Comments to CTAF on the Cost-Effectiveness of Sofosbuvir

Chronic hepatitis C is a major public health and medical concern in the United States. Hepatitis C is the leading causes of cirrhosis and liver cancer, and is the most common indication for liver transplant. The number of hosp discharges related to HCV has tripled in Los Angeels in three years (2007-2009) and the CDC estimates that prevalence of HCV is decreasing as a result of patients expiring.

Sofosbuvir represents major leap in the treatment of hepatitis C. The use of sofosbuvir makes therapy safer, more efficacious, and simpler than anything we have seen before. The use of sofosbuvir also addresses major unmet needs such as treating patients with cirrhosis. African Americans, patients co-infected with HIV, liver transplant candidates, and liver transplant recipients.

Cost effective models are used to compare the relative costs and efficacy of different diagnostic or therapeutic interventions. The accuracy, validity and generalizability depend on the assumptions and data inputed. In addition, even if a drug is found to be cost-effective it does not necessarily mean it has a role in clinical practice. For instance, telaprevir has been previously thought to be cost effective in select populations, but no one can tolerate it. Follow up studies shown that the cost of curing a patient using telaprevir can range from 136 to almost 200k.

The current model used by the committee to assess the pharmaeconominc benefits of sofosbuvir leaves much to be desired. There are number of specific issues with the current model used by CTAF that limit interpretation of the results.

1) **Transition rates** before different stages of liver disease are based on a single study over a 12 years old, is generally wrong. The rates used underestimate the likelihood of disease progression. The cohort does not appear to develop complications at the same rate that occur in real life. <u>This would underestimate the costs associated with liver complications.</u>
2) The **SVR** utilized in the model for genotype 1 patients is incorrect by almost 10% points. <u>An incorrect lower SVR would underestimate the benefits of antiviral therapy.</u> Indeed any model is very sensitive to estimates of treatment efficacy. If indeed the producers utilized a network analysis, did they realize that patients of the Neutrino study had many negative predictors of a sustained viral response? Thus, the SVR would have been even higher if applied to a different patient population.

3) The **Costs of Liver Complications** were lumped together into a single value of approximately $20k. This value is based on single study of Florida Medicaid Patients. This number is inconceivable when we consider the costs of treating complications of cirrhosis such as variceal bleeding, encephalopathy, and liver cancer. The cost of being in the hospital can be $2-5k/day, and in an ICU $5-10k/day. This number is in complete contrast to that reported by other well designed Gordon and McAdams et al using national databases. Thus, this inaccurate underestimate the costs of not curing hepatitis C.
4) The assumptions of **number of patients to be treated is also incorrect**. The current model assumes that 50-75% of HCV patients know they are infected. This is impossible given that less than a third of patients even know they are infected. In no treatment of any disease state is there a treatment rate of 50% achieved. Indeed, over the past 15 years less than 10% of infected patients have treated. It is inconceivable that this likelihood will over triple when most patients do not even know they are infected. Furthermore, not everyone with hepatitis C should be treated. Study after study have shown that most benefit is obtained from curing HCV in those patients with advanced fibrosis. Assuming 50% of patients are treated is unrealistic, unwarranted, and not necessary. The strategy of treating everyone would significantly incorrectly increase the overall costs of treatment. Many patients may never suffer the complications of HCV.
5) The impact of Q80K should not have been ignored. Of the two hepatitis C 1 genotype subtypes, 1a is the most common. Approximately 30% of patients with genotype 1a have the mutation. Patients with Q80K get no benefit from the addition of simeprevir to interferon and ribavirin.
6) Others – managing adverse effects, work productivity, and quality of life are not considered in the model.

In conclusion, the use of sofosbuvir represents a major breakthrough in the treatment of HCV. Patients with unmet needs should not be denied treatment. Treatment has become simpler, safer and more efficacious with major unmet needs being met. The model developed by CTAF is leaves much to be desired a because of incorrect assumptions regarding disease progression, likelihood of SVR,

costs of liver complications, and the number of patients that will be treated. We need to be selective of who will cure, and treat those that we believe we can increase their life expectancy. Alternative model developed by many leading hepatologist across the United States have found the use of sofosbuvir to be cost effective.

Sammy Saab, MD, MPH, AGAF
Professor of Medicine and Surgery
David Geffen School of Medicine at UCLA

California Technology Assessment Forum (CTAF)

To CTAF HCV staff

I would like to ask the CTAF to reconsider the statistics which were used in the recent document released from the meeting in San Francisco on March 10, 2014, concerning HCV treatment with the newly FDA-approved agents. I think it is clear that each epidemiological study that has been published with prevalence estimates has strengths and weaknesses. As the CDC has acknowledged,[i] the NHANES data used as a large part of the basis for the CDC estimate of CHC prevalence in the U.S. underrepresents populations that may be at increased risk for HCV infection such as incarcerated and homeless persons and people on active military duty.[ii,iii] In addition, the CDC has noted that multiple smaller racial/ethnic groups (including Native Americans, Alaskan Natives, and Asians), shown by a number of studies to potentially have higher rates of infection, are not adequately represented. [iv] I hope that CTAF is making efforts to consider these populations in your calculations of HCV treatment costs with the new therapies.

Based on NHANES data, the CDC has long estimated that there are 4.1 million (CI, 3.4 million to 4.9 million) anti-HCV-positive persons nationwide and 3.2 million persons (CI, 2.7 to 3.9 million) living with CHC in the U.S.[v] The most recent publication by CDC researchers has reported even lower numbers, with a reported estimated CHC prevalence of 1.0% (95% CI, 0.8% to 1.2%), corresponding to 2.7 million chronically infected persons (CI, 2.2 to 3.2 million persons).[vi] However, I believe that several studies bring this estimate into question. The 2011 review by Chak et al looked at all studies providing HCV prevalence data for populations *not* sampled by the NHANES survey, including the homeless, the incarcerated, nursing home residents, and those on active military duty.[vii] In addition, because of their low frequency and lack of availability in the NHANES data set, this review included studies of CHC prevalence in healthcare workers, long-term dialysis patients, and people living with hemophilia who received transfusions prior to 1992. In order to confirm NHANES findings, the review also included studies on drug users (for whom they report that based on identified studies the NHANES prevalence estimate is reasonable) and veterans.

The very wide range of prevalence estimates (5.4 to 41.7%) reported in large studies in recent years makes it difficult to accurately estimate prevalence in veterans. To address this, the Chak study assessed and then excluded 8 of 15 major studies of veterans published over the ten years prior to their assessment–including studies of those who were homeless, those with substance abuse and/or mental health disorders, and those who were HIV-coinfected–as likely not being representative of the general

6022 La Jolla Mesa Drive • San Diego, California 92037 • www.robertgish.com

Ofc 866-873-8877 Cell 858-229-9865 Fax 858-886-7093 info@robertgish.com

veteran population, leading to Chak et al's estimated prevalence in veterans of 5.4–10.7%. The same was done with the other populations assessed, with the exclusion of studies that focused on subgroups that were considered at higher risk than the group as a whole. It was also noted that more data is clearly needed on active duty military since only one study was carried out in this population.

Combining the NHANES estimates with the estimated number of anti-HCV-positive persons in all the increased risk groups which were either left out of the NHANES (the incarcerated, the homeless, residents of nursing homes, those on active military duty) or for which there was only a low frequency or a lack of availability in the NHANES data set (healthcare workers, persons on long-term hemodialysis, and hemophiliacs with transfusions prior to 1992) or for which their review concluded that the NHANES estimate was not accurate (veterans, for which they subtracted the number of HCV cases attributed to veterans in the NHANES survey before adding their estimate to prevent double counting), the reviewers concluded that the total number in the US population is 5,191,748 to 7,091,668 anti-HCV-positive persons. They are careful to note that they are unable to draw any conclusions regarding CHC prevalence because many of the studies included in their review did not include information on HCV RNA levels. However, using the standard CDC estimate that 75%-85% of newly infected persons develop CHC[viii] would lead to a conservative estimate of 3,893,811 to 4,412,986, and an upper limit estimate of 5,318,751 to 6,027,918 persons living with CHC in the U.S. This is obviously substantially higher than the most recent NHANES-based estimates, and with the exclusion of all of the groups considered high risk, this might actually be an underestimate. In a 2011 essay in *Nature*, it is hypothesized that if the NHANES survey has underestimated HCV infection similarly to the extent it has been shown to have underestimated HIV,[ix] i.e., by a factor of 1.4 to 2.0, then the true prevalence of HCV infection could be 6 to 8 million.[x]

I am very concerned that any decreased prevalence data may be explained by a high death rate in HCV-infected people. The Chronic Hepatitis Cohort Study (CHeCS) has clearly shown steadily increasing mortality rates in CHC patients, rising from 1.4 per 100 person-years in 2006 to 4.4 in 2010.[xi] Fourteen percent of the cohort patients had died (any cause) by the end of 2010, with most deaths occurring among persons in the 1945-1964 birth cohort, with an overall death rate of 33.0 per 1000 person-years. Disturbingly, despite the fact that 70% of patients assessed by CHeCS had pre-mortem ICD9 codes, liver biopsies, and FIB4 scores indicative of substantial liver damage, only 19% of the 1600 confirmed chronic HCV patients in CHeCS had HCV infection noted on their death certificate. This could mean a five-fold under-reporting of HCV-associated deaths. In addition, whatever the listed cause of disease, HCV-infected persons died 15 years younger than everyone else, a serious cost to society.

At least a partial explanation of the high rates of death at too-early ages may come from Holmberg et al who recently reported that only about half of HCV-infected people have been tested and know their status; only about a third have been referred for HCV care; and only 7-11% have been treated, with only 5 to 6% successfully treated.[xii] The need to expand our reach to locate, test, and successfully treat CHC patients is clear. It is also clear that the combination of under-estimation of HCV prevalence and under-reporting of HCV-associated deaths will automatically lead to an under-estimation of HCV-associated healthcare costs and societal costs.

If we consider these recent studies, it seems very possible that there are at least 5 million people chronically infected with hepatitis C in the United States, 94-95% of whom have not yet been successfully treated, a population of 4,700,000 to 4,750,000 people in need of treatment. This would mean that some current estimates of future HCV-associated costs are a drastic underestimate of what the true costs will ultimately be. We believe that it is important to consider that the NHANES data used by the CDC substantially underestimates the true prevalence of CHC, and that showing broader ranges of prevalence data could expand opportunities for advocacy and awareness, as well as provide a solid basis for supporting that the treatment with the new HCV medications are even more cost effective and less expensive, with the cost to treat per “cure” in the $100,000 range, or approximately one-half the greater than $200,000 cost per cure with the previously approved protease inhibitors (references on file).

