 2013a	SOF + R	PR	2, 3	Naïve	Yes	20%
POSITRON	Jacobson 2013	SOF + R	Placebo	2, 3	Naïve/Exp	Intolerant, unwilling, or ineligible	16%
FUSION	Jacobson 2013	SOF + R	None	2, 3	Experienced	Yes	34%
NEUTRINO	Lawitz 2013a	SOF + PR	None	1, 4, 5, 6	Naïve	Yes	17%
VALENCE		SOF + R	None	2, 3	Naïve/Exp	Yes	
Other							
SPARE	Osinusi 2013	SOF + R	None	1	Naïve	Yes	23%
COSMOS		SOF+SIM ± R	None	1	Experienced	Yes	
HIV co-infected							
PHOTON-1							
Pre-transplant							
P7977-2025		SOF + R	None	Any	Naïve/Exp	Yes	100% HCC

Several key differences between the studies of simeprevir and sofosbuvir emerge when looking at these two tables. First, simeprevir has only been studied in patients infected with genotype 1, while sofosbuvir has been studies across all genotypes. Second, all three of the phase 3 studies of simeprevir were randomized trials with PR as the control. Only one of the phase 3 trials of sofosbuvir was a randomized trial with PR as a control (FISSION), and one trial had a placebo control (POSITRON). The phase 3 randomized, placebo controlled trials for sofosbuvir were all in patients infected with HCV genotypes 2 or 3. Third, seven of the sofosbuvir trials are interferon-free. The only interferon-free regimen that includes simeprevir is a regimen in which simeprevir is combined with sofosbuvir (COSMOS). Finally, none of the trials in patients with HCV genotype 1 were randomized trials comparing a new regimen to the current standard of care for the treatment of genotype 1: boceprevir or telaprevir plus PR.

6.2 SVR Outcomes of Treatment of HCV Genotype 1 in Treatment-naïve Patients

Table 5 on the following page summarizes the results of the major studies of the two new DAAs in treatment-naïve patients with genotype 1. All of the studies excluded patients with HIV, hepatitis B, or other significant illnesses. The treatment dosing regiments that match the FDA indication are highlighted and in bold. The primary outcome for most studies was SVR12, but some of the early studies were designed to look at SVR24 and some studies report both. No studies report long-term outcomes.

Interferon-eligible patients

The PILLAR study was a randomized, double-blind, placebo controlled dose finding study comparing four different dosing regimens for simeprevir to standard PR therapy. The primary outcome was SVR24, which ranged from 75% to 86% compared to 65% for PR. The SVR12 results were slightly higher. The DRAGON study performed in Japan used a similar design with slightly lower doses of simeprevir and found similar results. Neither of these studies used the current standard dosing for simeprevir.

The two phase 3 trials, QUEST-1 and QUEST-2, randomized almost 400 patients 2:1 to 12 weeks of simeprevir 150 mg daily plus PR or to a placebo plus PR. The studies had almost identical results: the SVR12 was 80% for simeprevir plus PR vs. 50% for PR alone. Subgroup analyses that pooled the results for these two studies showed expected differences by risk factors for poor response to PR. In the IL28B CC genotype subgroup, the SVR12 was 95% for simeprevir plus PR and 80% for PR alone; in the less favorable IL28B TT genotype, the SVR12 was 61% for simeprevir plus PR and 21% for PR alone. The findings were similar in subgroups defined by the METAVIR fibrosis score and by genotype 1a and 1b: outcomes were worse across all poor prognosis subgroups, but the SVR12 of simeprevir plus PR was significantly greater than that of PR alone.

Table 5. HCV Genotype 1 Treatment-naïve Patients.

Study	Treatment Arm	N	SVR12	SVR24
IFN-eligible				
PILLAR	SMV 75 12 Weeks + PR	78	83%	82%
	SMV 75 24 Weeks + PR	75	76%	75%
	SMV 150 12 Weeks + PR	77	80%	80%
	SMV 150 24 Weeks + PR	79	86%	86%
	PBO + PR	77	66%	65%
QUEST 1	**SMV 150 12 Weeks + PR**	264	80%	
	PBO + PR	136	50%	
QUEST 2	**SMV 150 12 Weeks + PR**	257	81%	
	PBO + PR	134	50%	
DRAGON	SMV 50 12 Weeks + PR	27	78%	
	SMV 50 24 Weeks + PR	13	77%	
	SMV 100 12 Weeks + PR	26	77%	
	SMV 100 24 Weeks + PR	13	92%	
	PR	13	46%	
CONCERTO-1	SMV 100 12 Weeks + PR	123	89%	
	PBO + PR	60	62%	
CONCERTO-4	SMV 100 12 Weeks + PR	24	92%	
P7977-0221	SOF 100 4 Weeks + PR	16		56%
	SOF 200 4 Weeks + PR	18		83%
	SOF 400 4 Weeks + PR	15		80%
	PBO + PR	14		21%
PROTON	SOF 200 12 Weeks + PR	48	90%	85%
	SOF 400 12 Weeks + PR	47	91%	89%
	PBO + PR	26	58%	58%
ELECTRON	SOF 400 + R 12 Weeks	25	84%	84%
ATOMIC	**SOF 400 12 Weeks + PR**	52	90%	89%
	SOF 400 24 Weeks + PR	109	93%	89%
	SOF 400 36 Weeks + PR	155	91%	87%
QUANTUM	SOF 400 + R 12 Weeks	19	53%	
	SOF 400 + R 24 Weeks	19	47%	
NEUTRINO	**SOF 400 12 Weeks + PR**	292	89%	
SPARE	SOF 400 12W + Wt R	10	90%	
	SOF 400 12W + Wt R	25	68%	
	SOF 400 12W + low R	25	48%	
IFN-ineligible				
- No studies				

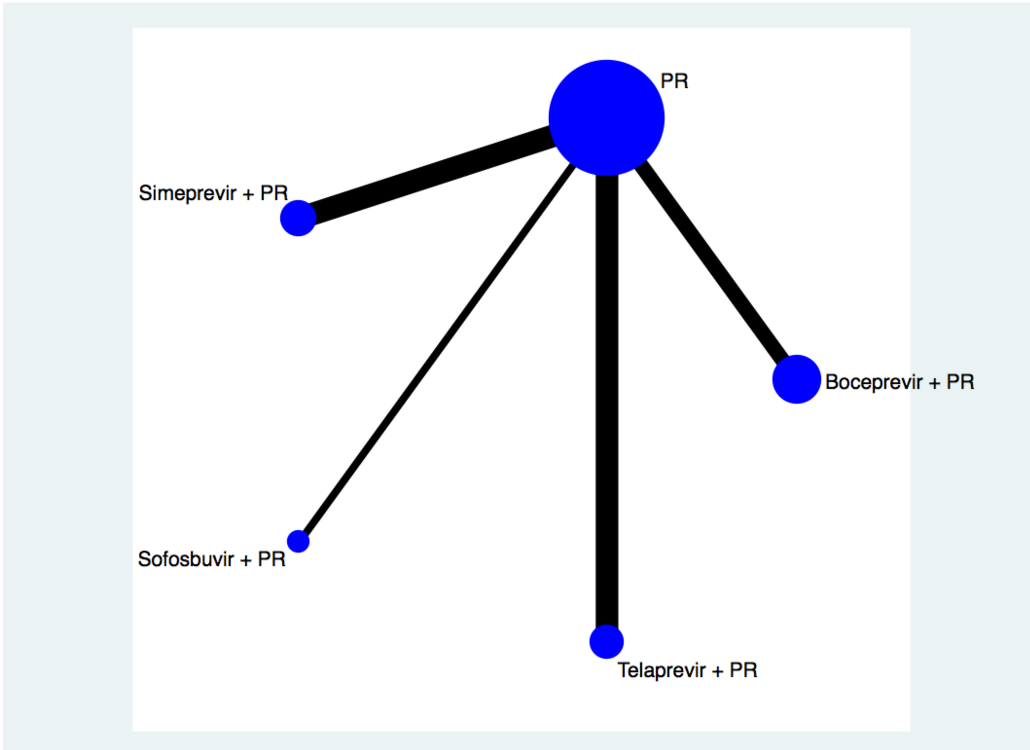
The one exception was the presence of the Q80K polymorphism. Among the 128 patients with the Q80K polymorphism, the SVR12 was only 58% for simeprevir and 52% for PR (difference NS). The prevalence of the Q80K polymorphism was 16% and it occurred almost exclusively in HCV genotype 1a.

The studies of sofosbuvir in treatment-naïve patients infected with genotype 1 were primarily dose finding studies. The largest was the ATOMIC study, which compared 12, 24, and 36 weeks of sofosbuvir in conjunction with PR, but had no control group without sofosbuvir. The SVR12 ranged from 90% to 93%. The NEUTRINO study was an open-label, single group study of sofosbuvir plus PR for 12 weeks that had the largest group of participants receiving the FDA indication dosing. The SVR12 in NEUTRINO was 89%. As with simeprevir, the SVR12 of sofosbuvir + PR varied by subgroups defined by known predictors of response to PR therapy. In the NEUTRINO study, the SVR12 for the IL28B CC genotype subgroup was 98% and in the less favorable non-CC genotype, the SVR12 was 87%. There was no control group for comparison. The SVR12 was 92% in patients with no cirrhosis and 80% in those with cirrhosis. Similarly, the SVR12 was 92% in patients with genotype 1a and 82% in those with genotype 1b.

Network Meta-Analysis Comparing Drug Regimens for Genotype 1 Treatment-naïve Patients

The lack of head-to-head trials makes it difficult to assess the relative efficacy of the different drug regimens for treatment-naïve patients infected with HCV genotype 1. Boceprevir + PR, telaprevir + PR, simeprevir + PR, and sofosbuvir + PR have all been compared to PR alone, but not to each other. Since the mix of patients with risk factors that influence response to therapy (IL28B genotype, fibrosis score, genotype 1a versus 1b, viral load, sex, race, age, etc.) vary from study to study, the SVR12 for any treatment group is not a fair assessment of the overall effectiveness of a treatment regimen. In order to assess the relative efficacy of the five treatment options, we performed a network meta-analysis, which allows for indirect comparisons between therapies as long as they share a common control group in randomized trials. This helps to control for differences in the patient mix across the studies. The structure of our network meta-analysis is depicted graphically in Figure 2 on the following page.

Figure 2. Network Plot for Clinical Trials of Treatment-naïve Patients with HCV Genotype 1.



The size of each node represents the number of participants receiving that treatment. The thickness of the line connecting them represents the number of patients in the comparison.

Three of the four trials of sofosbuvir in treatment-naïve patients with genotype 1 infections did not have a PR control group. Because these three trials (ELECTRON, ATOMIC, NEUTRINO) represent 93% of the patients treated with sofosbuvir, we think it is important to include them in the network meta-analysis. For each of the three trials, we assumed that there was a control group with an equal number of participants as the sofosbuvir + PR treatment group and assumed that the SVR12 in the control group would be the same as that observed in the control group of the PROTON trial (57.7%). Under those assumptions, the results of the network meta-analysis are shown in Table 6 on the following page.

Table 6. Summary Estimates from the Network Meta-Analysis for SVR12 Among Treatment-naive Patients Infected with HCV Genotype 1.

Treatment	SVR12	95% CI	P versus PR
PR	47%	41% to 52%	-
Boceprevir + PR	73%	68% to 77%	<0.001
Telaprevir + PR	74%	69% to 79%	<0.001
Simeprevir + PR	76%	70% to 81%	<0.001
Sofosbuvir + PR	83%	79% to 87%	<0.001

The summary estimates suggest that simeprevir-based therapy has very similar SVR12 results to triple therapy using either boceprevir or telaprevir, and the confidence intervals overlap substantially. Sofosbuvir + PR has the highest estimated SVR12, though it is important to remember that this estimate is based on extrapolations from uncontrolled trials and should be considered to have greater uncertainty than the confidence interval suggests.

The summary estimates for simeprevir and sofosbuvir from the network meta-analysis are lower than those observed in the clinical trials. This is because the meta-analysis estimates are based on the relative improvement compared to the SVR for the PR control group. The summary estimate from the meta-analyses for PR was 47%, which is similar to accepted estimates from the literature (40% to 50%).[39-41] However, the PR control groups in the trials of simeprevir and sofosbuvir were higher (50% to 65% for simeprevir and 57.7% for sofosbuvir). These differences in the SVR for the PR control groups likely reflect the underlying distribution of risk factors for response to therapy, with patients enrolling in the trials of simeprevir and sofosbuvir having a higher prevalence of favorable risk factors (or fewer unfavorable risk factors). For instance, the prevalence of cirrhosis was relatively low among patients in the trials of simeprevir and sofosbuvir (see Tables 3 and 4 above). The trials of the newer drugs may also have more patients with the favorable IL28B CC genotype and more 1a rather than 1b genotypes. One of the advantages of the network meta-analysis is that it partially accounts for the differences in the response rates for the control groups across all of the studies.

Interferon-ineligible patients

There were no studies for interferon-ineligible patients in this population. However, the COSMOS trial evaluated four interferon-free regimens in treatment-experienced patients and had a high SVR12. Treatment-naïve patients usually have higher SVR12s than similar patients who are treatment-experienced, so it is likely that the combination of simeprevir plus sofosbuvir would results in an SVR12 > 90% in treatment-naïve, interferon-ineligible patients.

In summary, for treatment-naïve patients infected with HCV genotype 1, simeprevir + PR and sofosbuvir + PR have greater SVR12 than PR alone. Simeprevir plus PR is about as effective as either boceprevir or telaprevir + PR. Sofosbuvir plus PR appears to have somewhat better response rates than treatment based on boceprevir or telaprevir, but most of the data come from uncontrolled studies. We did not identify any studies with SVR12 data on treatment-naïve patients who are interferon-ineligible.

6.3 SVR Outcomes of Treatment of HCV Genotype 1 in Treatment-experienced Patients

Table 7 on the following page summarizes the results of the major studies of simeprevir and sofosbuvir in treatment-experienced patients with genotype 1. All of the studies excluded patients with HIV, hepatitis B, or other significant illnesses. The treatment dosing regiments that match the FDA indication are highlighted and in bold. The primary outcome for most studies was SVR12, but some of the early studies were designed to look at SVR24, and some studies report both. No studies report long-term outcomes.

Interferon-eligible patients

The ASPIRE study was a randomized, double-blind, placebo controlled dose finding study comparing six different dosing regimens for simeprevir + PR to standard PR therapy. The primary outcome was SVR24, which ranged from 61% to 80% compared to 23% for PR. The SVR24 for the FDA approved dosing for simeprevir + PR was 67%. As expected, the results in this study are somewhat lower than those observed in the similar PILLAR study, which was performed in a treatment-naïve population.