Another major concern I have is the potential medico-legal consequences of mandating a liver biopsy prior to treatment or mandating that patients fail second-line treatment with the potentially serious complications of long-term interferon use (more than 12 weeks) and the known high rate of systemic complications of INF + Ribavirin + first generation protease inhibitors if used in patients with cirrhosis.

Regimen (per PI)	Duration (weeks)	Total Regimen Cost (Dec 2013)	Total Regimen Cost (Feb 2014)	Difference
SOVALDI + Pegasys + ribavirin	12	$93,473	$94,078	+$606
INCIVEK + Pegasys + ribavirin	24	$85,102	$86,312	+$1,210
	48	$104,050	$106,468	+$2,418
OLYSIO + Pegasys + ribavirin	24	$85,305	$86,516	+$1,211
	48	$104,250	$106,673	+$2,423

I hope the open forum that you recently provided and the fact that your group will embrace all relevant data will assist your team in a fair response to the great clinical need in the patient community where access to medications with an enhanced cure rate for this life threatening disease needs to be available to all.

Sincerely,

Signature line for letters:

Robert G. Gish M.D

Robert G Gish MD

Please see my website for full credentials and titles: robertgish.com

[i] Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Viral hepatitis. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/nchs/data/nhanes/databriefs/viralhep.pdf.

[ii] IOM (Institute of Medicine). Hepatitis and liver cancer: a national strategy for prevention and control of hepatitis B and C. 2010. Washington, D.C., The National Academies Press.

[iii] Waksberg J, Levine D, Marker D. Assessment of major federal data sets for analysis of Hispanic and Asian or Pacific Islander subgroups and Native Americans: extending the utility of federal databases. Rockville, MD: Department of Health and Human Services; 2000.

[iv] Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Viral hepatitis. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/nchs/data/nhanes/databriefs/viralhep.pdf.

[v] Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med. 2006 May 16;144(10):705-14.

[vi] Denniston MM, Jiles RB, Drobeniuc J, Klevens M, Ward JW, McQuillan GM, Holmberg SD. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. Ann Intern Med. 2014 March 4;160(5):293-300.

[vii] Chak E, Talal AH, Sherman KE, Schiff ER, Saab S. Hepatitis C virus infection in USA: an estimate of true prevalence. Liver Int. 2011 Sep;31(8):1090-101.

[viii] National Center for Infectious Diseases (U.S.), Division of Viral Hepatitis. Centers for Disease Control and Prevention. National hepatitis C prevention strategy: a comprehensive strategy for the prevention and control of hepatitis C virus infection and its consequences. 2001. Available at: http://stacks.cdc.gov/view/cdc/6458.

[ix] McQuillan GM, Khare M, Karon JM, Schable CA, Vlahov D. Update on the seroepidemiology of human immunodeficiency virus in the United States household population: NHANES III, 1988-1994. J Acquir Immune Defic Syndr Hum Retrovirol. 1997 Apr 1;14(4):355-60.

[x] Edlin BR. Perspective: test and treat this silent killer. Nature. 2011 May 25;474(7350):S18-9.

[xi] Moorman AC, Gordon SC, Rupp LB, Spradling PR, Teshale EH, Lu M, Nerenz DR, Nakasato CC, Boscarino JA, Henkle EM, Oja-Tebbe NJ, Xing J, Ward JW, Holmberg SD; Chronic Hepatitis Cohort Study Investigators. Baseline characteristics and mortality among people in care for chronic viral hepatitis: the chronic hepatitis cohort study. Clin Infect Dis. 2013 Jan;56(1):40-50.

[xii] Holmberg SD, Spradling PR, Moorman AC, Denniston MM. Hepatitis C in the United States. N Engl J Med. 2013 May 16;368(20):1859-61.

Submitted on Sunday, March 16, 2014 - 11:32pm Submitted by anonymous user: [75.80.96.192]
Submitted values are:

First name: Lisa
Last name: Nyberg
Occupation: Practicing clinician
Regarding: Feedback
Your email: lisamnyberg@gmail.com
Your message:
To: California Technology Assessment Forum (CTAF):

From: Lisa M. Nyberg, MD, MPH

Date: March 16, 2014

Re: Correction of reported proportion of interferon ineligible or intolerant chronic hepatitis C patients

I reviewed the CTAF document, "New Treatments For Hepatitis C," with great interest.

I also viewed the publicly available videos of the conference of March 10, 2014. I agree with the insightful comments made by Rachel McLean and by Dr. Sammy Saab.

In reference to my estimate of interferon ineligible or interferon intolerant patients (personal communication, Lisa M. Nyberg, MD, page 74), I would like to modify this figure. Since I spoke to Mr. Ollendorf, I have performed new analyses of this patient population. The data reveal that approximately 40% of those that know that they are infected with hepatitis C have a comorbid condition that could preclude treatment with interferon-based therapy.

Further, this population is more likely to be older and have other health conditions that predispose them to more advanced liver disease. These conditions include non alcoholic fatty liver disease, diabetes, cardiovascular disease and other comorbidities. This population would be expected to benefit greatly from treatment and cure of chronic hepatitis C.

I know that the CTAF strives for excellence and accuracy in their evidence-based assessments, thus I felt it important to report to you these latest results.

Sincerely,
Lisa M. Nyberg, MD, MPH

Gerald N. Rogan, MD
Rogan Consulting
107 Highley Court
Sacramento, California 95864
Office: 916-978-9636
Fax: 916-978-9637
Cell: 530-514-1139
http://www.roganconsulting.com
jerryroganmd@sbcglobal.net

3/17/2014

California Technology Assessment Forum
www.ctaf.org

RE: Treatment of Hepatitis C.

Dear Sirs:

Here are my comments to the Forum on Hepatitis C help March 10, 2014.

Relative cost

Here are the minimum relative costs for the shortest course of therapy.[1]

Drug	Duration	Cost	Regimen	TOTAL COST
Boceprevir 200 mg	24 weeks	$26,410	4 caps q 8 hrs w food	$46,447
Telaprevir 750 mg	12 weeks	$49,900	2 tabs q 8 hrs w fatty food	$67,075
Simeprevir 150 mg	12 weeks	$66,300	1 cap q 24 hrs with food	$83,475
Sofosbuvir 400 mg	12 weeks	$84,000	1 tab q 24 hrs	$92,588
Ribavirin plus Pegasys (B)	28 weeks	$20,037	3 caps bid plus one self-injection per wk	
Ribavirin plus Pegasys (T)	24 weeks	$17,175	3 caps bid plus one self-injection per wk	
Ribavirin plus Pegasys (Si)	24 weeks	$17,175	3 caps bid plus one self-injection per wk	
Ribavirin plus Pegasys (So)	12 weeks	$8,588	3 caps bid plus one self-injection per wk	

Comments:

[1] http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=13668

1. Vitamin B12 supplementation significantly improves SVR rates in HCV-infected patients who are naïve to antiviral therapy.[2]
2. For Boceprevir, A IL-28B test should be done. For genotypes TT and CT, another drug should be selected.[3]
3. For Simeprevir, NS3 Q80K polymorphism should be tested and results followed per the FDA label.[4]
4. The number of pills taken per day is not a meaningful patient burden and should be given minimal weight in medical decision making.
5. A regimen of every 8 hours with food disrupts meal time, but is not a meaningful patient burden and should be given minimal weight in medical decision making.
6. Reportedly, the fatty food required for Telaprevir may impair tolerance.[5]
7. Duration of side effects is directly proportion to the length of treatment with Ribavirin and Pegasys. Some patients may not be able to work. Treatment may be catabolic.
8. For some patients, duration of recovery from toxicity may equal the duration of therapy.
9. Side effects are moderately severe. Toleration requires
    a. A warm room.
    b. Warm clothes
    c. A bathtub for oatmeal soaks
    d. A supportive companion.
    e. Freedom from immediate financial worry.
    f. A social environment that does not promote depression.
    g. A heating pad.
10. Treatment compliance is more difficult for pills taken more than once a day.
11. Treatment compliance requires
    a. Personal determination and regimentation.
    b. A refrigerator to store ribavirin and pegasys.
    c. Complete avoidance of alcohol, marijuana, and other drugs of abuse.
12. Limitation of coverage to selected degrees of liver impairment seems inappropriate and may be legally unenforceable. All patients with Hepatitis C infection are candidates for treatment. Medical but not cost limitations are applicable. Expected toxicity will self-limit unmotivated patients.

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[2] http://www.ncbi.nlm.nih.gov/pubmed/22810757

[3] http://www.pbm.va.gov/clinicalguidance/clinicalrecommendations/PeginterferonalphaandribavirinincombinationwithDirectActingAntiviralsClinicalGuidance.pdf

[4] http://www.olysio.com/hcp/affordability?utm_source=google&utm_medium=cpc&utm_campaign=Olysio&utm_term=simeprevir%20cost&utm_content=Cost-+Broad%7Cmkwid%7CsgFAkpY1X_dc%7Cpcrid%7C36515605577

[5] Information from Gayle Witt, KP Hepatitis C treatment nurse.

13. Patient candidates should commit to successfully taking a full regimen as prescribed.
14. Patient candidates should commit to complete avoidance of alcohol and other drugs of abuse.
15. Hepatitis C treatment is usually curative.
16. The annual cost of treatment of the following incurable conditions mirror the cost of a curative treatment for hepatitis C. The relative cost per year of life saved should be considered.
    a. HIV treatment reportedly costs $17,000 per year.
    b. Revlamid and Velcade treatment of Multiple Myeloma following high dose chemotherapy and stem-cell transplant. Patients can live 20 years on treatment.
    c. TNF inhibitor treatment of methotrexate resistant rheumatoid arthritis and other indicated immunologic diseases. Patients may live 20 years on treatment.
    d. Gleevec costs $8,096 per month and can be taken for more than a year. Patients may live several years on treatment
    e. Provenge costs $93,000 for three doses total. Patients will usually live less than 1 year with treatment.
    f. Patients may life decades on treatment for blood factor deficiency diseases.
    g. Patients may live 40 years on treatment for cystic fibrosis.
17. In well-organized health systems, treatment is directed by a nurse practitioner with physician oversight. A physician visit may not be required.
18. To assure and motivate compliance, patients should maintain a written record of treatment including the date and times each pill and injection are taken, and bring the record to the treating practitioner.
19. Patients who receive off-label treatments should be reported in a treatment registry in order to gain effectiveness and safety information. (This expectation also should apply to off-label anti-cancer treatments.)