Table 7. Clinical Trial Results for HCV Genotype 1 Treatment-experienced Patients.

Study	Treatment Arm	N	SVR12	SVR24
IFN-eligible				
ASPIRE	SMV 100 12 Weeks + PR	66		70%
	SMV 100 24 Weeks + PR	65		66%
	SMV 100 48 Weeks + PR	66		61%
	SMV 150 12 Weeks + PR	66		67%
	SMV 150 24 Weeks + PR	68		72%
	SMV 150 48 Weeks + PR	65		80%
	PBO + PR	66		23%
PROMISE	**SMV 150 12 Weeks + PR**	264	79%	
	PBO + PR	136	37%	
CONCERTO-2	SMV 100 12 Weeks + PR	53	53%	
	SMV 100 24 Weeks + PR	53	36%	
CONCERTO-3	SMV 100 12 Weeks + PR	49	96%	
CONCERTO-4	SMV 100 12 Weeks + PR	55	71%	
ELECTRON	SOF 400 + R 12 Weeks	10	10%	10%
COSMOS	SOF + SMV 12 Weeks	14	93%	
	SOF + SMV + R 12 Weeks	27	96%	
	SOF + SMV 24 Weeks	15	93%	
	SOF + SMV + R 24 Weeks	24	79%	
IFN-ineligible				
- No studies				

The phase 3 trial, PROMISE, randomized 400 patients 2:1 to 12 weeks of simeprevir 150 mg daily plus PR or to a placebo plus PR. It is worth noting that the participants were all patients who had relapsed following prior treatment and not partial or null responders. This group tends to have a better response to retreatment than patients who never achieved complete viral suppression during prior therapy. In the PROMISE trial, the SVR12 was 79% for simeprevir + PR and was 37% for PR alone. Subgroup analyses in PROMISE showed expected differences by risk factors for poor response to PR. For example, in the less favorable genotype 1a subgroup, the SVR12 was 70% for simeprevir + PR and 26% for PR alone; in the genotype 1b subgroup, the SVR12 was 86% for simeprevir + PR and 43% for PR alone.

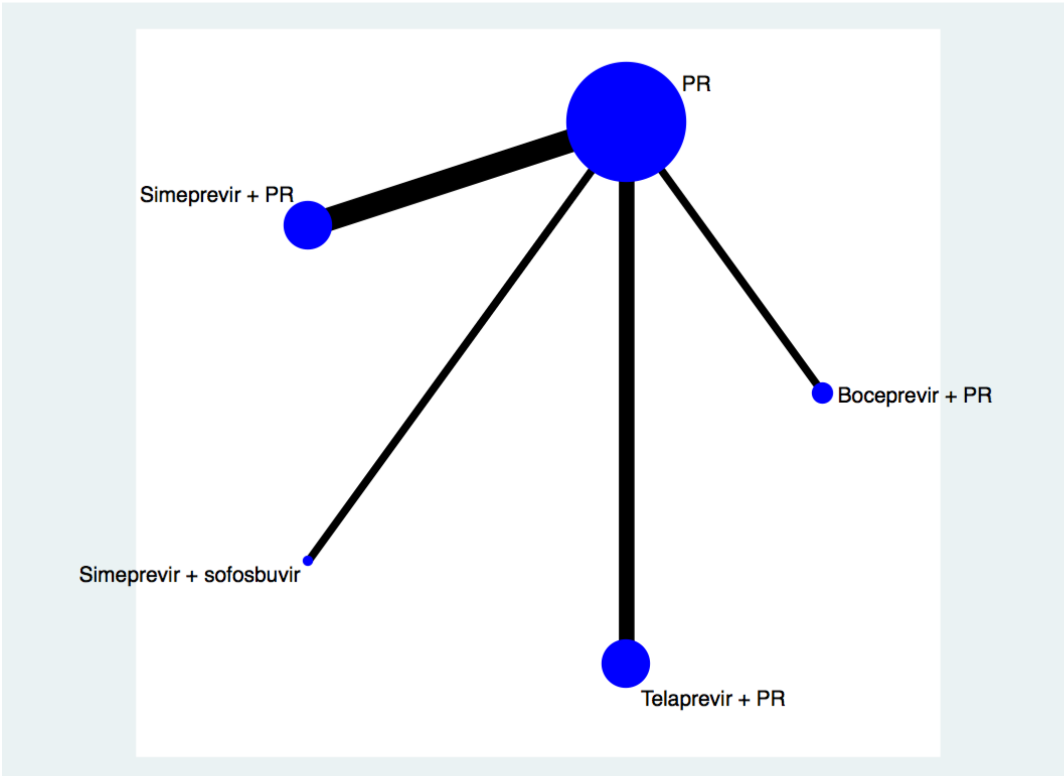
There is only one small, uncontrolled study of sofosbuvir in treatment-experienced patients infected with HCV genotype 1: a single arm of the ELECTRON study with 10 participants. These 10 individuals were treated with 400 mg of sofosbuvir and ribavirin for 12 weeks: only one participant achieved a sustained virologic response (SVR12 = 10%). This was an interferon-free regimen that does not correspond to the FDA approved dosing. Because there were essentially no data on sofosbuvir in treatment-experienced patients, the manufacturer's application to FDA extrapolated from the outcomes of patients in the treatment-naïve patients in the NEUTRINO study who had poor prognostic factors. Based on prior FDA publications,[94-96] the manufacturer argued, and the FDA accepted, that this would be a reasonable estimate for the SVR12 for treatment-experienced patients retreated with sofosbuvir + PR. The SVR12 for the 52 patients in NEUTRINO with “poor prognostic factors” was 71%.

Finally, there is one small study (COSMOS) that evaluated the combination of simeprevir and sofosbuvir with and without ribavirin for 12 or 24 weeks in 80 treatment-experienced genotype 1 patients with METAVIR F0 to F2 scores. There was no control arm for the study. Three of the four arms had remarkable 93% to 96% SVR12 outcomes. The fourth arm was the most intense (24 weeks of the combination plus ribavirin), but had the lowest SVR12 (79%). This appears to be due to participants lost to follow-up, although the data have only been presented in abstract form, so the details are not clear. Of note, there is a second part of the COSMOS trial in patients with METAVIR F3 or F4 fibrosis scores that has not yet announced its SVR12 results.

Network Meta-Analysis Comparing Drug Regimens for Genotype 1 Treatment-experienced Patients

Again, the lack of head-to-head trials makes it difficult to assess the relative efficacy of the different treatments for treatment-experienced patients infected with HCV genotype 1. In order to estimate the relative efficacy of the five treatment options, we performed a network meta-analysis (see Figure 3 on the following page).

Figure 3. Network Plot for Clinical Trials of Treatment-experienced Patients with HCV Genotype 1.



The size of each node represents the number of participants receiving that treatment. The thickness of the line connecting them represents the number of patients in the comparison.

We did not include sofosbuvir + PR regimens because of the lack of data. However, we did include data on sofosbuvir plus simeprevir from the COSMOS trial. We pooled the results from the four arms of this study because the results were similar, and we wanted to increase the power to evaluate the combination therapy (72/80 = 90% SVR12). We had to assume that there was a control group with an equal number of participants as the simeprevir + sofosbuvir treatment group and assumed that the SVR12 in the control group would be the same as the summary estimate for the control group of the other trials (22%). Under those assumptions, the results of the network meta-analysis are shown in Table 8 on the following page.

Table 8. Summary Estimates for the Network Meta-Analysis for SVR12 Among Treatment-Experienced Patients Infected with HCV Genotype 1.

Treatment	SVR12	95% CI	P versus PR
PR	22%	15% to 29%	-
Boceprevir + PR	64%	49% to 76%	<0.001
Telaprevir + PR	70%	61% to 77%	<0.001
Simeprevir + PR	67%	59% to 74%	<0.001
Simeprevir + sofosbuvir	90%	78% to 96%	<0.001

The summary estimates for the treatment-experienced population suggest that the SVR12 for simeprevir-based therapy is about the same as that for triple therapy with boceprevir and telaprevir with broadly overlapping confidence intervals. The combination of simeprevir plus sofosbuvir has the highest estimated SVR12, though it is important to remember that this estimate is based on extrapolations from one uncontrolled trial and should be considered to have greater uncertainty than the confidence interval suggests.

It is worth noting that the summary estimate for the combination of simeprevir plus sofosbuvir from the network meta-analysis is identical to the SVR12 derived from the COSMOS study. This is because there was only one study for that combination, and the estimate that we used for the PR control group was assumed to be identical to the summary estimate (22%) for the PR control group across all studies of treatment-experienced patients. If the true SVR12 for the 80 control patients enrolled in the COSMOS trial is higher than 22%, then our estimate for simeprevir plus sofosbuvir would be too high. Conversely, if the true SVR12 for the patients enrolled in the COSMOS trial is lower than 22%, then our estimate for simeprevir plus sofosbuvir would be too low.

Interferon-ineligible patients

There were no studies for interferon-ineligible patients in this population. However, the COSMOS trial evaluated four interferon-free regimens in treatment-experienced patients and had a high SVR12, which suggests that it could be considered for use in this population.

In summary, for treatment-experienced patients infected with HCV genotype 1, simeprevir + PR has a greater SVR12 than PR alone and appears to have similar response rates to boceprevir or telaprevir. The combination of simeprevir plus sofosbuvir may have the greatest SVR12, but the data are sparse, and it is not clear whether ribavirin is needed, though it appears that 12 weeks of treatment is about equivalent to 24 weeks of treatment. Finally there are insufficient data to evaluating sofosbuvir plus ribavirin and no data on sofosbuvir plus PR.

6.4 SVR Outcomes of Treatment of HCV Genotype 2 in Treatment-naïve Patients

The assessment of SVR outcomes is more straightforward for genotypes 2 and 3 because simeprevir, telaprevir, and boceprevir have not been evaluated or approved for genotypes 2 and 3. On the other hand, the SVR24 for PR alone is between 75% and 85% in this population, so there is less room for improvement. Table 9 on the following page summarizes the results of the major studies of sofosbuvir in treatment-naïve patients with genotype 2. Again, all of the studies excluded patients with HIV, hepatitis B, or other significant illnesses. The treatment dosing regimens that match the FDA indication are highlighted and in bold. The primary outcome for most studies was SVR12, but some of the early studies were designed to look at SVR24, and some studies report both. No studies report long-term outcomes.

Interferon-eligible patients

The ELECTRON study was a randomized, double-blind, dose finding study comparing six different dosing regimens for sofosbuvir. The study did not include a control arm with standard PR therapy. It also included a mix of both genotype 2 and 3 patients. Five of the six arms of the study had 100% SVR24, and two of them were interferon-free. The sofosbuvir-only arm had a lower 60% SVR24. Several other relatively small studies had similar findings.

Table 9. Clinical Trial Results for HCV Genotype 2 Treatment-naïve Patients.

Study	Treatment Arm	N	SVR12	SVR24
IFN-eligible				
ELECTRON	SOF 400 + R 12 Weeks + P 0 Weeks	10*	100%*	100%*
	SOF 400 + R 12 Weeks + P 4 Weeks	9*	100%*	100%*
	SOF 400 + R 12 Weeks + P 8 Weeks	10*	100%*	100%*
	SOF 400 + R 12 Weeks + P 12 Weeks	11*	100%*	100%*
	SOF 400 12 Weeks	10*	60%*	60%*
	SOF 400 + PR 8 Weeks	10*	100%*	100%*
PROTON	SOF 400 12 Weeks + PR	25*	92%*	92%*
QUANTUM	**SOF 400 + R 12 Weeks**	6*	67%*	
	SOF 400 + R 24 Weeks	6*	67%*	
FISSION	**SOF 400 + R 12 Weeks**	70	97%	
	PR 24 Weeks	67	78%	
VALENCE	**SOF 400 +R 12 Weeks**	32	97%	
IFN-ineligible				
POSITRON**	SOF 400 + R 12 Weeks	109**	93%**	
	PBO	34**	0%**	

*Mix of GT 2 and 3: the results were not presented separately
** Mix of treatment-naïve and experienced, but ~ 81% were treatment-naïve

The phase 3 trial, FISSION, was an open-label study that randomized 137 treatment-naïve genotype 2 patients to 12 weeks of sofosbuvir plus ribavirin or 24 weeks of PR. In the FISSION trial, the SVR12 was 97% for sofosbuvir plus ribavirin and was 37% for PR. Subgroup analyses in FISSION showed expected differences by risk factors for poor response to PR (see Table 10 on the following page).

Table 10. SVR12 for Key Subgroups of Patients with Genotype 2 in the FISSION Study.

Risk factor	**Sofosbuvir + ribavirin**	**PR**
Cirrhosis		
Yes	98%	81%
No	91%	62%
IL28B genotype		
CC	100%	82%
Non-CC	95%	72%
HCV RNA viral load		
< 6 log_{10} IU/ml	100%	74%
≥ 6 log_{10} IU/ml	96%	80%
Race		
Black	75%	50%
Non-black	98%	78%
Body mass index		
< 30 kg/m2	100%	78%
≥ 30 kg/m2	90%	77%

Interferon-ineligible patients

The POSITRON trial was a double-blind, placebo-controlled trial that randomized interferon-unwilling (47%), interferon-ineligible (44%) and interferon-intolerant (9%) patients to 12 weeks of sofosbuvir plus ribavirin or 12 weeks of identical placebos. It is the only trial addressing this group of patients. Because the majority of these patients (91%) were treatment-naïve, the results primarily apply here. As expected, the SVR12 was higher in the active treatment group (93% versus 0%) and similar to the SVR12 observed in the VALENCE and FUSION trials.

In summary, for treatment-naïve patients with genotype 2, sofosbuvir is a clear improvement over the standard of care. Treatment time is decreased from 24 to 12 weeks, and interferon is no longer needed, so the burden of injections and the side effects of interferon are avoided. In addition, the SVR12 is greater and it can be used to treat patients unwilling, unable, or intolerant of interferon.

6.5 SVR Outcomes of Treatment of HCV Genotype 2 in Treatment-experienced Patients

Interferon-eligible patients

There are fewer data for treatment-experienced patients with genotype 2 (see Table 11 below), and neither of the trials had a control group without sofosbuvir. In the FUSION trial, 36 treatment-experienced patients were treated with 12 weeks of sofosbuvir plus ribavirin. The SVR12 was 86% (95% CI 71% to 95%). Similarly, in the VALENCE trial, the SVR12 was 90% (95% CI 77% to 97%). Because both studies were uncontrolled, it is unclear how much better these results are than those that would have been obtained with retreatment with PR. In one recent published study, retreating with PR treatment-experienced patients with genotypes 2 or 3 led to SVRs ranging from 53% to 81%.[97] However, a treatment regimen of sofosbuvir plus ribavirin has the advantage of being both shorter and interferon-free.