Respectfully,

Gerald N. Rogan, MD
Primary Care

After attending the CTAF-ICER conference on HCV therapy online, I would like to clarify a few issues regarding the AASLD/IDSA HCV guidance document. Approximately one year ago, both the AASLD and IDSA governing boards approved grants of approximately $130,000 each to jointly sponsor a novel online, web-based practice guidance document for HCV therapy. No commercial or industry funding was used. IAS-USA was contracted to provide administrative support for the guideline, and this function was totally supported by the grants from the AASLD and IDSA. Again, no industry funds supported this activity of IAS-USA. Finally, 2 co-chairs from both AASLD and IDSA were appointed by the respective governing boards and a 5th co-chair was appointed by IAS-USA. No chairperson currently has received personal honoraria from industry, and all have been free of industry conflicts for >12 months.

Ten writing panel members were identified by each society governing board based upon their knowledge and expertise in hepatitis C; vetted by the co-chairs and an outside society leader; and their society conflicts of interest were reviewed by the entire panel. Additional panel members representing the CDC were invited for their particular expertise in HCV testing. The writing panels were initiated on October 6, 2013. 17 of 23 writing panel members have no current personal conflicts of interest with the HCV industry. Several panel members, however, have institutional research grants from industry clinical trials. For transparency, these conflicts have been posted under each panel member's name in the guidance document ever since the document was first available on January 29th. We will be adding a table of each member's conflicts to be more visible and easier to find.

Our goal in developing these guidance statements was to prepare thorough and up to date recommendations which would be nimble in response to the rapid developments in the field. Further, we wished to address as many clinical situations that providers would face as possible, even where the strength of evidence was relatively weak. We chose respected HCV authorities, many of whom had extensive first hand experience with the agents in clinical trials - an experience we judged to be essential for clinically useful recommendations. The public response and comments received have been uniformly positive and enthusiastic.

In the coming months, we will add new sections covering: 1.) Who and when to treat; 2.) Treatment of acute HCV infection; and 3.) Monitoring therapy. As new data and publications become available, we will update our online document in real time and alter the strength of evidence accordingly. Annually, we will publish a summary of the major recommendations and deliberations from the past year in a society journal.

We hope that this explanation will clarify an misconceptions regarding our guidance and the process taken in its development.

DONALD M. JENSEN, MD

University of Chicago Medicine

Co-chair; AASLD-IDSA HCV Guidance

I heard that the California Technology Assessment Forum rated sofosbuvir as “low value” last week
This obviously was an error, as it has been well shown that patients with hepatitis C have an increased risk of death even before they develop cirrhosis, and that clearing the virus normalizes their life expectancy.
While I realize that the cost of sofosbuvir is high, the fact that it cures a large number of patients with only 12 weeks of therapy actually ends up being cost effective.
It prevents the high cost of care of patients with cirrhosis who then develop hepatocellular carcinoma even if the virus is cleared when cirrhotic.
In addition, waiting to treat someone until they have cirrhosis decreases the effectiveness of the therapy, and continues to incur lifelong cost of these patients who require surveillance for hepatocellular carcinoma development and progression of their liver disease even for those who are lucky enough to clear virus.

Determining that this medication is low value is short-sighted, and ensures that we will have an epidemic of patients with cirrhosis to care for over the next 15 years.
Please reconsider your stance.

Catherine Frenette, M.D.
Medical Director of Liver Transplantation
Scripps Center for Organ Transplantation
10666 N. Torrey Pines Rd N200
La Jolla, CA 92037
Frenette.Catherine@scrippshealth.org
Office 858-554-4310
Cell 858-699-0662

Beth Israel Deaconess Medical Center

A major teaching hospital of Harvard Medical School

Camilla S. Graham, MD, MPH
Division of Infectious Diseases
Beth Israel Deaconess Medical Center
110 Francis Street, Suite GB
Boston, MA 02215

March 17, 2014

Comments to the California Technology Assessment Forum: "The Comparative Clinical Effectiveness and Value of Simeprevir and Sofosbuvir in the Treatment of Chronic Hepatitis C Infection" Draft Report

Dear CTAF members,

I read with interest your draft report on the assessment of sofosbuvir and simeprevir for the treatment of hepatitis C virus infection. Large amounts of data were synthesized for this report, which is a difficult task. There were a few areas that were inaccurate, which may diminish your final conclusions if not addressed. I have a few comments that I hope are helpful:

Table 1: "Die from cirrhosis or liver cancer = 1% – 5%". These data seem to imply that there is a 1 to 5% chance of someone ever dying of liver disease related to HCV. The CDC (Rein, Annals 2011) estimates that 37% of people with HCV infection will die of their HCV if no intervention/treatment is provided.

Section 3: Coverage Policies

The Massachusetts Medicaid program (MassHealth) has published guidelines for antiviral drugs used for hepatitis C, including prior authorization requirements:

https://masshealthdruglist.ehs.state.ma.us/MHDL/pubdownloadpdfcurrent.do;jsessionid=50C0C29D543D25E09182D8381DB8F726?id=660

https://masshealthdruglist.ehs.state.ma.us/MHDL/pubtheradetail.do;jsessionid=50C0C29D543D25E09182D8381DB8F726?id=44

Note that the all-oral combination of sofosbuvir plus simeprevir is encouraged for genotype 1 patients who are interferon intolerant.

Page 27: “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. Thus achieving an SVR24 will not prevent the complications of chronic HCV infection for all patients.”

This is an important point. The risk of HCC is reduced up to 80% if a patient with advanced liver fibrosis achieves SVR, but there is residual risk and these patients need life-long screening for HCC, which increases costs and patient distress. This should argue for treating people if they are diagnosed with HCV at the point they have developed cirrhosis, but not waiting to treat until someone has developed cirrhosis if they are diagnosed with HCV at a point where they have milder fibrosis.

Comments about Table 23:

“TEL + PR (12/24) (pre-DAA)”: About 1/3 of patients require 48 weeks of P/R

“SOF + PR (12) 830 SVR per 1000”: The overall SVR in naïve genotype 1 patients is 90%, so why is this number so low?

“SOF + SMV + R (12) 90% SVR, 50 discontinue for AE”: Why is this estimate for early discontinuation nearly as high as the 55 estimated for SMV+P+R x 24 weeks? I have a number of patients with very advanced fibrosis, with and without HIV coinfection, who are on SOF+SMV+/-RBV and this regimen is very well tolerated. I expect that the discontinuation rate, especially for SOF+SMV, will be similar to SOF+RBV x 12 weeks. Registries such as TARGET should help us understand the real-world outcomes (SVR and AEs) with this regimen.

Comments about Table 24:

“TEL + PR (12/24) (pre-DAA), 700 SVR per 1000”: Relapse patients have a higher SVR rate than overall naïve patients with DAA-containing regimens and should be averaged with naïve patients, not treatment experienced patients. Treatment experienced null responders (SVR 31%) would all have 48 weeks of P/R, not 24 weeks. Null responders +/- cirrhosis were the main group that was studied with SOF+SMV+/-RBV. If the appropriate comparison had been done, the cost-effectiveness of SOF+SMV would be far greater.

Page 75: “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.”
Not taking retreatment costs into account makes this analysis nonsensical. One could argue that 24 weeks of standard IFN would be the cheapest approach, even though it only cures 6% of genotype 1 patients.

Page 78: “….the costs per SVR generated in this analysis are generally higher than those previously published for telaprevir ($189,000), different regimens of PR ($17,000-$24,000)…”

If one just takes into account the costs of the drugs (using WAC prices), which underestimates the costs associated with managing adverse events associated with IFN-based regimens, the cost per cure for genotype 1, naïve patients is quite similar:

Regimen	SVR rates (Genotype 1, Naïve)	2014 WAC Price	Cost per SVR
Pegasys + Ribavirin (1,200 mg a day, generic)	40%	$41,758	$104,215
Telaprevir + Pegasys + Ribavirin x 24 weeks	79%	$86,843	$109,928
Sofosbuvir + Pegasys + Ribavirin x 12 weeks	90%	$94,421	$104,912

Your analysis has grossly underestimated the cost per cure for P/R.

Summary: Why were the multiple advantages of SOF+SMV x 12 weeks over SOF+RBV x 24 weeks in interferon-intolerant genotype 1 patients, as described throughout your document, not mentioned in the summary? SOF+SMV x 12 weeks is at least $90,000 less expensive on a cost-per-cure basis than SOF+RBV x 24 weeks in genotype 1 patients, yet you note that many insurers do not cover it. For our patients who have the most urgent need for immediate treatment and cure, such as those with advanced, compensated cirrhosis, your report does them a disservice.

In conclusion, I suspect the cost-benefit, especially of sofosbuvir-containing regimens, has been underestimated in this draft report. In spite of this, I found your 20-year net saving with many of the regimens to be encouraging. The costs of treatment are not going to be incurred over the course of one year. Even with intensive screening, finding and treating those who need it will take many years. I am concerned that an overall negative report, such as this, will delay needed uptake in awareness and screening programs, thus limiting the immediate cost-benefit that would be possible if those who currently have more advanced fibrosis were treated.

Thank you for your consideration of these points and I welcome further feedback or questions at cgraham@bidmc.harvard.edu.

Sincerely,

Camilla S. Graham, MD, MPH

Disclosures: Associate editor for the viral hepatitis section of the journal *Clinical Infectious Disease* and writer for UpToDate (the HCV genotype 2 and 3 section). Member of the Drug Utilization Review Board of MassHealth and the Massachusetts Viral Hepatitis Advisory Board. Advisor to the National Viral Hepatitis Roundtable on HCV awareness.

In the last 12 months I have received nothing of value from any pharmaceutical companies.

Dear CTFA:

Your conclusion that sofosbuvir is “low value” is clearly not based on data or science. There are a number of publications which demonstrate the cost of untreated hepatitis C and it exceeds the cost of treatment significantly, even at the cost of current regimens with SOF. As well, the QALY increment with SOF therapy is <50,000$/yr by any calculation used (Younossi Z, et al. J Hepatology Feb 2014). As a treating physician I can assure you that patients are no longer willing to fail first generation DAAs or PEG IFN and RBV before initiating treatment with SOF. Your conclusions are clearly based on inadequate or inaccurate information. Please reconsider.

Paul J. Pockros,MD
Director, Liver Disease Center
Scripps Clinic
La Jolla, CA 92037

MEMORANDUM

TO: CALIFORNIA TECHNOLOGY ASSESSMENT FORUM

FROM: PAUL JUSTISON

SUBJECT: FINAL COMMENTS ON DRAFT COSTS OF HCV TREATMENT REPORT

DATE: 4/2/2014

CC: MY HEPATOLOGISTS, AND ANY IT MAY CONCERN

First, I should disclose my conflict of interest. I've been a HCV patient since 2001, and have had five treatments. The current one is working, but co-pays of over $10k stimulate an interest in maintaining access to care at reasonable cost - selfishly and for others in my position. My comments are in five areas: timing bias; model reliability, validity, and assumptions; presentation errors; costs of care; and finally, conflicts of interest. Though, I've commented previously, these final comments should not be regarded as an exhaustive review of the report. As a private citizen, there's a limit to the time I can devote to this.