Table 11. Clinical Trial Results for HCV Genotype 2 Treatment-experienced Patients.

Study	Treatment Arm	N	SVR12	SVR24
IFN-eligible				
FUSION	**SOF 400 + R 12 Weeks** SOF 400 + R 16 Weeks	36 32	86% 94%	
VALENCE	**SOF 400 +R 12 Weeks**	41	90%	
IFN-ineligible				
POSITRON*	SOF 400 + R 12 Weeks PBO	17* 8*	76%* 0%*	

*Mix of GT 2 and 3: the results were not presented separately

Interferon-ineligible patients

The POSITRON trial was a double-blind, placebo-controlled trial that randomized 25 interferon-intolerant patients to 12 weeks of sofosbuvir plus ribavirin or 12 weeks of identical placebos. The treatment-intolerant must be treatment-experienced. The investigators did not present the data in this subgroup separately for genotype 2 and genotype 3. In the combined group, the SVR12 in the sofosbuvir + R group was 76.5% (95% CI 50% to 93%). It is the only trial addressing this group of patients.

6.6 SVR Outcomes of Treatment of HCV Genotype 3 in Treatment-naïve Patients

The clinical trial results for genotype 3 are a bit more complex (see Table 12 below). The results from the dose-finding ELECTRON study were encouraging as described above. However, in the genotype 3 subgroup of the phase 3 FISSION trial, 12 weeks of sofosbuvir plus ribavirin had a lower SVR12 than 24 weeks of PR (56% versus 62%). The SVR12 of the same regimen in the genotype 3 subgroup of the POSITRON study was similarly low at 61%. The uncontrolled VALENCE trial tested a longer 24 week regimen of sofosbuvir and ribavirin. In this cohort of patients infected with HCV genotype 3, the SVR12 was 93% (95% CI 87% to 97%). These results should be confirmed in a second trial, but they formed the basis for the FDA recommended dose. Again, this treatment has the advantage of being interferon-free, but for genotype 3, it is not shorter than PR retreatment.

Table 12. Clinical Trial Results for HCV Genotype 3 Treatment-naïve Patients.

Study	Treatment Arm	N	SVR12	SVR24
IFN-eligible				
ELECTRON	SOF + R 12 Weeks + P 0 Weeks	10*	100%*	100%*
	SOF + R 12 Weeks + P 4 Weeks	9*	100%*	100%*
	SOF + R 12 Weeks + P 8 Weeks	10*	100%*	100%*
	SOF + R 12 Weeks + P 12 Weeks	11*	100%*	100%*
	SOF 12 Weeks	10*	60%*	60%*
	SOF + R 8 Weeks	10*	100%*	100%*
PROTON	SOF 400 12 Weeks + PR	25*	92%*	92%*
QUANTUM	SOF + R 12 Weeks	6*	67%*	
	SOF + R 24 Weeks	6*	67%*	
FISSION	SOF + R 12 Weeks	183	56%	
	PR 24 Weeks	176	62%	
VALENCE	**SOF 400 + R 24 Weeks**	105	93%	
IFN-ineligible				
POSITRON**	SOF + R 12 Weeks	98**	61%**	
	PBO	37**	0%**	

*Mix of GT 2 and 3: the results were not presented separately
** Mix of treatment-naïve and experienced, but ~ 81% were treatment-naïve

6.7 SVR Outcomes of Treatment of HCV Genotype 3 in Treatment-experienced Patients

The story is similar for treatment-experienced patients with genotype 3 (see Table 13 on next page). In the uncontrolled FUSION and VALENCE trials, the SVR12 increased from 30% to 62% to 77% as the length of treatment increased from 12 weeks to 16 weeks to 24 weeks. Because neither of these studies randomized patients to a PR arm, it is unclear if this represents an improvement over results potentially achieved with retreatment. However, it is interferon-free.

Table 13. Clinical Trial Results for HCV Genotype 3 Treatment-experienced Patients.

Study	Treatment Arm	N	SVR12	SVR24
IFN-eligible				
FUSION	SOF 400 + R 12 Weeks SOF 400 + R 16 Weeks	64 63	30% 62%	
VALENCE	**SOF 400 +R 24 Weeks**	145	77%	
IFN-ineligible				
POSITRON*	SOF 400 + R 12 Weeks PBO	17* 8*	76%* 0%*	

*Mix of GT 2 and 3: the results were not presented separately

Interferon-ineligible patients

As noted for genotype 2 treatment-experienced patients, the POSITRON trial randomized 25 interferon-intolerant patients to 12 weeks of sofosbuvir plus ribavirin or 12 weeks of identical placebos. In the combined group of genotype 2 and 3 treatment-experienced patients, the SVR12 in the sofosbuvir + R group was 76.5% (95% CI 50% to 93%). This is much higher than the SVR12 reported in the other trials of 12 weeks of sofosbuvir + R for genotype 2, which suggests that the majority of the interferon-intolerant patients in the POSITRON study were genotype 2. It would be difficult to recommend 12 weeks of therapy for interferon-ineligible patients with genotype 3 after concluding that 24 weeks of the same therapy is required for both treatment-naïve and treatment-experienced genotype 3 patients.

In summary, for genotype 3 treatment-naïve and experienced patients, 24 weeks of sofosbuvir + R appears to be superior to 12 or 16 weeks of the same therapy. In the one trial comparing 12 weeks of sofosbuvir + R to 24 weeks of PR, the PR group had a nominally higher SVR12. The lack of control groups in the other trials makes it difficult to conclude that the SVR12 with 24 weeks of sofosbuvir + R is greater than that of 24 weeks of PR. The POSITRON data suggest that sofosbuvir + R is effective for interferon-ineligible patients with genotype 3, though the VALENCE trial suggests that 24 weeks of therapy would be more effective than 12 weeks.

6.8 Harms of Treatment

Harms of treatment with simeprevir

HCV genotype 1

It is reasonably straightforward to compare the harms of treatment with simeprevir in patients infected with HCV genotype 1 to the harms of treatment with PR because the three phase 3 trials (QUEST-1, QUEST-2, PROMISE) were all randomized comparisons with PR in patients with HCV genotype 1. In order to fairly assess the independent effect of simeprevir, just the first 12 weeks of therapy were compared. The adverse events (AEs) are summarized in Table 14 below.

Table 14. Summary of Adverse Events in the Randomized Trials of Simeprevir.

Adverse Event	**Simeprevir + PR (12 weeks) N = 781**	**Placebo + PR (12 weeks) N = 397**
Any Adverse Event	95%	95%
Significant Adverse Events	2.0%	2.5%
Grade 3 or 4 AE	23%	25%
Therapy stopped due to AE	2.6%	4.5%
Common AEs		
Fatigue	36%	40%
Headache	33%	36%
Flu-like illness	26%	21%
Insomnia	17%	17%
Anemia (hemoglobin < 10 g/dL)	12%	10%
Likely associated with SMV		
Pruritus	21%	14%
Nausea	22%	18%
Rash	14%	11%
Photosensitivity	3.3%	0.5%
Elevated bilirubin	2.0%	0.5%

Adverse events, significant adverse events, grade 3 or 4 AEs, and adverse events leading to treatment discontinuation were not more common with simeprevir. There was clearly more pruritis, photosensitivity-induced rashes, and hyperbilirubinemia due to simeprevir, but these were generally not severe and were easily managed. They did not result in the discontinuation of therapy. Importantly, there was no significant increase in anemia with the addition of simeprevir. As described in the background section above, the earlier protease inhibitors boceprevir and telaprevir nearly doubled the incidence of significant anemia.[42] Overall, the addition of simeprevir to PR did not markedly increase the risk for adverse events.

Harms of treatment with sofosbuvir

HCV genotype 1

It is more difficult to carefully assess the relative impact of sofosbuvir on adverse events because few of the trials randomized patients to a regimen based on sofosbuvir vs. a regimen without sofosbuvir. For patients infected with genotype 1, the relevant comparison is between patients on sofosbuvir plus PR and PR alone (see Table 15 below). Sofosbuvir plus PR was used in the NEUTRINO study and PR in the FISSION study. Since these are different studies and non-randomized comparisons, the comparisons may be between patients sampled from different populations.

Table 15. Summary of Adverse Events for Sofosbuvir + PR and PR Alone.

Adverse Event	**Sofosbuvir + PR (12 weeks) N = 327**	**PR (24 weeks) N = 243**
Any Adverse Event	95%	96%
Significant Adverse Events	1%	1%
Grade 3 or 4 AE	15%	19%
Therapy stopped due to AE	2%	11%
Common AEs		
Fatigue	59%	55%
Headache	36%	44%
Flu-like illness	16%	18%
Insomnia	25%	29%
Anemia (hemoglobin < 10 g/dL)	23%	14%
Pruritus	17%	17%
Nausea	34%	29%
Rash	18%	18%

HCV genotypes 2 and 3

For patients with genotype 2 and 3 infections, the relevant comparison is between patients on sofosbuvir plus R and PR alone. Sofosbuvir plus R was used in the FISSION, FUSION, and POSITRON studies and PR in the FISSION study. These adverse events are summarized in Table 16 on the next page. Since these are different studies and non-randomized comparisons, the comparisons may be between patients sampled from different populations.

Table 16. Summary of Adverse Events for Sofosbuvir + R and PR Alone.

Adverse Event	Sofosbuvir + R (12 weeks) N = 566	PR (24 weeks) N = 243
Any Adverse Event	88%	96%
Significant Adverse Events	4.0%	1%
Grade 3 or 4 AE	7.2%	19%
Therapy stopped due to AE	1.4%	11%
Common AEs		
Fatigue	40%	55%
Headache	23%	44%
Flu-like illness	2.8%	18%
Insomnia	16%	29%
Anemia (hemoglobin < 10 g/dL)	9%	14%
Pruritus	9%	17%
Nausea	20%	29%
Rash	8%	18%

It is evident here that the elimination of interferon from the treatment regimen markedly decreases the risk for most adverse events including fatigue, headache, flu-like illness, anemia, pruritis, nausea, and rashes. There were also significantly fewer grade 3 or 4 adverse events. This translates into a marked eight-fold reduction in discontinuation of therapy due to adverse events (from 11% with PR to 1.4% with sofosbuvir + R).

6.9 Summary

Genotype 1

Table 17 summarizes the key benefits and harms for the treatment options for genotype 1. Among treatment-naïve patients, the protease inhibitors increased the SVR12 from the 40% range with PR to the 70% range. The improved SVR was somewhat offset by an increase in the complexity of the drug therapy. A large number of pills had to be taken about every 8 hours. In addition, there were burdensome new side effects added to the flu-like symptoms of interferon and the anemia and teratogenicity of ribavirin. These included a marked increase in anemia and nausea for both drugs, 20% more patients experiencing taste disturbance for boceprevir, and 20% more patients experiencing generalized pruritus with telaprevir. The drugs also have a large number of important drug interactions. Despite these problems, triple therapy with one of the two protease inhibitors is the standard of care for treatment of genotype 1.

Table 17. Summary of Benefits and Harms for Genotype 1 by Prior Treatment Status and Interferon Eligibility.

Treatment Approach (weeks)	SVR12 (Percent)	Treatment Burden	Adverse effects	Interferon-ineligible
Genotype 1				
Treatment-naive				
PR (48)	47	48 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (≤ 30%)	No
BOC(24) + PR(48)	73	Add Q8 hour pills	Anemia (≤ 50%), more nausea and dysguesia, drug interactions	No
TVR(12) + PR(48)	74	Add Q8 hour pills	Anemia (≤ 50%), more nausea and pruritus, drug interactions	No
SMV(12) + PR(24-48)	76	1 pill to PR	No increase in anemia.	No
SOF(12) + PR(12)	83	1 pill to PR Fewer weeks	No increase in anemia.	No
SMV(12) + SOF(12)	No data (?>90)	No P, maybe no R	Not reported yet	Maybe
Treatment-experienced				No
PR (48)	22	48 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (up to 30%)	No
BOC(24) + PR(48)	64	Add Q8 hour pills	Anemia (≤ 50%), more nausea and dysguesia, drug interactions	No
TVR(12) + PR(48)	70	Add Q8 hour pills	Anemia (≤ 50%), more nausea and pruritus, drug interactions	No
SMV(12) + PR(24-48)	67	1 pill to PR	No increase in anemia.	No
SOF(12) + PR(12)	No data	1 pill to PR Fewer weeks	No increase in anemia.	Maybe
SMV(12) + SOF(12)	90	No P, maybe no R	Not reported yet	Yes

Abbreviations: Q8 = taken every 8 hours; P = pegylated interferon; R = ribavirin

Simeprevir does not appear to significantly improve the SVR12 compared with triple therapy. The primary benefits of simeprevir are the reduced incidence of anemia and the reduced pill burden: it only requires taking one pill a day. Adverse events specifically associated with simeprevir include pruritus, photosensitivity-induced rashes, and hyperbilirubinemia, but these were generally not severe and were easily managed. The increase in pruritus compared to PR was less than that seen with telaprevir. One important finding specific to simeprevir is that its effectiveness is markedly diminished in patients with the Q80K genetic polymorphism in HCV genotype 1. If the Q80K polymorphism is present, simeprevir should not be used. Simeprevir requires PR and cannot be used to treat interferon-ineligible patients. The primary weakness in the data is the lack of head-to-head trials comparing simeprevir and one of the protease inhibitors. As noted in section 5 above, there is a large (n=766) randomized trial comparing simeprevir to telaprevir that should complete data collection for its primary outcome in March 2014. In addition, there are no data on the impact of treatment on long term outcomes such as the incidence of cirrhosis, liver decompensation, HCC, transplant, or death.

Sofosbuvir plus PR also appears to have less anemia and certainly has a lower pill burden than standard triple therapy. It also requires only 12 weeks of PR rather than the 24 to 48 weeks with the protease inhibitors. There are less robust comparative data on sofosbuvir + PR compared to PR alone than for simeprevir, and there are no data comparing it to PR plus simeprevir, boceprevir, or telaprevir. However in the network meta-analysis, sofosbuvir + PR had nominally the highest SVR12. Because of the shorter course of PR, sofosbuvir + PR had fewer grade 3 and 4 AEs and less stopping treatment due to AEs, with no consistent pattern of an increase in AEs other than anemia (23% versus 14% for PR). As with simeprevir, this combination cannot be used in patients who are interferon-ineligible, and there are no long-term outcome data.

The preliminary data on simeprevir plus sofosbuvir with or without ribavirin are encouraging. The available SVR12 data from treatment-experienced patients averaged 90%; the SVR12 of treatment-naïve patients should be even better. It is interferon-free, so can be used in interferon-ineligible patients. Since it is interferon-free (and perhaps ribavirin-free), it should have markedly lower adverse event rates than PR based treatment. The data come from four different regimens in one small study without detailed published results and should be considered preliminary at this point.