Timing Bias

If the national news networks stopped their coverage of a presidential election after 10 states had reported and the polls were open everywhere else, there would be a national outcry over their incompetence. But what we have in this study is something very similar. The main events - the last 40 states so to speak - have not yet come forward. I speak of the all oral combinations sponsored by Gilead and Abbvie, which will be approved within the year. These combinations have a wealth of data supporting them, very high SVR rates, shorter treatment, and very low A/Es. Had the study included these, the results would have been far different. For example on page 78, the study gives the cost of an additional SVR for Telaprevir treatment at $189,000. This is more than the cited cost of an additional SVR for Sofusbuvir/Simeprevir (Sof/Sim) treatment at $171,000. Since the about to be approved therapies are similar to Sof/Sim, they will also be more cost effective than the outmoded Telaprevir treatment.

By giving short shift to emerging therapies, the report misleads. For example, on page 78 again, the report states "the incremental cost to achieve one additional SVR with the newer treatment regimens was greater than $300,000." Given the very near term approval of interferon free regimens, the number that should have been used is the $171,000 figure for Sof/Sim treatment.

CTAF has chosen to review a three act play, when the curtain has barely parted on the third act. Yet, fully conscious that the third act is about to begin, the report effectively ignores it and marches blindly to the principal conclusion that the emerging therapies provide low-value.

Model reliability, validity and assumptions

The report uses a 'model' to estimate the costs savings and expenditures of future care for HCV patients. Being simplifications of reality, all models suffer from the specific simplifications and assumptions they must make. So, models must be carefully constructed to insure that they give reasonable results, yet the report gives no evidence whatsoever regarding the reliability and validity of their model. Has it been back tested with similar conditions? Further, the model makes numerous assumptions, some of which are ludicrous. On page 59 the model assumes "patients would complete and be fully compliant with therapy." Since telaprevir therapy involves longer therapy, more rigorous dosing, and has far greater side effects than Sof/Sim and the new comparables, the assumption is biased. So is the assumption - "no differential costs assumed for identification and management of side effects and other drug related harms".

Costs for liver complications were taken from Florida Medicaid data. By itself the extrapolation of low-paying Medicaid data to an entire state is a bias. The use of Florida specific Medicaid data introduces a compounding bias of regional cost differences. The report does not indicate what corrections, if any, were made to the Florida data to make them relevant and unbiased to California.

To estimate future costs of HCV, the report relies on projections of cirrhosis and liver complications over a 20 year period. There certainly are many academic studies estimating the impact over that period. It is, however, a graduate student error to use these estimates to project future treatment costs. HCV is a progressive disease and the vast majority of HCV patients have had the virus for 30, 40, or 50 years. To use 20-year historical data with a mid-point of year 2000, or earlier, to project costs for a future with a mid-point of say, year 2025, is to seriously underestimate the impact of disease progression and the costs of untreated HCV. Actual rates of cirrhosis, liver complications, and costs of untreated HCV could be double or more your estimates. (See chart on page 4.)

While the report does give a table listing some of the assumptions in the model, it is not complete. For example, it does not include either the error from the Florida Medicaid data, or from using 20 year historical costs of care. Further, it does not include any information on the magnitude of the cumulative error caused by the assumptions, and by not doing so it presents biased information to decision makers.

Presentation errors

Tables 23 and 24 give the cost per additional SVR for therapies under consideration. Yet, no such cost is given in the table for the telaprevir option. Thankfully it is given on page 78 of the report as $189,000. Had that figure been included on Tables 23 and 24, it would have been immediately obvious that treatment with Sof/Sim is more effective at $171,000 than the telaprevir treatment.

Costs of Care

The report estimates the cost of treating Californians with HCV. But, it gives no time period for the costs, and without a time period it generates a very scary headline number of $32 billion. But what is this number based on? Treatment over 10 years? 5 years? There are only a limited number of Hepatologists and Gastroenterologists in California, and a reasonable projection of the costs of care in California, would be based on how many they could actually treat within a given timeframe. This report clearly did not do that.

Conflict of Interest

CTAF is rigorous in asking for conflicts of interest of others, and I agree, conflicts of interest should be clearly stated by all. Of course, this should include the health insurance industry itself. CTAF and its parent appear to be dominated by the health insurance industry. The facts about this relationship should be made clear and transparent, including that of panel members whose business models are dependent on links to the insurance industry.

The curious role of UCSF should also be noted. The world class status of UCSF is unquestioned, but is, to put it politely, unseemly, when so many members of the same institution serve as judge, prosecutor, witness and jury in a matter of importance to the entire nation.

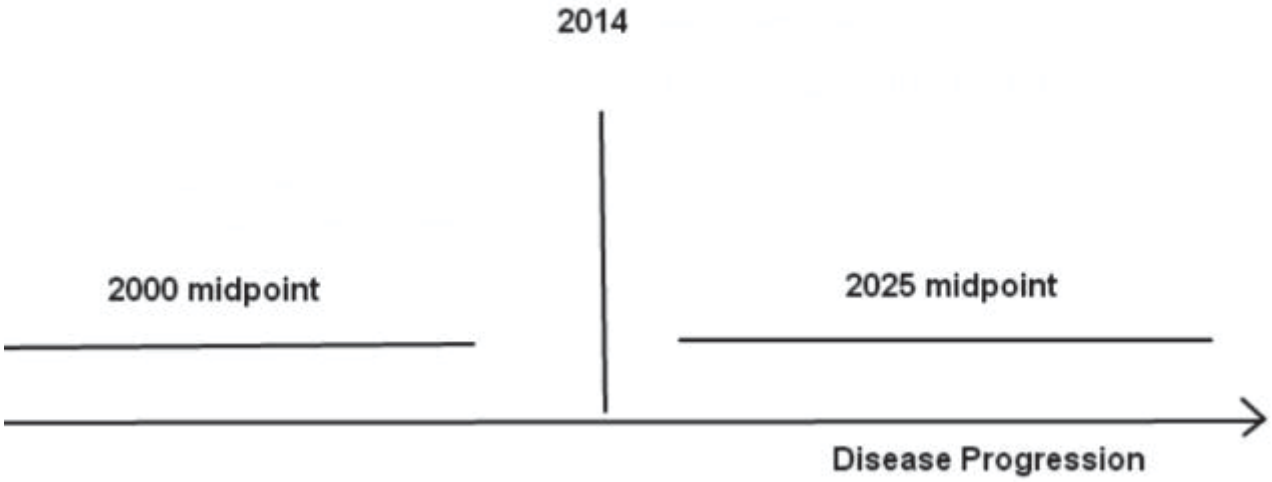
This panel reviewing and voting on this report assigned a low value to the newest approved therapies. What would they have concluded had the therapies that will be approved this year had been included? What would they have concluded had all of the errors reducing the future costs of untreated HCV been corrected? How would they have voted, if they themselves had more thoroughly critiqued and analyzed this deeply flawed report?

Paul Justison

20 Humphrey Place, Oakland, California 94610

pauljustison@comcast.net

Problem using historical data to project future HCV morbidity



To Whom It May Concern,

I want to thank you for the opportunity for public comment on this important issue. I was pleased to see that CTAF took on this topic, but I have several concerns about the process and several of the statements made by the panel on the day of the meeting. As Ryan Clary stated at the morning session of the policy roundtable discussion, we have HCV management and treatment guidelines put forth by the American Association for the Study of Liver Disease (AASLD) and Infectious Disease Society if American (IDSA), and these should be the recommendations that guide treatment decisions between provider and patient.

Throughout the day, there were several mischaracterizations of HCV screening and treatment recommendations. I fear that these mischaracterizations could lead to uninformed votes and result in recommendations by the panel based on bad information. I will highlight some of the errors I heard throughout the day:

1. On many occasions, panelists remarked how it did not make sense to screen "everyone", only to add stress to the lives of the people who test positive but feel no symptoms.

The screening guidelines for hepatitis C do no call for testing everyone. Rather they are directed towards two populations, both of whom are significantly burdened but the morbidity and mortality of HCV: People born between 1945 and 1965, and people who engage in behaviors that put them at risk for infection. These are targeted screening recommendations, both given a score of a recommendation score of a "B" by the United States Preventative Services Task Force.

Within the birth cohort, with an HCV prevalence of between 3-4%, the impact of screening would be dramatic. Several studies have shown that by screening this population, over 800,000 previously unknown infections would be discovered, up to 121,000 deaths averted, and up to 19,000 liver transplants averted (Rein 2012, McGarry 2012). People who inject drugs and other at risk account for most of the incidence of HCV, and screening and treatment of this population, in addition to averting deaths and preventing HCV-associated liver complications, has the additional benefit of preventing new infections.

As to the concern about increasing the stress to a previously undiagnosed person without symptoms, the USPSTF directly addresses this issue in their recommendations:

"The USPSTF recognizes that increased screening and the resulting increased diagnoses and treatment could result in increased overall harms because not all treated persons will benefit from treatment, including those who will never develop signs or symptoms of disease (overdiagnosis). The USPSTF weighed this potential harm against the potential harm of undertreatment attributable to underdiagnosis. It is hoped that future research will reduce overtreatment by clarifying which persons are most likely to benefit from early diagnosis and treatment. However, given that persons in the birth

cohort have been living with HCV infection for 20 or more years, the potential benefit of screening and early treatment will probably be at its highest now and in the near future before becoming smaller. After weighing the competing harms of overtreatment and underdiagnosis, the USPSTF recommends 1-time screening for this cohort."

Similarly, the American Association for the Study of Liver Disease (AASLD) and Infectious Disease Society of America (IDSA) provide guidance on delivering education and interventions aimed at reducing progression of liver disease and preventing transmission of HCV:

1. Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection;

2. Evaluaton for other conditions that may accelerate liver fibrosis, including HBV and HIV infections, is recommended for all persons with HCV infection;

3. Evaluation of advanced fibrosis, using liver biopsy, imaging, or non-invasive markers, is recommended in all persons with HCV infection to facilitate an appropriate decision regarding HCV treatment strategy and determine the need for initiating additional screening measures (eg, hepatocellular carcinoma (HCC) screening);

4. Vaccination against hepatitis A and hepatitis is recommended for all persons with HCV infection who are susceptible to these types of viral hepatitis;

5. All persons with HCV infection should be provided education on how to avoid HCV transmission to others.

Thus, contrary to what several panelists expressed, there are significant benefits to screening the birth cohort and those at risk for HCV infection beyond merely offering them treatment. Additionally, as was stated several times by members of the policy roundtable advising the panel, HCV is an asymptomatic disease, making the presence or absence of disease a non-factor in determining infection. An HCV antibody test, followed by a confirmatory viral load test is the only way to determine infection. If one waits for symptoms, significant damage to the liver has already occurred, damage that may be mitigated by the above guidance.

2. When voting on the clinical effectiveness and value of a simeprevir-based regimen versus a telaprevir-based one, a panelist remarked that since interferon was the cause of the severe side effects of both regimens, both PIs were essentially the same. In fact, a telaprevir based regimen is much more difficult to tolerate, as indicated by both the drug label, and several research studies presented at scientific conferences. Indeed, in a PowerPoint presentation from earlier in the day, a summary of the burdens of a boceprevir or telaprevir based regimen was provided:

- More pills: 6-12 a day on a q 8 hour schedule

- Increase in anemia from 30% to 50%
- Dysguesia, rash, drug interactions

The most recent HCV therapies are both more effective with higher SVR rates, but also better tolerated. Side effect management, completion of therapy and the reduced need to re-treat with the new HCV regimens are significant improvements to previous ones.

3. One point in the discussion, the moderator of the policy roundtable stated that the AASLD/IDSA Recommendations for Testing, Managing and Treating Hepatitis C recommended a combination of sofosbuvir and simeprevir as front line therapy, and he highlighted the high cost of this combination. In fact, the AASLD/IDSA Guidelines, recommend sofosbuvir + ribavirin + pegylated interferon as the first choice of HCV therapy. The group does recommend a combination of sofosbuvir + simeprevir with or without ribavirin for patients who are treatment naïve but who are ineligible to receive interferon, however, they note: "This regimen should be considered only in those patients who require immediate treatment, because it is anticipated that safer and more effective IFN-free regimens will be available by 2015 " (19).

It is very important to not mis-represent the treatment recommendations when voting on the clinical effectiveness and value of said regimens. These three examples serve to illustrate the importance of having experts in hepatitis C making decisions on the effectiveness and value of HCV treatments.

Finally, its worth briefly discussing the most recent mortality data presented from the CHeCS Study, to highlight the importance of screening and treating HCV in a effort to avert deaths from this disease. Reena Mahajan and colleagues analyzed data from the CHeCS study and found that HCV was a significantly under-reported cause of death, and may in fact lead to approximately 80,000 deaths per year. The mortality rate for people with HCV is twelve times higher than the general population. The average life expectancy for people with HCV is 59 years of age, compared to 74 years of age for people without HCV.These numbers are significantly worse than what has been previously thought, leading the authors to conclude: “For purposes of public health, policy planning, disease modelling and medical care, this is a huge burden that should be reported and hopefully spur public health action as curative, all-oral therapies are becoming available to treat HCV” (11).

The cost of these HCV therapies is high, of that I think we agree. But we can work with advocacy organizations like the Fair Pricing Coalition ad National Viral Hepatitis Roundtable to support measures to make the drugs more affordable for both State Medicaid programs and private insurance alike. CTAF can be a valuable partner in that effort. That said, we have treatment guidelines developed by leaders in the field of hepatology and HCV, and I would encourage CTAF to support them and recommend that they serve as the standard of care for treating patients with HCV. Moving forward, I look forward to working with CTAF on the issue of cost, and I encourage the inclusion of advocates and HCV providers, including those on your policy roundtable and those who gave public comment, to work with you as well.

Please feel free to contact me going forward should you have any questions.

Sincerely,

Andrew Reynolds

Andrew Reynolds
Hepatitis C Education Manager
Project Inform
415-580-7308
The Support Partnership
1-877-HELP-4-HEP
"One call. Lots of help."

I wanted to share some additional thoughts after this week's CTAF meeting.

First, I would reiterate the points I made in my earlier comments and ask the report's authors to address the limitations of their methodology. Specifically, I think the outcomes would have been very different had the authors factored in the anticipated (and most likely shorter) life expectancies of persons who have had HCV for 30 years prior to diagnosis. Many people with HCV will die of all-cause mortality before ever being screened, diagnosed, or treated. Additionally, the model does not appear to account for the costs that will be borne by Medicare given the age range of prevalent cases. Also, it is not clear from the methodology at what point the HCV natural history "clock" was started—at the time of infection (like 30 years ago) or at the time of diagnosis (in the model, around age 60). This is important because it will affect the number/severity of liver complications expected in the theoretical patient cohort.

Second, I would address a few issues that came up during the meeting that concerned me.

A. Regarding the natural history of HCV and the previous standard of care with boceprevir and telaprevir for genotype 1, I am not a clinician, but follow FDA label updates closely and send them to the members of the California Viral Hepatitis Clinical Task Force, which includes primary care providers and specialists. Both the labels for BOC and TLV have had numerous label updates to account for their considerable side effects and toxicities, and these considerations did not seem to be given sufficient weight in the panel's deliberations. One panelist suggested that the toxicity of PEG/RIBA plus BOC/TLV was due to the interferon. However, updated FDA labeling for both drugs contradicts this assertion.

The updated labels for boceprevir (VICTRELIS) and telaprevir (INCIVEK), which have been changed to reflect clinical experience, now include the following FDA warnings, respectively:

VICTRELIS

WARNINGS AND PRECAUTIONS

Anemia -The addition of VICTRELIS to peginterferon alfa and ribavirin is associated with an additional decrease in hemoglobin concentrations compared with peginterferon alfa and ribavirin alone. (5.2)

•

Neutropenia - The addition of VICTRELIS to peginterferon alfa and ribavirin may result in worsening of neutropenia associated with peginterferon alfa and ribavirin therapy alone. (5.3)

•

Hypersensitivity – Serious acute hypersensitivity reactions (e.g., urticaria, angioedema) have been observed during combination therapy with VICTRELIS, peginterferon alfa and ribavirin. (5.5)

ADVERSE REACTIONS

The most commonly reported adverse reactions (greater than 35% of subjects) in clinical trials in adult subjects receiving the combination of VICTRELIS with PegIntron and REBETOL were fatigue, anemia, nausea, headache and dysgeusia. (6.1)

INCIVEK

WARNINGS AND PRECAUTIONS

Serious Skin Reactions/Rash: Fatal and non-fatal serious skin reactions (including SJS, DRESS, and TEN) have been reported. Patients with mild to moderate rash should be monitored for progression. If rash progresses and becomes severe, INCIVEK should be discontinued. For serious skin reactions, including rash with systemic symptoms or a progressive severe rash, INCIVEK, peginterferon alfa, and ribavirin must be discontinued immediately. Consider discontinuing other medications known to be associated with serious skin reactions. (5.1)

•

Anemia: Monitor hemoglobin prior to and at regular intervals during INCIVEK combination treatment. Follow dose modifications for ribavirin; discontinue INCIVEK if required. (5.2)

ADVERSE REACTIONS

The most common adverse drug reactions to INCIVEK (incidence at least 5% higher with INCIVEK than in controls) were rash, pruritus, anemia, nausea, hemorrhoids, diarrhea, anorectal discomfort, dysgeusia, fatigue, vomiting, and anal pruritus. (6.1)

B. Not discussed by the panel were the considerable extra-hepatic complications of chronic HCV infection, regardless of disease stage (Louie, 2012), which may have limiting effects on patients' quality of life and life expectancy. The panel also focused on symptoms, yet most people with chronic HCV have no symptoms, even while liver disease is actively progressing to advanced cirrhosis/fibrosis or hepatocellular carcinoma.

C. Also raised during the discussion was the question of whether baby boomers should be screened for HCV. This question has been settled by CDC and USPSTF, and most payers are now required under the Affordable Care Act to provide this preventive service without patient cost-sharing.

Third, I wanted to address the panel's question about the HCV reproduction ratio or R_0 "(r-nought" or number of persons someone is likely to infect). I was only able to find papers estimating transmission patterns for injection drug users, which account for more than two-thirds of new HCV infections.

Generally, for an epidemic to continue, the R_0 must be >1. Greek researchers (Magiorkinis, 2013) estimated the R_0 among IDUs for HCV genotypes 1a and 1b (which account for 75% of infections in the U.S.) of 3.4 and 4.5, respectively; however, these estimates have not been validated by additional sources. Transmission rates among IDUs are dependent on the duration of injection-drug using behaviors (in years) and the frequency of syringe-sharing behaviors. Australian researchers (Kwon, 2009) estimated that IDUs sustain the HCV epidemic after 2.3 years of injecting; and that treating IDUs and all their contacts for chronic HCV infection (similar to ring vaccination) is the most effective approach to reducing HCV incidence and preventing reinfection (Rolls, 2013).

Thanks,

Rachel

I was recently informed of Blue Shield of CA decision to restrict use of sofosbuvir to cirrhosis pts only.

I strongly disagree as this is the biggest breakthrough in the treatment of chronic viral treatments ever. You fail to realize this a 12 week treatment and curative in over 80% of cases. No HIV treatment is curative and all are lifelong with open ended costs that will exceed that of sofosbuvir.

Restricting its use to cirrhotics only is very short-sighted. If we use this therapy we will prevent cirrhosis from occurring in many cases. Need I remind you how much you spend on one cirrhotics pt as they go through transplant with its attendant complications and long term expensive immunosuppressant therapies?

Be advised, your decision to restrict the use of one of the greatest breakthroughs in viral treatment will not stop us from appealing repeatedly to you. It's in the best interests of every hep C pt that I do it. I already spent 2.5 hours on the phone convincing an out of state insurance to cover it in a 35 yo who now has undetectable viral load. Get ready, we are going to call every time if we have to in order to get use of this truly revolutionary life saving therapy.

Dr. Craig Ennis

Sent from my iPhone

I am an infectious disease specialist working in an FQHC/Community clinic environment treating mostly unfunded and/or Medi-Cal patients. I have been treating HIV and Hepatitis C for the past 7 years after fellowship training. I've been involved in HIV and Hepatitis education in Seattle at the University of Washington, as well as abroad via PEPFAR-funded programs.

I have been on the front lines of what seems to be a class war. Most infectious diseases specialists are well aware that poverty is the single biggest risk factor for suffering from a life-threatening infection. HIV, Hepatitis C, Tuberculosis, and Malaria, not to mention upper respiratory infections and diarrheal diseases are all more common in those with lower incomes, less access to healthcare, clean water, healthy food. The World Health Organization and the international medical community has taken this issue head-on with recent reports emphasizing the Social Determinants of Health.

Yet in the United States, healthcare is much more of a marketplace than an actual system. Our citizens, especially if they are poor, are not offered timely, relevant, compassionate treatment unless they are able to 'buy in' to the insurance marketplace. What we're seeing in the realm of Hep C therapeutics is a battle royale between all-powerful insurance giants and all-powerful Pharmaceutical companies. In the meantime the patients (and their tireless providers) are the ones that suffer.