Genotype 2

For genotype 2, the story is more straightforward (see Table 18 below). The combination of sofosbuvir plus ribavirin is a win on all fronts. Among treatment-naïve patients, there was a large increase in SVR12 seen in the randomized FISSION trial and supported by the VALENCE trial, although that was not randomized. The SVR12 for treatment-experienced patients was 86% and 90% in the two uncontrolled studies, but high enough to assume at least non-inferiority to PR therapy. The sofosbuvir-based regimen is interferon-free, which decreases grade 3 and 4 adverse events, markedly decreases stopping therapy because of adverse events, and reduces interferon-associated adverse event such as fatigue, fever, myalgias, and headaches. Sofosbuvir therapy does not come with an increase in the anemia seen with the first generation protease inhibitors – in fact, the incidence of anemia was lower in the sofosbuvir arms of the trials. The treatment course is also half as long (12 versus 24 weeks). Since the sofosbuvir-based regimen is interferon-free, the benefits should be even greater in those genotype 2 patients who are treatment-naïve but ineligible for interferon because of psychiatric or other co-morbidities. In the POSITRON trial, the SVR12 was 93% compared to 0% for treatment-naïve patients, and 76% versus 0% for treatment-experienced patients.

Table 18. Summary of Benefits and Harms for Genotype 2 by Prior Treatment Status and Interferon Eligibility.

Treatment Approach (weeks)	**SVR12 (Percent)**	**Treatment Burden**	**Adverse effects**	**Interferon-ineligible**
Genotype 2				
Treatment-naive				
PR (24)	78	24 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (up to 30%)	No
SOF(12) + R(12)	97	Shorter, no P	Less fatigue, less anemia	Yes
Treatment-experienced				
PR (24)	No data	24 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (up to 30%)	No
SOF(12) + R(12)	88	Shorter, no P	Less fatigue, less anemia	Yes

Abbreviations: P = pegylated interferon; R = ribavirin

Genotype 3

For genotype 3 the story is more complex (see Table 19 below). The combination of sofosbuvir plus ribavirin for 12 weeks did not increase SVR12 compared to PR among treatment-naïve patients in the FISSION trial. However, the SVR12 consistently increased with increasing lengths of therapy to 16 and 24 weeks (56% to 93% in the uncontrolled VALENCE trial). The SVR12 for treatment-experienced patients increased from 30% (12 weeks) to 62% (16 weeks) to 77% (24 weeks). The sofosbuvir-based regimen is interferon-free, which as noted above, decreases grade 3 and 4 adverse events, markedly decreases stopping therapy because of adverse events, and reduces interferon-associated adverse event such as fatigue, fever, myalgias, and headaches. Sofosbuvir therapy has a lower incidence of anemia than PR in the phase 3 trials. The treatment course is the same as PR, but without the injections and side effects of interferon. Since the sofosbuvir-based regimen is interferon-free, the benefits should be even greater in those genotype 3 patients who are treatment-naïve but ineligible for interferon because of psychiatric or other co-morbidities. In the POSITRON trial, the SVR12 was 61% compared to 0% for treatment-naïve patients, and 76% versus 0% for treatment-experienced patients.

Table 19. Summary of Benefits and Harms for Genotype 3 by Prior Treatment Status and Interferon Eligibility.

Treatment Approach (weeks)	**SVR12 (Percent)**	**Treatment Burden**	**Adverse effects**	**Interferon-ineligible**
Genotype 3				
Treatment-naive				
PR (24)	62	24 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (up to 30%)	No
SOF(12) + R(12)	93	Shorter, no P	Less fatigue, less anemia	Yes
Treatment-experienced				
PR (24)	No data	24 weeks with weekly injections	Fatigue (50-60%), fever (40-45%), anemia (up to 30%)	No
SOF(12) + R (12)	77	Shorter, no P	Less fatigue, less anemia	Yes

Abbreviations: P = pegylated interferon; R = ribavirin

7. Model of Clinical and Economic Outcomes of Treatment Strategies for Hepatitis C

As noted in this review, new medications for hepatitis C have the potential to change clinical expectations for achieving sustained virologic response in many more patients than previously thought possible. However, these medications also have the potential to substantially increase health-system costs. We developed a cohort model to compare the possible clinical and economic outcomes from the use of sofosbuvir and simeprevir in multiple patient populations.

For comparison purposes, we also identified published studies of the cost-effectiveness of both existing and proposed treatment options for hepatitis C treatment, which are summarized in the section immediately following. We limited our summary to those studies published from 2011 onwards as representative of current costs of hepatitis C management. However, we also report on any available studies that used a “cost per treatment success” measure of cost-effectiveness, as that was a central output of our model (see Summary, Section 7.4).

7.1 Prior Published Evidence on Costs and Cost-effectiveness

We identified a number of studies published in the era of direct-acting antiviral agents (i.e., from 2011 to the present) that evaluated the economic impact of hepatitis C therapy, including an in-press publication examining the cost-effectiveness of sofosbuvir.[98] The methods and results of these studies are summarized below by therapeutic approach. As can be seen in these summaries, most model results were highly sensitive to the estimated cost of treatment, and all focused exclusively on improvements in overall or quality-adjusted life expectancy (i.e., impacts on intermediate outcomes such as disease progression and liver transplantation were not described).

Cost-Effectiveness of Sofosbuvir

As noted above, we identified a single study assessing the economic impact of sofosbuvir.[98] This was an industry-funded, lifetime simulation model conducted from the perspective of the Italian National Health Service, and it involved separate comparisons of triple therapy with sofosbuvir vs. boceprevir and telaprevir in genotype 1 patients who were naïve to treatment and age 50 years. Strategies with an incremental cost per life-year gained less than €25,000 (~$35,000) were considered to be cost-effective. Costs included those of therapy, management of side effects, and disease-related complications.

On an overall basis, sofosbuvir triple therapy was estimated to increase life expectancy by approximately eight months relative to boceprevir and three months vs. telaprevir. Discounted lifetime costs in the sofosbuvir strategy (~$63,000) were 35-40% higher than those in the boceprevir and telaprevir strategies, even after accounting for improved survival with sofosbuvir. Sofosbuvir was considered to be cost-effective in comparison to either of the competing strategies, but not universally so across all subgroups. For example, sofosbuvir was considered to be cost-effective among cirrhotic patients and those with the IL28b CC allele, but not in patients with lower levels of fibrosis or in patients with the genotype 1b subtype. Of interest for this analysis, model findings were most sensitive to changes in the price of sofosbuvir, which was assumed to be $4,800 per week in the base case; the current price in the U.S. is $7,000 weekly.

Cost-Effectiveness of All-Oral Hepatitis C Regimens

While all-oral regimens for hepatitis C are not yet available, two simulation models have assessed the potential cost-effectiveness of hypothetical combinations of oral drugs.[4,99] Hagan and colleagues assessed cost-effectiveness of a hypothetical 2-drug regimen over a lifetime vs. standard care (i.e., triple therapy or PR) across all genotypes in a 50 year-old treatment-naïve cohort using a societal perspective in an NIH-funded analysis.[4] All-oral therapy resulted in an overall gain of five months of quality-adjusted life expectancy while generating approximately $20,000 more in costs. The resulting cost-effectiveness ratio was $45,000 per quality-adjusted life year (QALY) gained. The base case cost estimate for a course of all-oral therapy was estimated to be $70,000, and such therapy was no longer considered cost-effective in this model (at a $50,000 per QALY threshold) at prices exceeding $75,000. Given that the average wholesale prices for courses of sofosbuvir and simeprevir are already at least $84,000 and $66,000 respectively, the true cost of combination all-oral therapy will likely be much higher. A second, industry-funded analysis produced a lower cost-effectiveness ratio ($15,709 per QALY gained), which appears to be closely tied to the assumption that all-oral drug costs would be equivalent to those of existing triple therapy with telaprevir.[99]

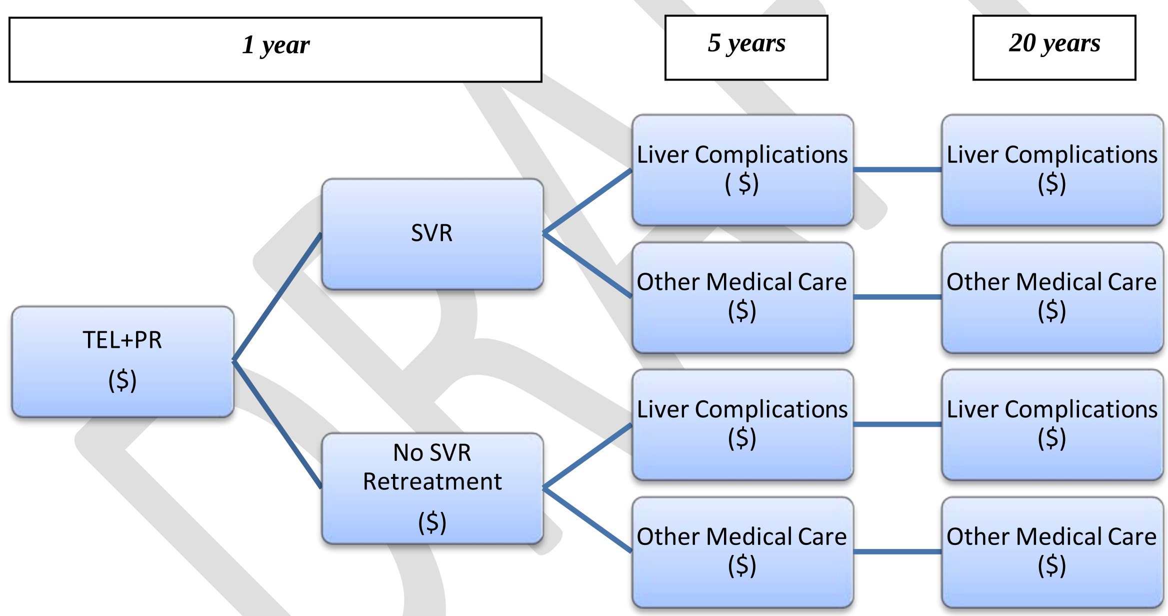
Cost-Effectiveness of Telaprevir and/or Boceprevir

We also identified six recent studies evaluating the cost-effectiveness of telaprevir and boceprevir, all of which used simulation techniques to evaluate outcomes and costs on a lifetime basis.[100-105] Cost-effectiveness ranged widely in these studies, from $11,000-$70,000 per QALY gained. Results were sensitive to whether patients had mild or advanced fibrosis, response to prior PR therapy, and of course, the assumed costs of therapy itself, as many of these studies assumed costs for telaprevir and boceprevir that are markedly less than current average wholesale prices for these agents.

7.2 Model Overview

To examine the potential clinical and economic impact of the introduction of sofosbuvir and simeprevir in California, we developed a cohort model that assessed these effects over time horizons of one year, five years, and 20 years in hypothetical cohorts of chronic hepatitis C patients organized by genotype, prior treatment status (i.e., treatment-naïve vs. treatment-experienced), and eligibility for interferon therapy. Within each of these strata, outcomes and costs were assessed for 1,000 hypothetical patients, age 60 years. We focused on genotypes 1, 2, and 3, as these represent over 97% of the hepatitis C population. Strata were designed to purposely align with those used in the recently published AASLD/IDSA/IAS treatment guidelines.[106] We adopted the perspective of a third-party payer for these analyses. Figure 4 below depicts the model schematic for 1,000 patients receiving telaprevir+PR.

Figure 4. Example of Model Schematic for 1,000 Patients Receiving Telaprevir+PR.



NOTE: "$" indicates model elements with calculated cost
TEL: Telaprevir; PR: Pegylated interferon + ribavirin; SVR: Sustained virologic response

<u>Patient Outcomes</u>

We employed a variety of patient outcome measures for this analysis. The rates of SVR for each treatment strategy were drawn from the network meta-analysis or individual studies as previously described. Because the effectiveness of retreatment with newer regimens is not yet known, estimates of SVR (presented on a per 1,000 basis) were based on the *initial treatment course only*.

Pooled estimates of the percentage of patients discontinuing therapy due to an adverse event were obtained from all available trial reports for each treatment strategy (see pages 46-48), and were also presented on a per 1,000 basis. All patients were assumed to be at risk of downstream liver-related complications (e.g., cirrhosis, liver cancer, transplantation). Relatively little is known about the detailed natural history of hepatitis C infection. However, a systematic review of 57 epidemiologic studies estimated the rate of advanced liver disease/cirrhosis at 20 years to be 24%, and suggested that the rate of progression was reasonably linear.[23] We used this as our estimate of liver-related complications at 20 years across all patients, and derived a 5-year estimate of 6% based on the linear assumption. For patients with advanced liver fibrosis (i.e., METAVIR scores of F3 or F4), we assumed that the rate of progression would be double that of the overall cohort (i.e., 48% and 12% at 20 and five years respectively) based on a comparison of findings in patients with advanced fibrosis vs. all patients in a second systematic review of observational studies of hepatitis C complications.[107] These rates were applied to patients who would not achieve SVR with initial therapy. Among patients achieving SVR, rates of liver-related complications were assumed to be reduced by 80% (i.e., rate ratio of 0.2), as multiple observational studies have shown risk reductions of this level or better for a variety of liver-related complications.[90,107,108] Rates of liver-related complications averted were presented per 1,000 patients treated.

Treatment Strategies

Treatment strategies varied by cohort and included a "best usual care" regimen prior to the availability of simeprevir and sofosbuvir. Additional treatment strategies were based on those recommended in the AASLD/IDSA/IAS guidelines. Strategies of interest, along with estimated SVR rates, are presented in Table 20 on the following page. SVR rates were obtained from the network meta-analysis or individual studies as appropriate (see Section 6). The guidelines do not make distinctions regarding interferon eligibility in some cases. We therefore assumed pooled SVR rates within subpopulations of genotype /prior treatment status were equivalent for those eligible and not eligible for interferon (unless study/meta-analysis data were available within interferon eligibility strata). Also of note, we used triple therapy with older protease inhibitors as a "referent" strategy for genotype 1. However, because boceprevir and telaprevir involve markedly different dosing and duration, we opted to focus on triple therapy with telaprevir as the previous standard for our model given that it held a 70% share of the triple therapy market prior to the introduction of the newer DAAs.[109] Impact was assessed during the year of treatment initiation as well as five and 20 years after treatment.

We also assessed the impact of use of newer drug regimens by applying the measures above to the entire California chronic hepatitis C population based on expected numbers of patients within each genotype who would present for treatment; scenarios were employed alternatively for all patients as well as those with advanced liver fibrosis (i.e., fibrosis score of F3 or F4) only (see page 73 for a summary of methods and results of these analyses).