Treating and curing Hepatitis C has innumerable benefits, that are just beginning to be uncovered by an anemic national research agenda. Achieving a Sustained Virologic Response (SVR) results in a 90% reduction in liver disease, a 70% reduction in Hepatocellular Carcinoma, and a 50% reduction in all-cause mortality. There is evidence that treating Hep C actually improves neurocognitive functioning and can reverse pre-diabetes. There is likely to be a great deal more evidence on the basic science front regarding the chronic inflammation that subsides when Hep C is cured. There are thousands of baby-boomers who are actually dying NOW of liver disease that could have been avoided if their Hep C was treated much earlier.

The current battle over the price of Hep C treatments will go down just as the already-fought battle over HIV drug prices did. Eventually we will realize that it is absolutely INHUMANE to offer state-of-the-art curative treatment, with many benefits only to the wealthy, while the most affected populations suffer ongoing consequences.

I urge the health officials, insurance executives, and pharmaceutical companies to work together to negotiate a solution that allows patients that need treatment to be treated. What we have currently is an inequitable, prejudiced, unfair system that systematically excludes the poor from accessing a potentially dramatic improvement in health status.

Sincerely,
CR

Christian B. Ramers, MD, MPH
Director, Graduate Medical Education - Assistant Medical Director (Research/Special Populations)
Family Health Centers of San Diego
- 823 Gateway Center Way, San DIego, CA 92102-4541 - ph: 619.798.3649, fax: 619.906.4564 - www.fhcsd.org

HIV/HCV Distance Education Specialist
- Northwest AIDS Education & Training Center (NWAETC) - www.nwaetc.org - www.nwaetcecho.org
- Pacific AIDS Education & Training Center (PAETC) - www.paetc.org

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Family Health Centers of San Diego- Exceptional in Every Way

To: **California Technology Assessment Forum**

From: **Gregg Alton**
Executive Vice President, Corporate and Medical Affairs
Gilead Sciences, Inc.

Date: **March 17, 2014**

Re: **Comments on " The Comparative Clinical Effectiveness and Value of Simeprevir and Sofosbuvir in the Treatment of Chronic Hepatitis C Infection" Draft Report**

After attending the public forum regarding CTAF report entitled "The Comparative Clinical Effectiveness and Value of Simeprevir and Sofosbuvir in the Treatment of Chronic Hepatitis C Infection", we wanted to take the opportunity to provide clarification regarding the clinical effectiveness and cost effectiveness data that has been generated with SOVALDI (sofosbuvir).

Executive Summary

Sofosbuvir , the first FDA approved NS5B nucleotide polymerase inhibitor, provides an interferon-limiting or interferon-free regimen for patients infected with HCV genotypes (GT) 1 and 4, interferon-free for GT 2 and 3, and treatment options for interferon-ineligible and -intolerant patients.

- Sofosbuvir represents a new paradigm for treating chronic hepatitis C infection because, for most patients, it offers a cure. This opens the way not just to manage the disease as a chronic condition, but to eradicate it.
- Physicians have long sought better treatments for HCV because the standard approach required patients to take up to 12 pills a day, combined with interferon injections that cause flu-like symptoms and depression. The cure rate for patients who complied with this regimen has been about 75%, but studies have shown that some half of patients discontinue treatment owing to the severity of side effects. From the patient's perspective, Sofosbuvir is much more tolerable and more effective than the standard treatment, with a far shorter duration. In consequence, a high percentage of Sofosbuvir patients remain on treatment until they are cured.
- The CTAF report significantly underestimates the full lifetime costs of treating chronic HCV. In addition, the CTAF analysis unduly discounts the value of initiating treatment at early stages of disease, thus reducing the human and economic costs of cirrhosis, liver cancer, liver transplants and deaths from HCV. A 2011 Henry Ford Foundation study of patients with end-stage liver disease estimated their annual medical cost at $60,000.
- The Sofosbuvir development program was robust with 6 Phase 3 trials that were inclusive of real-world patients: 20% cirrhotics (F4), Black and Hispanic patients proportional to the US population, no upper limit of age or BMI, and patients receiving opiate replacement therapy, which is unique to our trials and differentiates our clinical profile from all other agents approved for the treatment of HCV.
- Sofosbuvir-based regimens allow clinicians, payers and policy makers to begin moving from a chronic disease state management model to a curative and preventive model
- Sofosbuvir-based regimens provide:
    - The highest efficacy rates, shortest treatment duration regimen (12 weeks) in combination with RBV + PegIFN for patients infected with GT 1 or 4
    - The highest efficacy rates, and the first all oral HCV regimen in combination with RBV for patients infected with GT 2 (12 weeks) and GT 3 (24 weeks)
    - Excellent safety and tolerability profile, with low discontinuation rates due to AEs from 0 to 2%

- First all oral regimen for patients who have no treatment options who are interferon -ineligible or – intolerant
- FDA approved for patients of all genotypes with HCC meeting Milan criteria (awaiting liver transplantation)
- The only approved DAA available for patients with HCV/HIV-1 coinfection, with SVR rates and a safety/tolerability profile similar to those observed for HCV monoinfected patients
- Lack of food effect, once daily administration, and very limited drug-drug interactions

Sofosbuvir brings significant value to payers, providers, patients and society by providing the following:

- Gilead priced SOF comparable to other DAA regimens, especially when taking into account the total cost of an SVR. It is important to consider the overall value of Sofosbuvir regimens and total cost of cure

Regimen	Duration (weeks)	Total Regimen Cost
Sofosbuvir + Pegasys + RBV	**12**	**$94,078**
Sofosbuvir + RBV	**12**	**$84,823**
	24	**$169,646**
Telaprevir + Pegasys + RBV	**24**	**$86,312**
	48	**$106,468**
Simeprevir + Pegasys + RBV	**24**	**$86,516**
	48	**$106,673**
Boceprevir + PegIntron + RBV	**28**	**$64,825**
	36	**$85,257**
	48	**$95,845**

- Economic analysis shows that, compared with current treatment regimens, sofosbuvir-based regimens yield the most favorable future health outcomes and the fewest cases of liver disease complications and HCV-related deaths across patients infected with all HCV genotypes (1, 2, 3, and 4), levels of treatment experience, fibrosis and cirrhosis stages, as well as patients with or without HIV coinfection.
- In the one-year analysis, the cost per SVR for the Sofosbuvir-based regimen is lowest of all currently approved regimens due to higher efficacy rates, a high barrier to resistance, and improved tolerability. In the long-term, the Sofosbuvir-based regimens are the most cost-effective treatment options for patients infected with HCV genotype 1, because of fewer treatment failures, fewer adverse events, and averted liver-disease costs.
- Earlier initiation of the more effective Sofosbuvir-based treatment yields better health and economic outcomes compared with later initiation, reducing advanced liver disease complications and the downstream costs associated with advancing disease.
- IFN-free regimens and regimens of shorter duration with PegIFN+RBV are associated with better health status and substantial declines in fatique and depression during treatment. Patients achieving SVR showed improvement in their activity, work productivity and presenteeism scores compared to their baselines.

Comparative Clinical Effectiveness

SOF is an HCV nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C in adults as a component of a combination antiviral treatment regimen. SOF efficacy has been established in subjects with HCV GT 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma (HCC) meeting Milan criteria (awaiting liver transplantation [LT]) and those with HCV/HIV-1 co-infection (SOVALDI package insert).

Gilead performed six Phase 3 clinical trials comprising 1,851 patients to demonstrate the effectiveness of SOF-based regimens. The real-world nature of HCV patients was reflected by expanded inclusion criteria that enrolled a proportionate number of non-white patients as in the general population, had no upper limit of age or BMI, allowed for opiate replacement therapy, and included approximately 20% cirrhotics (Jacobson et al, NEJM 2013; Lawitz et al, NEJM 2013; Sulkowski et al, AASLD 2013; Zeuzem et al, AASLD 2013).

Genotype 1

Among patients with genotype 1, is the evidence adequate to demonstrate that the combination of sofosbuvir with pegylated interferon and ribavirin (PegIFN + RBV) is equivalent or superior to triple therapy with telaprevir or boceprevir + PegIFN + RBV?

Based on clinical trial data, SOF+PegIFN+RBV for 12 weeks has many advantages for patients compared to regimens containing PI+PegIFN+RBV for 24-48 weeks:

- SOF+PegIFN+RBV achieved the highest overall SVR rates of an FDA-approved regimen (90%), the highest efficacy in GT1 with SVR rates of 89%, in GTs 4, 5 & 6 (97%), and the highest overall SVR rate in cirrhotics (80%)
- SOF+PegIFN+RBV was a well tolerated regimen, with few treatment discontinuations (<2%), no additional AEs in addition to PEG-IFN+RBV, no increase in anemia,neutropenia, rash or phototoxicity, and no need for blood transfusions or bone marrow stimulating agents such as erythopoetin, filgrastim or eltrombopag
- High barrier to resistance - no resistance in any Phase 3 trial
- SOF+PegIFN+RBV is administered orally, once daily, without regard to food, for a finite 12 week duration vs 24-48 weeks of Response Guided Therapy with protease inhibitors
- SOF is renally cleared, with a lower potential for drug-drug interactions (DDIs) than protease inhibitors with numerous CYP450 interactions

NEUTRINO is a phase 3, open-label, historical control, single-arm trial that evaluated SOF + PegIFN + RBV for 12 weeks of treatment in 327 treatment-naïve (TN) subjects infected with HCV GT 1, 4, 5 or 6, with no response guided algorithm (Lawitz et al, NEJM 2013). SVR was the primary endpoint, defined as HCV RNA < 25 IU/mL, at 12 weeks after the end of treatment. The primary endpoint was compared to a predetermined historical control response rate of 60% for protease inhibitor + PegIFN + RBV triple therapy based on discussions with the FDA, modeled to reflect the characteristics of patients in NEUTRINO with a target of 20% cirrhotics. A sample size of 300 subjects provided 90% power to detect a 9% improvement in SVR12 rate from 60% to 69% using a two-sided one-sample binomial test at the 0.05 significance level. The basis for this 60% null hypothesis SVR rate is derived from: 1) a historical SVR rate of ~65% calculated from the telaprevir (ADVANCE study) and boceprevir (SPRINT2 study) data after adjusting for the expected proportion of subjects with cirrhosis (~20%). It is a calculated weighted average to model what the responses would be for telaprevir and boceprevir if they had a similar number of cirrhotic patients as in the NEUTRINO study. The data is estimated to be ~70% in non-cirrhotic subjects and 44% in cirrhotic subjects. The SVR rate for the historical control in this study (ie, a patient population of 80% noncirrhotics and 20% cirrhotics) was then calculated to be ~65% (ie, 0.8 × 70% + 0.2 × 44%). As noted above, the 60% null hypothesis SVR rate is obtained after allowing for a 5% trade-off in efficacy exchanged for an expected improved safety profile and shorter treatment duration.