Table 20. Treatment Strategies of Interest, by HCV Genotype, Prior Treatment Status, and Interferon Eligibility.

Prior Rx Status, IFN eligibility	Genotype 1	*SVR (%)*	Genotype 2	*SVR (%)*	Genotype 3	*SVR (%)*
Treatment-naïve						
IFN-eligible	***TEL+PR (12/24)*** **SMV+PR (12/24)** **SOF+PR (12)**	**74** **76** **83**	***PR (24)*** **SOF+R (12)**	**78** **97**	***PR (24)*** **SOF+PR (12)** **SOF+R (24)**	**62** **92** **93**
IFN-ineligible	***No Rx*** **SOF+R (24)** **SOF+SMV+R (12)**	**0*** **71** **90**	***No Rx*** **SOF+R (12)**	**0*** **93**	***No Rx*** **SOF+R (24)**	**0*** **61**
Treatment-experienced						
IFN-eligible	***TEL+PR (12/24)*** **SMV+PR (12/24)** **SOF+PR (12)** **SOF+SMV+R (12)**	**70** **67** **83** **90**	***PR (24)*** **SOF+PR (12)** **SOF+R (12)**	**78** **92** **88**	***PR (24)*** **SOF+PR (12)** **SOF+R (24)**	**62** **83** **77**
IFN-ineligible	***No Rx*** **SOF+R (24)** **SOF+SMV+R (12)**	**0*** **71** **90**	***No Rx*** **SOF+R (12)**	**0*** **88**	***No Rx*** **SOF+R (24)**	**0*** **61**

NOTES: Duration of therapy in parentheses; "/" indicates situations in which different components have different durations.
SVR rates obtained from ICER network meta-analysis or individual studies as necessary
"Best usual care" italicized and highlighted in yellow
TEL: Telaprevir; R: ribavirin; PR: pegylated interferon/ribavirin; SMV: simeprevir; SOF: sofosbuvir; No Rx: no standard treatment available
*Assumed rate of 0 for No Rx category (no assumed spontaneous SVR)

Costs

The model first presents the estimated cost per patient for the initial course of therapy. Based on this cost and the estimated SVR rate, the cost per additional SVR is calculated (also on a per patient basis). We also calculated expected *total* drug costs in the first year, based on an assumption that those not achieving SVR initially would be retreated with the most effective regimen available within each genotype, prior treatment status, and interferon eligibility combination (see Table 20 on the previous page for most effective regimens). It is important to note that this was done only to provide an accurate picture of likely drug costs over one year for the cohort, *not* to assess the potential impact of SVR from sequential treatment. Total one-year drug costs are presented for the entire 1,000 patient cohort in order to compare these costs to any cost offsets from prevention of liver-related complications and greater achievement of SVR (see below).

Annual costs of liver-related complications were calculated based on an analysis of advanced liver disease in Florida Medicaid claims,[110] while annual costs of maintenance care for patients achieving and not achieving SVR were derived from a study comparing post-treatment costs by SVR status among patients treated in the Kaiser health system.[111] In this study, the annual costs of care following hepatitis C treatment were estimated for patients achieving and not achieving SVR, including outpatient care, inpatient care, laboratory, and pharmacy. Costs were approximately $3,800 higher for patients without SVR vs. those with successful treatment.

We estimated the costs of medication using published wholesale acquisition costs or average wholesale prices.[112] All costs were expressed in 2013 dollars. Costs incurred in future years were discounted by 3% in accordance with generally-accepted practice for economic evaluations.[113] We did not consider short-term costs of adverse-event management or monitoring during treatment (the Manos study focused on costs after treatment was completed). We also based our estimates of treatment success on data from the initial course of treatment only. The cost offsets associated with prevention of liver-related complications and greater achievement of SVR at five and 20 years after treatment are presented on a per 1,000 basis to facilitate comparisons to one-year drug costs (see above).

Key model estimates are presented in Table 22 on page 60. Key model assumptions, many of which are described above, are also summarized in Table 21 on the following page.

Table 21. Key Assumptions Used in Model Development.

Key Assumption	Rationale
Cost per SVR and downstream cost offsets based on effectiveness of initial course of therapy	No available data on effectiveness of retreatment with newer regimens
Patients would complete and be fully compliant with therapy	Compliance data not available for all regimens and populations of interest
Clinical benefits limited to SVR and its effects on downstream liver-related complications	Intent was to develop policy-based model rather than to document natural history
Costs limited to drug therapy and downstream management of liver disease and other medical care	Intent was to develop policy-based model rather than to create full accounting of costs
No differential costs assumed for identification and management of side effects and other drug-related harms	Inclusion of such measures would dilute the model focus on differential SVR rates and their impact on downstream events and costs
Costs were measured for assumed retreatment regimens, but effectiveness was not	Focus of model was on clinical impact of initial course of therapy

Table 22. Estimates for Cohort Model of Hepatitis C Treatment.

Measure	Estimate	Sources
Discontinuation due to adverse events, %		CTAF Evidence Review
PR	8.4	
Telaprevir (+PR)	14.0	
Simeprevir (+PR)	6.4	
Sofosbuvir (+PR)	5.5	
Sofosbuvir (+R)	1.3	
Sofosbuvir+Simeprevir (±R)	5.0	
Risk of liver-related complications, %		Freeman, 2001; Singal, 2010
At 5-years		
All patients	6.0	
Advanced fibrosis only	12.0	
At 20-years		
All patients	24.0	
Advanced fibrosis only	48.0	
Hazard ratio for composite liver complications with SVR	0.20	Van der Meer, 2012; Singal, 2010; Pearlman, 2011
Annual costs of care, $		
Patients with liver complications	25,728	Menzin, 2012
Patients without SVR	10,149	Manos, 2013
Patients with SVR	6,301	Manos, 2013
Weekly drug costs, $		Red Book® Online, 2013
Ribavirin	348	
Pegylated interferon	691	
Telaprevir	4,920	
Simeprevir	5,530	
Sofosbuvir	7,000	

PR: Pegylated interferon/ribavirin

7.3 Model Results

Genotype 1, Treatment-naïve, Interferon-eligible

Table 23 on the following page presents model results for all patients with genotype 1 who are treatment-naïve. Among a population of 1,000 interferon-eligible patients, we estimate that SVR will be achieved for 830 treated with sofosbuvir+PR; for 760 treated with simeprevir+PR; and for 740 patients treated with telaprevir+PR. Fifty patients would require treatment with simeprevir+PR to obtain one additional SVR when compared with the SVR rates of telaprevir+PR; the corresponding figure is 11 patients per additional SVR for sofosbuvir+PR. The number of patients discontinuing therapy due to adverse events is 2-3 times greater for telaprevir+PR vs. the newer regimens.

Drug costs for the initial treatment course are 9% and 15% greater for the newer regimens ($91,296 and $96,468 for simeprevir and sofosbuvir, respectively) than older triple therapy ($83,976). The cost per additional SVR when looking just at the initial treatment course was estimated to be $366,000 for simeprevir+PR and $138,800 for sofosbuvir+PR. While not presented in the table, the cost per additional SVR for sofosbuvir+PR vs. simeprevir+PR was estimated to be $73,885.

Total drug costs over one year were tabulated for an entire 1,000 person cohort under the assumption that all patients who do not achieve SVR with initial therapy are then prescribed sofosbuvir+PR. These costs were estimated to total $109 million for telaprevir, $114 million for simeprevir, and $113 million for sofosbuvir. The incremental one-year drug costs for the entire 1,000 patient cohort over the costs for telaprevir+PR would be $5.4 million for simeprevir+PR and $3.8 million for sofosbuvir+PR.

Over five years, the simeprevir and sofosbuvir regimens would reduce the number of liver-related complications per 1,000 when compared with telaprevir+PR by one and four patients, respectively. The cost offset over five years per 1,000 patients that is created by savings from fewer liver complications and greater number of patients achieving SVR is estimated to be approximately $500,000 for simeprevir+PR and $2.1 million for sofosbuvir+PR, representing 9% and 57% of estimated incremental one-year drug costs. Over a 20-year time horizon, the two newer regimens would result in four and 17 fewer liver-related complications per 1,000. At 20 years, the cost offset for simeprevir+PR would be approximately $1.5 million (or approximately 30% of incremental one-year drug costs), while the offset for sofosbuvir+PR would be $7 million, which would completely offset the initial incremental drug cost and result in net savings.

Table 23. Clinical and Economic Impact of Treatment Options Among 1,000 60 year-old Patients with Hepatitis C Genotype 1 Who Are New to Treatment (Treatment-naïve).

	Evidence Review Data					*Modeled 1-Year Drug Costs*		*Modeled Long-Term Effects of Achieving SVR*			
								Liver Events Averted		Total Estimated Cost Offset†	
Population/regimen	**SVR per 1000**	**NNT for 1 add'l SVR**	**Discontinued due to AE (per 1000)**	**Cost for initial Rx (per patient)**	**Cost per add'l SVR**	**Total Drug Costs* (per 1000)**	**Incremental (vs. pre-DAA)**	**5 years (per 1000)**	**20 years (per 1000)**	**5 years (per 1000, vs. pre-DAA)**	**20 years (per 1000, vs. pre-DAA)**
IFN-eligible											
TEL + PR (12/24) (pre-DAA)	740	---	140	$83,976	---	$109,057,680	---	---	---	---	---
SMV + PR (12/24)	760	50	64	$91,296	$366,000	$114,448,320	$5,390,640	(1)	(4)	($478,684)	($1,545,912)
SOF + PR (12)	830	11	55	$96,468	$138,800	$112,867,560	$3,809,880	(4)	(17)	($2,154,078)	($6,956,605)
IFN-ineligible											
No Rx (pre-DAA)	0	---	0	$0	---	$0	---	---	---	---	---
SOF + R (24)	710	1	13	$176,352	$248,383	$221,167,440	$221,167,440	(34)	(136)	($16,993,282)	($54,879,887)
SOF + SMV + R (12)	900	1	50	$154,536	$171,707	$169,989,600	$169,989,600	(43)	(173)	($21,540,780)	($69,566,054)

*Includes costs of initial therapy and retreatment with most effective regimen available for those not achieving SVR initially

†Total estimated cost offset includes cost savings from liver events averted and reduced annual costs from greater numbers of patients achieving SVR

SVR: sustained virologic response; NNT: number needed to treat; DAA: direct-acting antivirals

Genotype 1, Treatment-naïve, Interferon-ineligible

Among interferon-ineligible patients, comparisons were made between sofosbuvir+R (24 weeks), sofosbuvir+simeprevir+R (12 weeks), and no drug therapy (as these patients previously had no treatment options). The combination of sofosbuvir+simeprevir+R was most effective (900 achieving SVR per 1,000 vs. 710 for sofosbuvir+R). Both regimens are very expensive: ~$176,000 for 24 weeks of sofosbuvir+R and ~$155,000 for 12 weeks of sofosbuvir+simeprevir+R. Assuming retreatment of patients failing to achieve SVR with sofosbuvir+simeprevir+R, one-year drug costs for 1,000 patients treated with sofosbuvir+R for 24 weeks would total $221 million, while sofosbuvir+simeprevir+R for 12 weeks would generate $170 million in drug costs per 1,000 patients.

At five years, cost offsets per 1,000 patients due to averted liver complications and greater achievement of SVR would total approximately $17 million for sofosbuvir+R and $22 million for sofosbuvir+simeprevir+R, or about 10% of incremental drug costs for these regimens; even at 20 years, cost offsets relative to no drug treatment would represent 40% of these totals at most (for sofosbuvir+simeprevir+R).

Genotype 1, Treatment-experienced, Interferon-eligible

Findings for genotype 1 patients who have been treated previously can be found in Table 24 on the following page. Among patients eligible for interferon therapy, comparisons were made for simeprevir+PR, sofosbuvir+PR, and sofosbuvir+simeprevir+R vs. a "best usual care" of telaprevir+PR. Based on the network meta-analysis findings, simeprevir+PR was less effective and more expensive than older triple therapy, resulting in both additional costs *and* additional long-term liver-related complications. Sofosbuvir+simeprevir+R was the most effective therapy (900 SVR per 1,000 patients vs. 830 and 700 for sofosbuvir+PR and telaprevir+PR, respectively). Eight patients would need to be treated with sofosbuvir+PR or five treated with sofosbuvir+simeprevir+R to achieve one additional SVR over telaprevir+PR.

The cost per additional SVR could not be calculated for simeprevir+PR because it was less effective and more expensive than telaprevir+PR. The cost per additional SVR for sofosbuvir+PR was estimated to be $96,092. The cost per additional SVR for sofosbuvir+simeprevir+R was much higher ($352,800), as the treatment cost is nearly twice that of telaprevir+PR (~$155,000 vs. ~$84,000). When the sofosbuvir regimens were compared to each other, the cost per SVR of sofosbuvir+simeprevir+R was estimated to be $829,543 (data not shown), as this regimen is 60% more expensive than sofosbuvir+PR yet is only seven percentage points more effective in achieving SVR in this population.

Table 24. Clinical and Economic Impact of Treatment Options Among 1,000 60 year-old Patients with Hepatitis C Genotype 1 Who Have Been Treated Previously (Treatment-experienced).

	Evidence Review Data					*Modeled 1-Year Drug Costs*		*Modeled Long-Term Effects of Achieving SVR*			
Population/regimen	SVR per 1000	NNT for 1 add'l SVR	Discontinued due to AE (per 1000)	Cost for initial Rx (per patient)	Cost per add'l SVR	Total Drug Costs* (per 1000)	Incremental (vs. pre-DAA)	Liver Events Averted (per 1000): 5 years	Liver Events Averted (per 1000): 20 years	Total Estimated Cost Offset† (per 1000, vs. pre-DAA): 5 years	Total Estimated Cost Offset† (per 1000, vs. pre-DAA): 20 years
IFN-eligible											
TEL + PR (12/24) (pre-DAA)	700	---	140	$83,976	---	$130,336,800	---	---	---	---	---
SMV + PR (12/24)	670	N/C	64	$91,296	N/C	$142,292,880	$11,956,080	1	6	$718,026	$2,318,868
SOF + PR (12)	830	8	55	$96,468	$96,092	$122,739,120	($7,597,680)	(6)	(25)	($3,111,446)	($10,048,430)
SOF + SMV + R (12)	900	5	50	$154,536	$352,800	$169,989,600	$39,652,800	(10)	(38)	($4,786,840)	($15,459,123)
IFN-ineligible											
No Rx (pre-DAA)	0	---	0	$0	---	$0	---	---	---	---	---
SOF + R (24)	710	1	13	$176,352	$248,383	$221,167,440	$221,167,440	(34)	(136)	($16,993,282)	($54,879,887)
SOF + SMV + R (12)	900	1	50	$154,536	$171,707	$169,989,600	$169,989,600	(43)	(173)	($21,540,780)	($69,566,054)

*Includes costs of initial therapy and retreatment with most effective regimen available for those not achieving SVR initially

†Total estimated cost offset includes cost savings from liver events averted and reduced annual costs from greater numbers of patients achieving SVR

N/C: Not calculable

SVR: sustained virologic response; NNT: number needed to treat; DAA: direct-acting antivirals

Over one year, the use of sofosbuvir+PR is projected to *reduce* overall drug costs per 1,000 patients relative to telaprevir+PR due to fewer patients requiring retreatment with the most effective and most expensive regimen, sofosbuvir+simeprevir+R. The sofosbuvir+simeprevir+R treatment regimen would increase drug spending by approximately $40 million per every 1,000 treated patients relative to older triple therapy. While liver-related complications would be substantially reduced at both five and 20 years (by 10 and 38 patients per 1,000 respectively), cost offsets would total at most 39% of drug costs.