Treated subjects had a median age of 54 years; 89% had HCV GT 1 and 11% had HCV GT 4, 5 or 6; 17% had cirrhosis; 29% had the *IL28B* CC allele, 55% had the CT allele, and 16% had the TT allele; 64% were male; 79% were

White; 17% were Black; 14% were Hispanic or Latino; mean BMI was 29 kg/m^2; and 78% had baseline HCV RNA > 6 $\log_{10}$ IU/mL. Because of the expanded inclusion criteria, NEUTRINO had a large number of patients with traditional negative predictors of response to PegIFN + RBV regimens, due to cirrhosis, older age, high BMI and non-white patients.

The overall SVR12 rate (90% [295/327]) was superior to historical control SVR rate of 60% ($P < 0.001$). SVR12 was achieved by 89% (261/292) of subjects with HCV GT 1 (GT 1a- 92% [206/225]; GT 1b-82% [54/66]). The difference in GT1a and GT1b response rates is accounted for by a lower proportion of *IL28B* CC genotype in the GT1b subjects (20%) than among GT 1a subjects (32%). The SVR12 rate in cirrhotic patients was 80% overall and 81% in GT1 patients, which is the highest efficacy published in a phase 3 clinical trial to date.

High SVR12 rates were achieved across all GT 1, 4, 5, and 6 subjects despite the presence of traditional negative predictive factors [91% SVR in non-Black vs. 87% SVR in Black subjects; 90% SVR in BMI <35 kg/m^2 vs. 91% SVR for BMI ≥35 kg/m^2; 91% SVR in *IL28B* non-TT vs. 86% SVR in *IL28B* TT] (Mangia et al, AASLD 2013).

No subject experienced virologic breakthrough on-treatment. No resistance-associated mutations, including *S282T*, were observed by population or deep sequencing (1% cut-off) among subjects who did not achieve SVR.

The safety assessment of the short duration of SOF + PegIFN + RBV for 12 weeks is based on the overall population of GT 1, 4, 5, and 6 subjects. The safety profile was consistent with that of PegIFN + RBV alone, with 1.5% (5/327) discontinuations due to AEs, which is lower than historically been seen with longer durations (24-48 weeks) of response guided therapy with PegIFN + RBV + PIs (13-14%).

For the purposes of determining a control SVR rate for the network meta-analysis, based on the calculated historical control SVR rate of 60% for PI + PegIFN + RBV triple therapy in NEUTRINO, any estimate of an SVR rate for double therapy with PegIFN + RBV must be lower than 60%. Historical SVR rates for PegIFN + RBV have consistently been in the low 40% range (McHutchison, et al.). Recent PegIFN + RBV control arms from QUEST-1 and QUEST-2 containing a lower proportion (11-13%) of cirrhotic patients and a higher proportion of GT1b subjects yielded SVR rates of 50% (FDA Antiviral Drugs Advisory Committee Meeting Background Package). Thus, the SVR input to the network meta-analysis of 57% based on 26 patients from the PROTON study which was in non-cirrhotic patients is spuriously high, and the inputs to the CTAF network meta-analysis require downward revision to more closely represent a comparison to NEUTRINO which enrolled 17% cirrhotic patients.

The recently published, independently developed AASLD/IDSA HCV Guidance Recommendations for Testing, Managing, and Treating Hepatitis C recommend SOF + PegIFN + RBV x 12 weeks regardless of subtype, with Class I/Level A evidence and strength, indicating that it is "Optimal treatment favored for most patients". The combination of PegIFN + RBV ± TVR or BOC x 24-48 weeks is specifically not recommended, meaning that the "Treatment is clearly inferior or is deemed harmful. Unless otherwise indicated, such regimens should not be administered to patients with HCV infection" (AASLD/IDSA HCV Guidance, 2014).

Among patients with genotype 1, is the evidence adequate to demonstrate that sofosbuvir + PR is equivalent or superior to simeprevir + PR?

NEUTRINO (SOF + PegIFN + RBV x 12 weeks, no response guided therapy) and QUEST-1 and QUEST-2 (SMV + PegIFN + RBV x 24-48 weeks, with response guided therapy) were studies conducted contemporaneously in HCV subjects infected with GT1 virus, however with different Inclusion and Exclusion criteria, and different patient Baseline Characteristics. The FDA combined QUEST-1 and QUEST-2 due to identical study designs, and reference is made to the FDA Antiviral Drugs Advisory Committee Meeting Background Package for NDA 205123: Simeprevir; October 24, 2013.

NEUTRINO specifically targeted increased enrollment of patients with cirrhosis (17%), had no upper age or BMI limits, permitted opiate replacement therapy, and had lower limits of platelets (≥ 90,000/mm) and neutrophils (≥ 1500/mm^3 or 1000/mm^3 in Black subjects). This is represented in the table below, illustrating that the NEUTRINO trial enrolled more patients with historical negative predictors of SVR than the QUEST-1 and QUEST-2 trials.

Comparison of baseline characteristics between NEUTRINO and QUEST-1/QUEST-2

Inclusion criterion	**NEUTRINO**	**QUEST-1/QUEST-2**
Median age, years	54	46-48
Median BMI, kg/m^2	29	26-27
Genotype 1a/1b/4,5,6	69%/20%/11%	41-56%/44-58%/0%
% Caucasian/% Black	79%/17%	89%/8%
IL28B CC %	29%	29%
% cirrhotic	17%	9.4%*

*Simeprevir data actually pools F3 (bridging fibrosis) with F4 (cirrhosis)

The overall SVR rate from NEUTRINO for GT1 subjects was 89%, compared to the overall SVR rates from the combined QUEST-1 and QUEST-2 trials of 80%. Among cirrhotic patients, the GT1 SVR rate in NEUTRINO was 81%, compared to 58-65% in QUEST-1 and QUEST-2 or 59% as a pooled analysis. If you were to then model in more cirrhotic patients (17% instead of 9.4%) in QUEST 1 and 2 to make them more comparable to NEUTRINO, then the overall response rate for SMV would be 78%.

The SVR rates for other historical negative predictive factors are shown below:

SVR	**NEUTRINO**	**QUEST-1/QUEST-2**
Overall GT1	89%	80%
No cirrohsis	92%	82%%
Cirrhosis	81%	59%
Black subjects	87%	67%
IL28B non-CC	87%	66%
Baseline HCV RNA > 800,000	89%	77%
Age > 50 (NEUTRINO) or Age >45 (QUEST 1 and 2)	88%	75%
Combination of *IL28B* non-CC alleles, HCV RNA >800,000 IU/mL and Metavir F3/F4 fibrosis	71%	51%

The activity of simeprevir is susceptible to the presence of the Q80K resistance mutation is greatly reduced, which is present at baseline in 40-50% of HCV patients infected with GT1a virus. In the pooled QUEST-1 and QUEST-2 trials, the SVR12 rate in GT1a subjects with the Q80K polymorphism was 58% in the SMV+PegIFN+RBV group, and 55% in the PegIFN+RBV Group (p=NS). While the FDA requires resistance testing to be done prior to initiation of SMV therapy in HCV GT1a patients to determine if the Q80K is present, this is not standard of practice for clinicians. Fortunately, the Q80K mutation does not affect viral sensitivity to sofosbuvir, and the SVR rate for GT1a patients in NEUTRINO was 92%.

Among patients who are ineligible for or intolerant to interferon, is the evidence adequate to demonstrate that sofosbuvir + R is equivalent or superior to no treatment?

The SVR rate is zero for interferon-ineligible or –intolerant chronic HCV patients who do not receive treatment. All currently approved HCV regimens, with the exception of SOF + RBV, require PegIFN, and are therefore contraindicated in interferon-ineligible or –intolerant patients. SOF+RBV provides treatment options to HCV

infected patients who would not otherwise receive treatment, and whose liver disease would progress unchecked.

POSITRON is a phase 3, randomized, double-blind, PBO-controlled trial that evaluated 12 weeks of treatment with SOF + RBV (n = 207) compared to PBO (n = 71) in IFN-intolerant, -ineligible, or -unwilling subjects infected with HCV GT 2 or 3 (Jacobson et al, NEJM 2013). Subjects were randomized in 3:1 ratio and stratified by cirrhosis (presence vs. absence). Treated subjects (N = 278) had a median age of 54 years; 49% had HCV GT 3; 16% had cirrhosis; 54% were male; 91% were White; 5% were Black; 11% were Hispanic or Latino; mean BMI was 28 kg/m^2; and 70% had baseline HCV RNA levels > 6 $\log_{10}$ IU/mL. The proportions of subjects who were IFN-intolerant, -ineligible, or -unwilling were 9%, 44%, and 47%, respectively. Most subjects (81%) had no prior HCV treatment.[3]

The overall SVR12 rate was 78% with SOF + RBV and 0% with PBO *(P* < 0.001). SVR in GT 2 subjects was 93% on SOF + RBV and 0% on PBO. SVR in GT 3 subjects was 61% on SOF + RBV and 0% on PBO.

No subject experienced virologic breakthrough on-treatment. No resistance-associated mutations, including *S282T*, were observed by population or deep sequencing (1% cut-off) among subjects who did not achieve SVR.

The safety profile of SOF + RBV was consistent with that of RBV alone. The most commonly reported AEs were fatigue, nausea, headache and insomnia. Discontinuation due to AEs occurred in 2% of subjects in the SOF + RBV arm vs. 4% in the PBO arm.

Additional data, from HCV/HIV-1 co-infected patients further support that SOF + RBV is an effective and well-tolerated regimen. PHOTON-1 is a phase 3, open-label study conducted to evaluate 12 or 24 weeks of SOF + RBV in subjects with HCV/HIV-1 co-infection (Sulkowski et al, AASLD 2013). Many HCV/HIV-co-infected patients are considered IFN-ineligible.

Because of the lower chance of drug-drug interactions, SOF + RBV was effectively co-administered with multiple ARV agents including inhibitors of HIV-1 protease, reverse transcriptase (non-nucleoside/nucleoside) and integrase. Among GT 1 subjects, 76% achieved SVR12 following 24 weeks of SOF + RBV. SVR rates in subjects with HCV GT 1 were 80% (24/30) in subjects with baseline IL28B CC allele and 75% (62/83) in subjects with baseline IL28B non-CC alleles.

The safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects. SOF was well-tolerated, with a low rate of treatment discontinuations due to AEs overall of approximately 3%. The most commonly reported AEs were fatigue, insomnia, headache, and nausea.

Among patients who are ineligible for or intolerant to interferon, is the evidence adequate to demonstrate that the combination of sofosbuvir + simeprevir is equivalent or superior to sofosbuvir + R?