Genotype 1, Treatment-experienced, Interferon-ineligible

Among treatment-experienced patients with genotype 1 infections not eligible for interferon, "best usual care" is represented in the model by no active treatment, and the newer regimens examined included sofosbuvir+simeprevir+R for 12 weeks as described above as well as a 24-week regimen of sofosbuvir+R, the identical regimens assessed for treatment-naïve patients. In the absence of available outcomes data stratified by prior treatment history, we also assumed that effectiveness of these newer regimens would be identical among interferon-ineligible and interferon-eligible patients. Based on this assumption, the incremental drug costs at one year for the newer regimens are identical to that estimated for interferon-eligible patients: every 1,000 patients treated with sofosbuvir+R would generate an additional $221 million in drug costs, and sofosbuvir+ simeprevir+R would cost $170 million. Even at 20 years, cost offsets relative to no drug treatment would represent 40% of these totals at most.

Genotype 2, Treatment-naïve, Interferon-eligible

Table 25 on the following page presents results for patients with genotype 2 who are new to hepatitis C treatment. Among interferon-eligible patients, a regimen of 12 weeks of sofosbuvir+R was compared to the previous standard of 24 weeks of PR alone. Sofosbuvir+R was highly effective in this population (970 per 1,000 achieving SVR initially), but PR is also relatively effective in genotype 2 patients (780 per 1,000). The number needed to treat to achieve an additional SVR for sofosbuvir+R was 5. Rates of discontinuation due to adverse events was very low in the sofosbuvir+R group (13 vs. 84 per 1,000 for PR). The costs of sofosbuvir+R are nearly four times that of PR (~$88,000 vs. ~$25,000), resulting in a cost per additional SVR of $332,482.

Over one year, sofosbuvir+R would be expected to generate an additional $46 million in drug costs per 1,000 patients treated. The newer regimen would prevent nine and 36 liver-related complications per 1,000 over five and 20 years respectively, and generate cost offsets of approximately $4.5 and $15 million during these periods. These offsets represent 10% of the incremental drug costs for sofosbuvir at five years and 32% of drug costs at 20 years.

Table 25. Clinical and Economic Impact of Treatment Options Among 1,000 60 year-old Patients with Hepatitis C Genotype 2 Who Are New to Treatment (Treatment-naïve).

Population/regimen	SVR per 1000	NNT for 1 add'l SVR	Discontinued due to AE (per 1000)	Cost for initial Rx (per patient)	Cost per add'l SVR	Total Drug Costs* (per 1000)	Incremental (vs. pre-DAA)	Liver Events Averted (per 1000): 5 years	Liver Events Averted (per 1000): 20 years	Total Estimated Cost Offset† (per 1000, vs. pre-DAA): 5 years	Total Estimated Cost Offset† (per 1000, vs. pre-DAA): 20 years
	Evidence Review Data					*Modeled 1-Year Drug Costs*		*Modeled Long-Term Effects of Achieving SVR*			
IFN-eligible											
PR (24) (pre-DAA)	780	---	84	$24,936	---	$44,334,720	---	---	---	---	---
SOF + R (12)	970	5	13	$88,176	$332,842	$90,821,280	$46,486,560	(9)	(36)	($4,547,498)	($14,686,167)
IFN-ineligible											
No Rx (pre-DAA)	0	---	---	$0	---	$0	---	---	---	---	---
SOF + R (12)	930	1	13	$88,176	$94,813	$94,348,320	$94,348,320	(45)	(179)	($22,258,806)	($71,884,923)

*Includes costs of initial therapy and retreatment with most effective regimen available for those not achieving SVR initially

†Total estimated cost offset includes cost savings from liver events averted and reduced annual costs from greater numbers of patients achieving SVR

SVR: sustained virologic response; NNT: number needed to treat; DAA: direct-acting antivirals

Genotype 2, Treatment-naïve, Interferon-ineligible

Among patients with genotype 2 infections not eligible for interferon, 12 weeks of sofosbuvir+R is estimated to be slightly less effective than in interferon-eligible patients, resulting in achievement of SVR by 930 patients per 1,000 treated. Use of this regimen would generate approximately $94 million in drug costs per 1,000 patients treated over one year in a population without any historical treatment options. Sofosbuvir+R would prevent 45 and 179 liver-related complications per 1,000 over five and 20 years, respectively; because of the relatively low cost of sofosbuvir+R (~$88,000) vs. other sofosbuvir-based regimens, cost offsets at these time points ($22 million and $72 million, respectively) represented a higher percentage of drug expenditures (24% and 76%).

Genotype 2, Treatment-experienced, Interferon-eligible

Table 26 on the following page presents model findings for 1,000 genotype 2 patients previously treated for hepatitis C. For interferon-eligible patients, "best usual care" is 24 weeks of PR, and newer options include 12 weeks of either sofosbuvir+PR or sofosbuvir+R. Sofosbuvir+PR was the most effective of the three regimens (920 SVRs per 1,000 treated vs. 880 for sofosbuvir+R and 780 for PR). The numbers needed to treat to achieve one additional SVR over PR were seven for sofosbuvir+PR and 10 for sofosbuvir+R. The numbers of patients discontinuing therapy due to adverse events were highest for PR (84 vs. 55 and 13 for sofosbuvir+PR and sofosbuvir+R respectively). In comparison to treatment-naïve patients, the cost per additional SVR was higher for both new regimens ($510,943 and $632,400 for sofosbuvir+PR and sofosbuvir+R, respectively) owing to large differences in treatment costs (~$88,000-$96,000 vs. ~$25,000) coupled with only moderate improvements in SVR rates over the previous standard. When compared to each other, the cost per additional SVR for the more effective sofosbuvir+PR regimen was estimated to be $207,300 vs. sofosbuvir+R (data not shown).

Over one year, both newer regimens would be expected to add over $50 million in drug costs for a 1,000-patient cohort. Sofosbuvir+PR would prevent liver-related complications in seven and 27 patients per 1,000 at five and 20 years, respectively; corresponding figures for sofosbuvir+R were five and 19. Cost offsets at five years were modest for both newer regimens ($3.3 and $2.4 million, respectively), as the incremental reductions in liver complications compared to treatment with PR were smaller in this population. At 20 years, cost offsets were estimated to be $10.8 million for sofosbuvir+PR (19% of incremental drug costs) and $7.7 million for sofosbuvir+R (14% of incremental drug costs).

Table 26. Clinical and Economic Impact of Treatment Options Among 1,000 60 year-old Patients with Hepatitis C Genotype 2 Who Have Been Treated Previously (Treatment-experienced).

	Evidence Review Data					*Modeled 1-Year Drug Costs*		*Modeled Long-Term Effects of Achieving SVR*			
								Liver Events Averted (per 1000)		Total Estimated Cost Offset† (per 1000, vs. pre-DAA)	
Population/regimen	**SVR per 1000**	**NNT for 1 add'l SVR**	**Discontinued due to AE (per 1000)**	**Cost for initial Rx (per patient)**	**Cost per add'l SVR**	**Total Drug Costs* (per 1000)**	**Incremental (vs. pre-DAA)**	**5 years**	**20 years**	**5 years**	**20 years**
IFN-eligible											
PR (24) (pre-DAA)	780	---	84	$24,936	---	$46,158,960	---	---	---	---	---
SOF + PR (12)	920	7	55	$96,468	$510,943	$104,185,440	$58,026,480	(7)	(27)	($3,350,788)	($10,821,386)
SOF + R (12)	880	10	13	$88,176	$632,400	$99,752,160	$53,593,200	(5)	(19)	($2,393,420)	($7,729,562)
IFN-ineligible											
No Rx (pre-DAA)	0	---	0	$0	---	$0	---	---	---	---	---
SOF + R (12)	880	1	13	$88,176	$100,200	$98,757,120	$98,757,120	(42)	(169)	($21,062,096)	($68,020,142)

*Includes costs of initial therapy and retreatment with most effective regimen available for those not achieving SVR initially

†Total estimated cost offset includes cost savings from liver events averted and reduced annual costs from greater numbers of patients achieving SVR

SVR: sustained virologic response; NNT: number needed to treat; DAA: direct-acting antivirals

Genotype 2, Treatment-experienced, Interferon-ineligible

Among genotype 2 patients previously-treated for hepatitis C who are not eligible for interferon, there has been no standard effective treatment. Sofosbuvir+R for 12 weeks is now recommended by the recent AASLD/IDSA/IAS guidelines and would be expected to achieve SVR in 880 patients per 1,000 treated. Over one year, use of this regimen would generate approximately $99 million in drug costs for the 1,000-patient cohort. Because a large number of liver-related complications would be averted relative to no treatment (42 and 169 per 1,000 at five and 20 years), potential cost offsets are relatively high. At five years, cost offsets would total $21 million (20% of drug costs). At 20 years, these offsets would total approximately $68 million (70% of drug costs).

Genotype 3, Treatment-naïve, Interferon-eligible

For the genotype 3 population, the previous standard of care was PR therapy for 24 weeks. Newer regimens available for comparison included sofosbuvir+PR for 12 weeks and sofosbuvir+R for 24 weeks. The numbers of patients per 1,000 achieving SVR were estimated to be 620 for PR alone, 920 for sofosbuvir+PR, and 930 for sofosbuvir+R resulting in a number needed to treat of 3 to obtain an additional SVR for both regimens (see Table 27 on the following page). As with prior comparisons, PR therapy would result in a greater rate of discontinuation due to adverse events per 1,000 (84) compared with sofosbuvir+PR (55) and sofosbuvir+R (13). As with previous comparisons, costs for the newer regimens are much higher than for PR; sofosbuvir+PR is nearly four times the cost of PR alone ($96,468 vs. $24,936), and the 24-week sofosbuvir+R regimen is over seven times the cost of PR alone ($176,352). The costs per additional SVR for the newer regimens vs. PR alone are estimated to be $238,440 for sofosbuvir+PR and $488,429 for sofosbuvir+R. When these two regimens are compared to each other, the cost per additional SVR for the more expensive sofosbuvir+R regimen is $7.9 million, given that the absolute difference in effectiveness is only 1%.

Under the assumption that all patients failing to achieve SVR would receive the sofosbuvir+R regimen, one-year drug costs for the 12-week sofosbuvir+PR regimen are increased by $19 million per 1,000 treated relative to PR alone. The 24-week sofosbuvir+R regimen would increase drug costs by approximately $97 million in this 1,000-person cohort. Because the estimated effectiveness of the two newer regimens is so similar, the resulting numbers of patients avoiding liver-related complications at five years (14-15 per 1,000) and 20 years (58-60 per 1,000) are essentially identical. So too are cost offsets, which are estimated to total approximately $7 million and $24 million at five and 20 years for both regimens. At 20 years, the additional drug costs of sofosbuvir+PR would be completely offset by savings from fewer clinical complications, while approximately 25% of the costs of sofosbuvir+R would be offset.

Table 27. Clinical and Economic Impact of Treatment Options Among 1,000 60 year-old Patients with Hepatitis C Genotype 3 Who Are New to Treatment (Treatment-naïve).

	Evidence Review Data					*Modeled 1-Year Drug Costs*		*Modeled Long-Term Effects of Achieving SVR*			
Population/regimen	SVR per 1000	NNT for 1 add'l SVR	Discontinued due to AE (per 1000)	Cost for initial Rx (per patient)	Cost per add'l SVR	Total Drug Costs* (per 1000)	Incremental (vs. pre-DAA)	Liver Events Averted (per 1000) 5 years	Liver Events Averted (per 1000) 20 years	Total Estimated Cost Offset† (per 1000, vs. pre-DAA) 5 years	Total Estimated Cost Offset† (per 1000, vs. pre-DAA) 20 years
IFN-eligible											
PR (24) (pre-DAA)	620	---	84	$24,936	---	$91,949,760	---	---	---	---	---
SOF + PR (12)	920	3	55	$96,468	$238,440	$110,576,160	$18,626,400	(14)	(58)	($7,180,260)	($23,188,685)
SOF + R (24)	930	3	13	$176,352	$488,439	$188,696,640	$96,746,880	(15)	(60)	($7,419,602)	($23,961,641)
IFN-ineligible											
No Rx (pre-DAA)	0	---	---	$0	---	$0	---	---	---	---	---
SOF + R (24)	610	2	13	$176,352	$289,102	$245,129,280	$245,129,280	(29)	(117)	($14,599,862)	($47,150,326)

*Includes costs of initial therapy and retreatment with most effective regimen available for those not achieving SVR initially

†Total estimated cost offset includes cost savings from liver events averted and reduced annual costs from greater numbers of patients achieving SVR

SVR: sustained virologic response; NNT: number needed to treat; DAA: direct-acting antivirals

Genotype 3, Treatment-naïve, Interferon-ineligible

Among patients with genotype 3 infections not eligible for interferon therapy, there has been no standard effective treatment. The 24-week sofosbuvir+R regimen has now been recommended in the recent AASLD/IDSA guidelines. The effectiveness of this regimen is lower among patients not eligible for interferon, however, with SVR achieved in only 610 per 1,000 vs. 930 per 1,000 among interferon-eligible patients. As a result, the use of this regimen, including retreatment for those not achieving SVR initially, would add $245 million in drug costs per 1,000 patients treated. While use of sofosbuvir+R would reduce liver-related complications per 1,000 by 29 at five years and 117 at 20 years, cost offsets at these time points would be $15 million and $47 million, respectively, or just 6% and 19% of one-year drug costs.

Genotype 3, Treatment-experienced, Interferon-eligible

Outcomes and costs for patients with genotype 3 who have received prior hepatitis C therapy are presented in Table 28 on the following page. The standard "best usual care" has been PR for 24 weeks. New recommended regimens are identical to those for treatment-naïve genotype 3 patients, but the incremental effectiveness of these regimens is less than that seen among treatment-naïve patients. Among treatment-experienced patients eligible for interferon, PR for 24 weeks is still estimated to produce SVR in 620 patients per 1,000 treated. The 12-week sofosbuvir+PR regimen would result in SVR for 830 patients per 1,000; and the 24-week sofosbuvir+R regimen would achieve SVR in 770 patients per 1,000. The number needed to treat to obtain an additional SVR was five for sofosbuvir+PR and seven for sofosbuvir+R. Because cost differences were the same as for treatment-naïve patients, but incremental effectiveness was lower, the cost per additional SVR estimates are higher in this population ($340,629 and $1.1 million for sofosbuvir+PR and sofosbuvir+R respectively). The two newer regimens could not be compared to each other, as sofosbuvir+R was both less effective and more expensive than sofosbuvir+PR.

Over one year, sofosbuvir+PR and sofosbuvir+R would be expected to add $51 million and $137 million in drug costs, respectively, per 1,000 treated. The numbers of liver-related complications averted would total 10 and 40 per 1,000 and five and 20 years respectively for sofosbuvir+PR, which would translate into cost offsets of $5 million and $16 million at these time points (representing 10% and 32% of drug costs). Sofosbuvir+R would prevent seven and 29 liver-related complications per 1,000 at five years and 20 years, resulting in cost offsets of $3.5 and $11.5 million at these time points. Because of the cost of sofosbuvir, however, these values would only offset 3% and 8% of drug costs at five and 20 years.

Table 28. Clinical and Economic Impact of Treatment Options Among 1,000 60 year-old Patients with Hepatitis C Genotype 3 Who Have Been Treated Previously (Treatment-experienced).

	Evidence Review Data					*Modeled 1-Year Drug Costs*		*Modeled Long-Term Effects of Achieving SVR*			
								Liver Events Averted (per 1000)		Total Estimated Cost Offset† (per 1000, vs. pre-DAA)	
Population/regimen	**SVR per 1000**	**NNT for 1 add'l SVR**	**Discontinued due to AE (per 1000)**	**Cost for initial Rx (per patient)**	**Cost per add'l SVR**	**Total Drug Costs* (per 1000)**	**Incremental (vs. pre-DAA)**	**5 years**	**20 years**	**5 years**	**20 years**
IFN-eligible											
PR (24) (pre-DAA)	620	---	84	$24,936	---	$61,593,840	---	---	---	---	---
SOF + PR (12)	830	5	55	$96,468	$340,629	$112,867,560	$51,273,720	(10)	(40)	($5,026,182)	($16,232,079)
SOF + R (24)	770	7	13	$176,352	$1,009,440	$198,539,640	$136,945,800	(7)	(29)	($3,590,130)	($11,594,342)
IFN-ineligible											
No Rx (pre-DAA)	0	---	---	$0	---	$0	---	---	---	---	---
SOF + R (24)	610	2	13	$176,352	$289,102	$245,129,280	$245,129,280	(29)	(117)	($14,599,862)	($47,150,326)

*Includes costs of initial therapy and retreatment with most effective regimen available for those not achieving SVR initially

†Total estimated cost offset includes cost savings from liver events averted and reduced annual costs from greater numbers of patients achieving SVR

SVR: sustained virologic response; NNT: number needed to treat; DAA: direct-acting antivirals

Genotype 3, Treatment-experienced, Interferon-ineligible

Because there were no studies evaluating the effectiveness of sofosbuvir+R in genotype 3 who had received prior hepatitis C therapy and were ineligible for interferon, we assumed the same effectiveness for this regimen as among patients who were ineligible for interferon (610 achieving SVR per 1,000 treated). Use of this regimen would increase drug costs by $245 million per 1,000 treated, would prevent 29 and 117 liver-related complications per 1,000 at five and 20 years respectively, and would result in offsets to this cost of approximately $15 million (6%) and $47 million (19%) at five and 20 years.

Estimates of Budget Impact in California for Different Treatment Scenarios

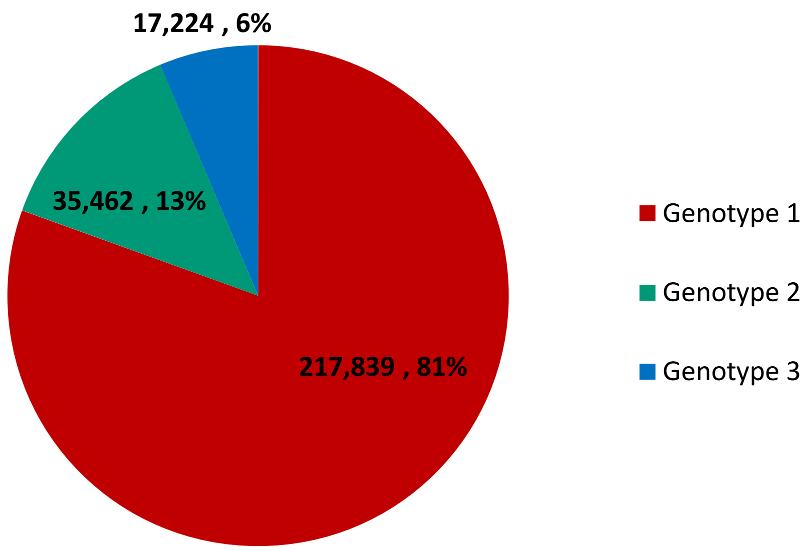
As mentioned above, we also applied estimates of the budgetary impact as well as 5- and 20-year clinical benefits and cost offsets to the California hepatitis C population. In this case, the budgetary impact was compared for the previous standard of care and the most effective regimen in each genotype/prior treatment status/interferon eligibility stratum based on the estimated drug costs for *initial therapy* with these regimens—we did not assume any retreatment for population-based analyses. We estimated liver complication rates and related costs as well as annual costs for patients achieving and not achieving SVR for each patient subgroup of interest. We also discounted future costs in this analysis.

We estimated the size of the chronic hepatitis C population in California to be approximately 560,000 based on information from the 1999-2002 screening round of the National Health and Nutrition Examination Survey (NHANES)[7] as well as estimates of the numbers of incarcerated and homeless individuals living with the disease.[114,115] Of these patients, approximately 540,000 (97%) would be infected with genotypes 1, 2, or 3.[17]

It is commonly recognized, however, that a substantial percentage of patients do not know they are infected. This proportion has been historically reported to be approximately 50% of infected patients,[29] but in recent years more patients may have become aware of their status due to efforts increase awareness of the disease and expand screening efforts. We therefore alternatively evaluated budgetary impact based on assumptions that either 50% (~270,000) or 75% (~405,000) of infected individuals would know they were infected and would be considered for treatment.

Figure 5 below shows the estimated distribution of the California hepatitis C population by genotype using the assumption that 50% of infected individuals know they are infected. The distribution of patients by genotype was obtained from an analysis of 275 NHANES participants with laboratory-confirmed hepatitis C.[17]

Figure 5. Estimated Numbers of Californians with Chronic Hepatitis C, by Genotype (Based on Assumption of Awareness of Infection by 50% of Infected Individuals).



As described previously in this report, genotype 1 is dominant, representing over 80% of the 270,000 Californians who have chronic hepatitis C and are aware of the infection, followed by genotypes 2 (13%) and 3 (6%) respectively.

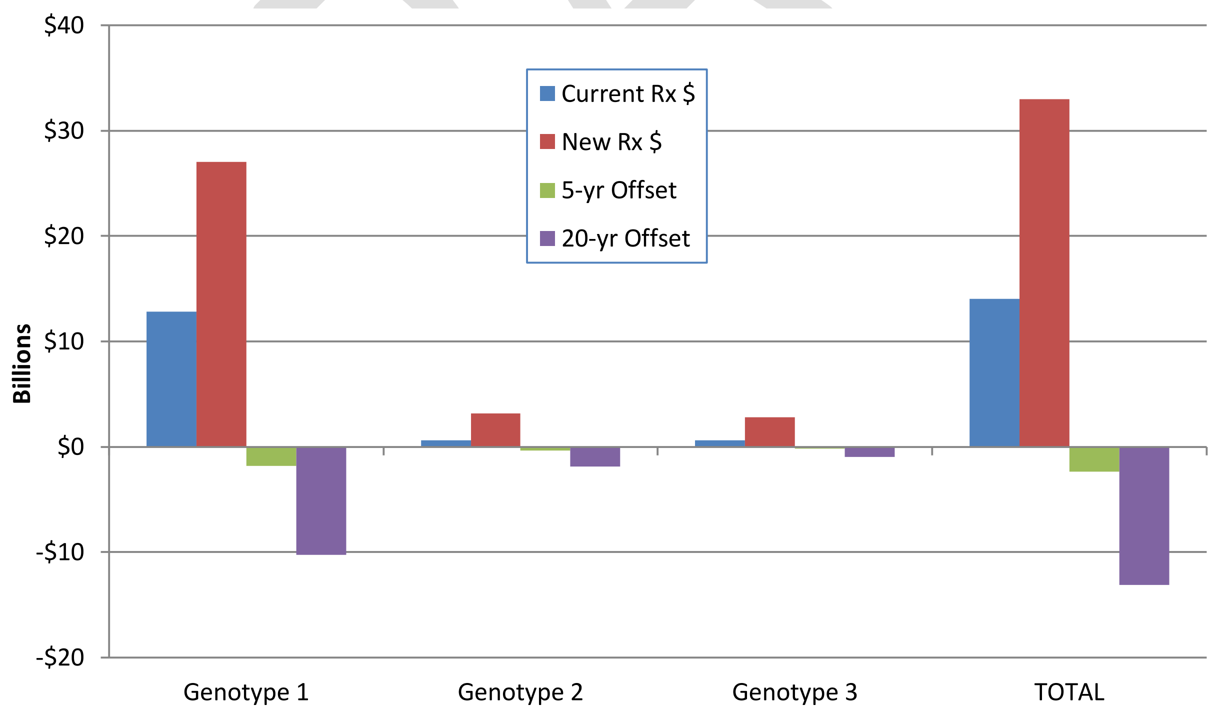
Within each genotype, we also estimated the numbers of patients who would be treatment-naïve vs. previously treated, as well as the numbers who would be expected to be eligible for interferon therapy vs. not. We estimated that 75% of patients would be naïve to treatment based on the proportion of previously-treated patients in a large VA patient registry.[92] Estimates of ineligibility for interferon therapy vary greatly and have been reported to be as high as 60% at the VA.[116] We used a more conservative estimate of 30% based on expert opinion regarding the proportion of patients in broader insured populations who know they are infected and have contraindications to interferon therapy such as significant psychiatric disorders, autoimmune disease, and severe cardiovascular or pulmonary disease (personal communication, Lisa M. Nyberg, MD).

For the California population of hepatitis C patients, we evaluated two different treatment scenarios. In Scenario 1, all patients with known hepatitis C infection are treated. In Scenario 2, only those patients with advanced liver fibrosis (METAVIR scores of F3 or F4) receive treatment. The proportion of infected patients with F3 or F4 scores was estimated to be 33.1% based on a multicenter study of the natural history of fibrosis progression.[117] Within each genotype, analyses of clinical and economic outcomes were based on a change from the previous standard of care to the most effective therapeutic regimen within each of the strata defined by prior treatment status and interferon eligibility.

Results of California-based Analyses

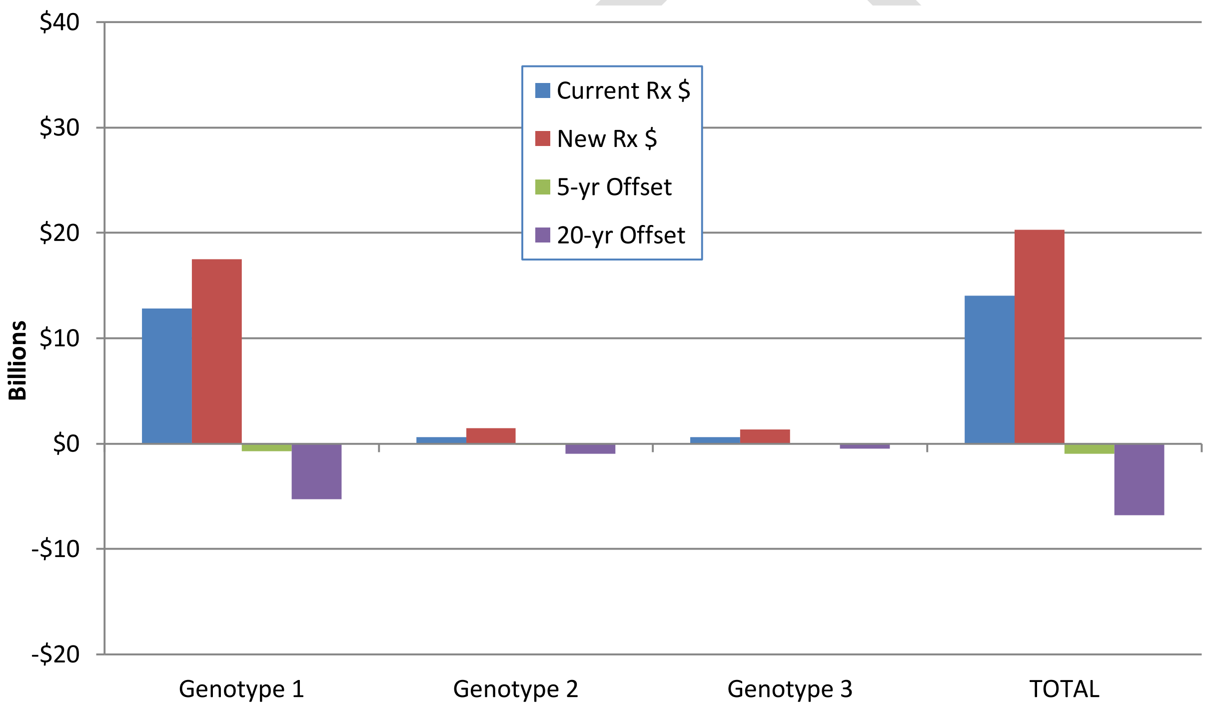
Figure 6 below depicts the budgetary impact and potential cost offsets if 50% of the estimated total California chronic hepatitis C population were to be treated (n=217,839). Drug costs to treat all these patients with the previous standard of care are estimated to total approximately $14 billion across all genotypes. Were these patients all treated instead with the most effective new regimen, treatment costs would grow by $18 billion to a total of $32 billion. Over five years, our model estimates that only approximately 10% of the $18 billion in additional costs would be offset by reductions in the cost of treating liver-related complications and other medical care for patients not achieving SVR. By 20 years, however, cost offsets would grow to $12.2 billion, or approximately two-thirds of the additional drug expenditures incurred initially.

Figure 6. Total Budgetary Impact and Potential Cost Offsets from Use of Newer Drug Regimens in the Chronic Hepatitis C Population in California: 50% of Infected Patients Are Treated (n=217,839).



In our second scenario, we measured the impact of a switch to the most effective new treatment regimens only for patients with evidence of advanced liver fibrosis (i.e., METAVIR scores F3 or F4). As shown in Figure 7 below, treating this smaller group resulted in an increase in drug expenditures of $6.3 billion, only one-third of the extra amount needed to treat all infected patients. Costs saved by reducing liver-related complications in this subgroup would total $965 million (15% of added drug costs) at five years. But at 20 years, estimated cost offsets of $6.7 billion would exceed the initial incremental drug expenditures of $6.3 billion, producing a net savings of approximately $400 million.

Figure 7. Total Budgetary Impact and Potential Cost Offsets from Use of Newer Drug Regimens in the Chronic Hepatitis C Population with Advanced Fibrosis in California: 50% of Infected Patients Are Treated (n=217,839).



We repeated all these different treatment scenarios under the alternative assumption that 75% of the chronic hepatitis C population in California would be aware of their infection and present for treatment. Figures 8 and 9 on the following page depict the increases in drug expenditures and potential cost offsets at five and 20 years if all patients were treated and if only those with advanced fibrosis were treated. The budget impact of initial treatment is obviously higher with more patients treated, but the relation of potential downstream cost offsets remains the same, with relatively little cost offset over the initial five years and an estimated net savings after 20 years if only those patients with advanced liver fibrosis are treated.

Figure 8. Total Budgetary Impact and Potential Cost Offsets from Use of Newer Drug Regimens in the Chronic Hepatitis C Population in California: 75% of infected Patients Are Treated (n=326,759).

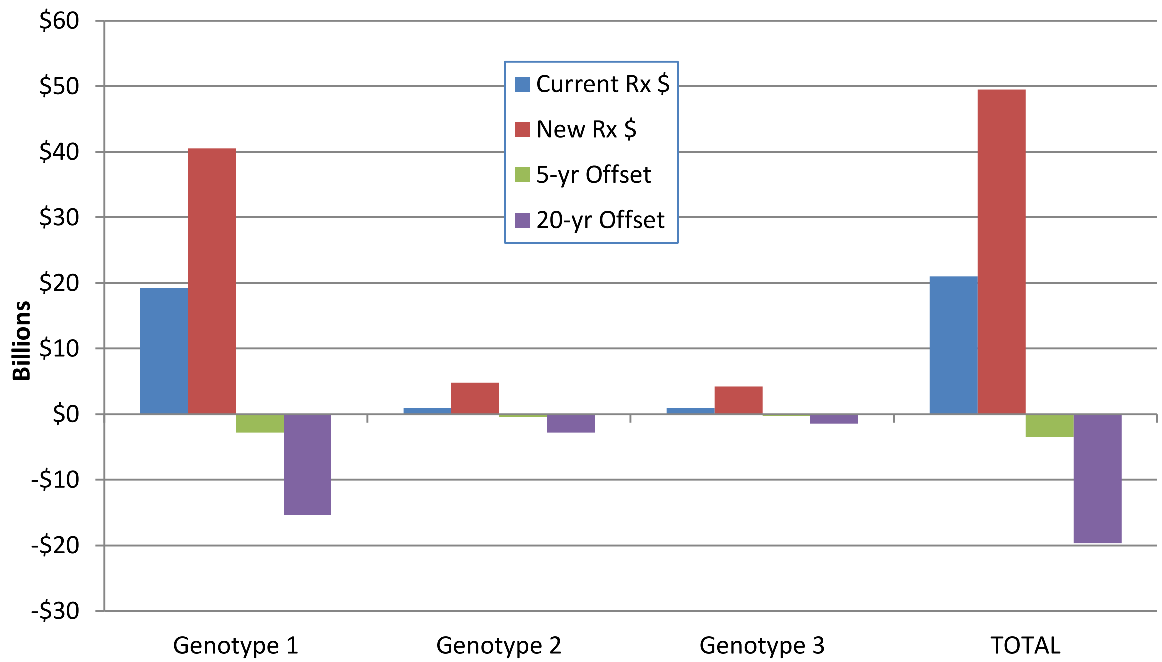
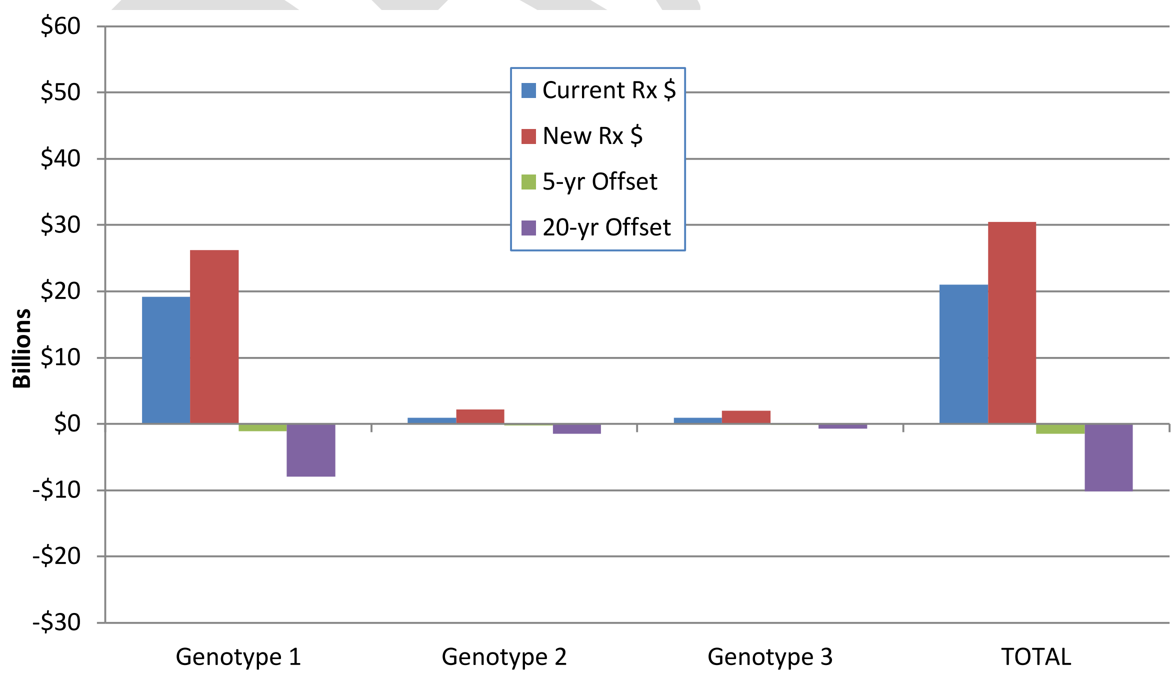


Figure 9. Total Budgetary Impact and Potential Cost Offsets from Use of Newer Drug Regimens in the Chronic Hepatitis C Population with Advanced Fibrosis in California: 75% of Infected Patients Are Treated (n=326,759).



7.4 Summary

Consistent with the findings of the systematic review, our model demonstrates that therapeutic regimens containing sofosbuvir have the potential to substantially increase the number of patients achieving SVR relative to previous therapeutic options, as well as to provide the first effective interferon-free option to patients ineligible or intolerant to interferon. These advantages are considerable. By contrast, use of simeprevir with pegylated interferon and ribavirin appeared to provide limited benefit over the previous standard of care.

For many patient subpopulations, however, the benefits of sofosbuvir and simeprevir come at a substantially increased cost. The costs for initial treatment regimens including sofosbuvir or simeprevir are expected to range from a low of approximately $88,000 to a high exceeding $175,000 per patient, depending on the drug selected and the time course of initial treatment. Many patients who are treated with an initial course and who fail to achieve a prolonged SVR would be expected to be retreated, adding further to the estimated treatment costs over a one-year time frame.

For many comparisons with the historical standard of care, the incremental cost required to achieve one additional SVR with newer treatment regimens was greater than $300,000. While the “cost per additional SVR” is not a common measure of cost-effectiveness in the literature, the costs per SVR generated in this analysis are generally higher than those previously published for telaprevir ($189,000),[118] different regimens of PR ($17,000-$24,000),[119] and even highly active antiretroviral therapy in HIV patients ($1,000-$79,000).[120]

So the clinical advantages of newer treatment regimens would come with a substantial potential impact on health care budgets should a large number of patients be treated. As estimated by our model, we anticipate cumulative one-year treatment costs per 1,000 patients to be somewhere between $100-$200million. For example, if a risk-bearing integrated provider group is responsible for the care of 500,000 patients, and one assumes an underlying infection rate of 1.7%, there would be approximately 8,500 patients in this population infected with Hepatitis C. If even 50% of this population comes forward for treatment, the immediate one-year budget impact for the provider group would be estimated to be well over $400 million. It would be impossible for this magnitude of immediate increased spending to be accommodated within the budgets established by current health care premium structures, provider risk-sharing contracts, and patient co-payments.

Using an estimate of the number of infected individuals in California who know of their infection and would be considered for treatment, we estimate that replacing current care with sofosbuvir-based regimens would raise drug expenditures by $18-$29 billion. We looked for potential cost offsets to drug treatment resulting from downstream reductions in liver-related complications that would be expected with successful treatment of hepatitis C infection. At a 5-year time horizon, however, cost offsets would be estimated to represent less than 10-20% of upfront treatment costs. Even at a 20-year horizon, if all patients infected with hepatitis C are treated with new regimens, the cost offset will only cover approximately two-thirds of initial drug costs.

The budget impact and cost offset figures change substantially under our second treatment scenario in which only patients with advanced liver fibrosis are started on the new treatment regimens, with other patients treated with existing pre-DAA regimens. Treating this smaller group of patients is estimated to result in an increase in initial drug expenditures of “only” $6.3 billion for the population of California, one-third of the extra amount needed to treat all infected patients. Costs saved by reducing liver-related complications in this subgroup would total only 15% of added drug costs at five years, but at 20 years, estimated cost offsets would produce a net savings to the health care system of approximately $400 million.

We must emphasize several limitations of our analysis. First, while there were sufficient data to perform a network meta-analysis for patients with genotype 1 infection, estimates could not be generated for all stratifications of interest for the model, and we could not even attempt quantitative synthesis for patients with genotypes 2 or 3. We therefore often had to resort to basing the input to the model on point estimates from individual studies, which in some cases involved small numbers of patients. Our results are therefore quite sensitive to the estimates of drug effectiveness and should therefore be viewed with caution.

In addition, as described previously, we modeled only the immediate clinical effects of treatment as well as the potential downstream benefits of preventing liver-related complications and having greater numbers of patients achieve SVR. While we presented pooled rates of discontinuation due to adverse events from available clinical trial data, we assumed equally across all drug regimens that all patients completed their course of therapy and were fully compliant while doing so. This assumption may not adequately reflect the benefits of better adherence to newer regimens with shortened courses of interferon or no interferon at all.

Finally, our analysis did not consider other possible benefits to patients from greater treatment success, such as improved quality of life and reduced absenteeism from work or school. Full analysis of all potential outcomes and costs of these new treatment options will only be possible through additional data collection and/or the development of simulation models that approximate the natural history of hepatitis C and its treatment.

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This is the first review of this technology **by the California Technology Assessment Forum.**

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APPENDIX

Search Strategies

PubMed (NLM), run date 1/8/14

(sofosbuvir OR simeprevir) AND (randomized controlled trial[pt] OR randomized controlled trials[mh] OR controlled clinical trial[pt] OR controlled clinical trials as topic[mh] OR placebo[tiab] OR drug therapy[sh] OR random*[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh]) NOT news[pt]
59 refs (trials)

(sofosbuvir OR simeprevir) AND (systematic[sb] OR meta-analysis[pt] OR systematic[tiab] OR meta-anal*[tiab] OR metaanal*[tiab] OR guideline*) NOT (animals[mh] NOT humans[mh]) NOT news[pt]
4 refs (systematic reviews/guidelines)

Embase (Elsevier), run date 1/8/14

139 (trials)

#2 sofosbuvir OR simeprevir AND ('controlled study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR 'controlled clinical trial (topic)'/de OR 'controlled clinical trial'/de) OR ('hepatitis c' AND (sofosbuvir OR simeprevir) AND (placebo:ab,ti OR random*:ab,ti OR trial:ab,ti OR groups:ab,ti)) NOT ([animals]/lim NOT [humans]/lim)

23 (systematic reviews/guidelines)

#1 sofosbuvir OR simeprevir AND ([cochrane review]/lim OR [meta analysis]/lim OR [systematic review]/lim OR systematic:ab,ti OR 'meta-analysis' OR metaanaly* OR 'practice guideline') NOT ([animals]/lim NOT [humans]/lim)

The Cochrane Library (Wiley), run date 1/8/14

sofosbuvir or simeprevir (Word variations have been searched)

All Results (10): • Cochrane Reviews (0) • All • Review • Protocol • Other Reviews (0) • **Trials (6)** • Methods Studies (0) • **Technology Assessments (4)** • Economic Evaluations (0) • Cochrane Groups (0)

Cochrane Database of Systematic Reviews: Issue 1 of 12, January 2014
Cochrane Central Register of Controlled Trials (Central): Issue 12 of 12, Dec 2013
Other Reviews (DARE) **Issue 4 of 4, Oct 2013**
Methods Studies **Issue 3 of 4, Jul 2012**
Technology Assessments **Issue 4 of 4 Oct 2013**
Economic Evaluations
Cochrane Groups **Issue 12 of 12, Dec 2013**

BIOSIS Previews & Web of Science (Thomson Reuters), run date 1/8/14; search for meeting abstracts

Final count: 31 from WOS; 18 from BIOSIS = **49 meeting abstracts** (duplicates removed)

BIOSIS Previews

Set	Results	
# 2	41	Topic=(sofosbuvir OR simeprevir) Refined by: Document Types=(MEETING) Databases=BIOSIS Previews Timespan=All years
# 1	67	Topic=(sofosbuvir OR simeprevir) Databases=BIOSIS Previews Timespan=All years

WOS

Set	Results	
# 2	33	Topic=(sofosbuvir OR simeprevir) Refined by: Document Types=(MEETING ABSTRACT) Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=All years
# 1	76	Topic=(sofosbuvir OR simeprevir) Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=All years

Trip Database (http://www.tripdatabase.com/), run date 1/8/14

sofosbuvir OR simeprevir
43 refs

8 Evidence-based Synopses
4 Systematic Reviews
1 Guidelines
5 Key Primary Research
12 Controlled Trials
16 Extended Primary Research

Trip is a clinical search engine designed to allow users to quickly and easily find and use high-quality research evidence to support their practice and/or care.