COSMOS is an ongoing, phase 2a, open-label study evaluating the use of SOF 400 mg daily + SMV 150 mg daily ± weight-based RBV for 12 or 24 weeks in GT 1 prior null responders with METAVIR scores of F0-F2 (Cohort 1, n = 80), and treatment-naïve and prior null responders with METAVIR scores of F3-F4 (Cohort 2, n = 87). Prior null response was defined as a failure to achieve a > 2 $\log_{10}$ decline in HCV RNA by Week 12 of a Peg-IFN + RBV regimen (Jacobson et al, AASLD 2013).

Subjects were randomized 2:1:2:1 to SOF + SMV + RBV 12 weeks, SOF + SMV 12 weeks, SOF + SMV + RBV 24 weeks and SOF + SMV 24 weeks. In Cohort 1, 78% of subjects had GT1a, 50% had Q80K baseline polymorphism, 94% had *IL28B* CT or TT haplotype, and 59% had METAVIR score F2. In Cohort 2, 78% of subjects had GT1a, 40% had Q80K baseline polymorphism, 79% had *IL28B* CC or TT haplotype, 47% had METAVIR score F4 and 54% were prior null responders.

Due to the complexity of the COSMOS study design, the SVR results of the subgroups are presented in the table below for Cohort 1 (SVR12 pooled for 12 and 24 weeks arms) and SVR4 rates in Cohort 2 (12 weeks arms only; 24 week data have not been presented) among GT 1a with Q80K and without Q80 K and for GT 1b subjects. Q80K at baseline reduced SVR rates by 10% in SMV-based regimens.

Virologic Response in Cohort 1 and Cohort 2 from the COSMOS Study

	Cohort 1 **SOF + SMV ± RBV** **Pooled 12 and 24 weeks**	**Cohort 2** **SOF + SMV ± RBV** **12 weeks**
SVR 4		
GT1a with Q80K	-	91% (10/11)[b]
GT1a without Q80K	-	100% (21/21)
GT1b	-	100% (8/8)
SVR12		
GT1a with Q80K	89% (24/27)[a]	-
GT1a without Q80K	100% (30/30)	-
GT1b	100% (17/17)	-

[a] 3 relapsed (with baseline Q80K); [b] 1 relapsed (with baseline Q80K)

SOF + SMV ± RBV was generally safe and well-tolerated across both Cohorts 1 and 2. AEs leading to treatment discontinuation were reported in 4 subjects (2%). The most common AEs were fatigue (30%), headache (20%) and nausea (14%). Serious AEs were reported in 3 subjects (anemia, injury, retinal tear). Anemia and hyperbilirubinemia occurred mainly in the RBV-containing arms.

The recent independent AASLD/IDSA HCV Guidance Recommendations for Testing, Managing, and Treating Hepatitis C recommend SMV+ SOF $\pm$ RBV x 12 weeks for interferon-ineligible GT1 patients, with Class I/Level B evidence and strength, indicating that it is “Optimal treatment favored for most patients”. The combination of SOF + RBV x 24 weeks, regardless of GT 1 subtype, is an alternative regimen for these patients.

Cost-effectiveness

The draft CTAF report concludes that for the majority of patients, the downstream medical cost benefit of treating most hepatitis C patients with sofosbuvir (SOF) is not outweighed by the upfront cost of treatment. Any cost offsets downstream of treatment with SOF (from fewer liver-related complications) would represent less than 10%-20% of upfront treatment expenditures after 5 years, and only recoup about 66% of upfront treatment costs after 20 years. However, the report finds a stronger value proposition after 20 years for the use of SOF in patients with advanced liver fibrosis.

These findings are in contrast to several recent publications supporting the cost-effectiveness of SOF-based regimens vs. other comparators. (Younossi ZM, et al. AASLD 2013. #368, Younossi ZM, et al. AASLD 2013. #369, Younossi ZM, et al. ISPOR EU 2013, Abstracts accepted to DDW and ISPOR 2014). When evaluated by ICER (incremental cost-effectiveness ratio) or the cost per SVR, SOF-based therapies were shown to be the most cost-effective treatment option for patients infected with HCV GT 1, including those who are difficult to treat (Table 1). These analyses were based on a decision-analytic model that projected health and economic outcomes for patients with chronic HCV infection treated with SOF-based regimens compared with currently available comparators. The state-transition model had six health states with annual transitions: without cirrhosis, compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), liver transplant and death.

Table 1. Genotype 1 Short-term Base-Case Results: 1-Year Total Cost per Sustained Virologic Response

	Cost per SVR	Increase From Sofosbuvir-based Regimen	Percentage Difference
Treatment naïve			
All patients			
SOF + PegIFN2a/RBV	$116,068	—	—
SMV + PegIFN2a/RBV	$125,950	$9,882	9%
TVR + PegIFN2a/RBV	$136,644	$20,576	18%
BOC + PegIFN2b/RBV	$133,644	$17,576	15%
Without cirrhosis			
SOF + PegIFN2a/RBV	$113,148	—	—
SMV + PegIFN2a/RBV	$119,878	$6,730	6%
TVR + PegIFN2a/RBV	$132,114	$18,966	17%
BOC + PegIFN2b/RBV	$129,803	$16,655	15%
With cirrhosis			
SOF + PegIFN2a/RBV	$132,592	—	—
SMV + PegIFN2a/RBV	$166,165	$33,573	25%
TVR + PegIFN2a/RBV	$163,394	$30,802	23%
BOC + PegIFN2b/RBV	$155,460	$22,868	17%
HIV-coinfected			
SOF + PegIFN2a/RBV	$135,830	—	—
SMV + PegIFN2a/RBV	$155,868	$20,038	15%
TVR + PegIFN2a/RBV	$175,551	$39,721	29%
BOC + PegIFN2b/RBV	$193,096	$57,266	42%
Treatment experienced			

All patients			
SOF + PegIFN2a/RBV	$145,628	—	—
SMV + PegIFN2a/RBV	$161,485	$15,857	11%
TVR + PegIFN2a/RBV	$206,626	$60,998	42%
BOC + PegIFN2b/RBV	$234,592	$88,964	61%

BOC = boceprevir; HIV = human immunodeficiency virus; PegIFN2a = peginterferon alfa-2a; PegIFN2b = peginterferon alfa-2b; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response; TVR = telaprevir.

When considering the lifetime incremental cost per QALY gained, sofosbuvir + PegIFN/RBV was shown to be the most cost-effective treatment option for genotype 1 patients. The sofosbuvir regimen dominated (i.e., is less costly and more effective than) simeprevir + PegIFN/RBV, telaprevir + PegIFN/RBV and boceprevir + PegIFN/RBV.

Furthermore, initiation of HCV therapy at an earlier disease stage (i.e., in patients without cirrhosis, with METAVIR fibrosis scores F0-F3) yielded substantially fewer cases of CC, DCC, HCC, liver transplant, and HCV-related death, stemming from higher SVR rates among non-cirrhotic patients than cirrhotic patient. Consequently, the downstream total cost of care associated with advanced disease will be reduced substantially with earlier initiation of treatment. For patients infected with HCV genotype 1, cases of liver disease complications were threefold lower, and total costs of care were 38% to 46% lower when therapy was initiated at the non-cirrhotic stage than at the cirrhotic stage.

Several assumptions and model inputs may explain the discrepancies between these analyses and the CTAF report, which are outlined below:

1. Clinical considerations represented in model
   The most sensitive drivers in any HCV cost-effectiveness model are drug costs and SVR rates of the various regimens. The CTAF network analysis for SOF estimated an SVR of 83% among GT 1 treatment-naïve patients, whereas clinical studies with SOF showed SVR rates of 89-91%. Among GT 1 treatment-experienced patients, the CTAF model estimated an SVR rate of 67%; however, 71% is the estimated response rate based on analysis conducted by the FDA utilizing multiple baseline factors traditionally associated with lower response to interferon-based treatment that would predict the response rate in patients who previously failed pegylated interferon and ribavirin therapy (SOF US Prescribing Information). To ensure consistency of the analysis, it is important to understand the details of how the patient populations were defined (ie. proportions of nulls/partials/relapsers in the treatment-experienced population). For example, 90% was quoted as simeprevir's SVR12 in treatment-experienced trials, which reflects the SVR in relapsers and not null or partial responders. The FDA analysis estimated an SVR rate of 51% for SMV + PegIGN + RBV for patients with the combination of *IL28B* non-CC alleles, HCV RNA >800,000 IU/mL and Metavir F3/F4 fibrosis.
   In addition, the draft CTAF report did not provide estimates of SVR rates for SOF in certain subpopulations vs. comparators (e.g., SOF in cirrhotic vs. non-cirrhotic or HIV/HCV co-infection) for GT 1 patients. These data are provided in the response to Question 3, above.
   Sofosbuvir phase 3 clinical trials had expanded inclusion criteria that reflected patient characteristics in real-world settings. The sofosbuvir trials overall included 20% of patients with cirrhosis and also patients who were older than 65 years, and had no restrictions for body weight, depression, or methadone use. The efficacy of sofosbuvir has been established in patients HCV across all genotypes, including those with HCC meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 coinfection. Based on registrational trial data and described in the new AASLD/IDSA guidelines, sofosbuvir-based regimens are expected to result in the following clinical benefits to the overall treatment goal of SVR. High SVR rates with a 12- or 24-week duration of therapy across HCV genotypes 1, 2, 3, 4, 5, and 6:
   - Improved safety and tolerability, with no incremental adverse events, resulting in low discontinuation rates (1%-3%)

- High barrier to resistance, with no patients developing resistance to sofosbuvir when used in combination with ribavirin ± peginterferon and no baseline resistance screening required
- Simplified dosing (once daily, no food requirements, no response-guided therapy, minimal drug-drug interactions)
- Efficacy in the real-world setting across a broad spectrum of patients with HCV, including those who have compensated cirrhosis, are elderly, have a high BMI, receive methadone, have psychiatric comorbidities, are awaiting a liver transplant, are reinfected with HCV post-transplant, or are coinfected with HIV

The draft CTAF report utilized adverse event rates based on clinical trials, and reports of adverse events and discontinuations from real world studies were not mentioned.

In the HCV-TARGET cohort, an observational analysis of patients treated with protease inhibitors s at 103 academic and community centers, serious adverse events occurred in 8% of telaprevir-treated patients and 13% of boceprevir-treated patients. As in the French cohort, hepatic decompensation events occurred in 5% of patients in the HCV-TARGET cohort, and early discontinuation of all HCV drugs due to an adverse event occurred in 10% of patients. Respectively, 33% and 40% of telaprevir-treated patients and boceprevir-treated patients used epoetin-alfa to manage anemia (Gordon et al., 2013b). As noted in studies by Bichoupan and colleagues (2013a; 2013b) and Sethi colleagues (2013) evaluating cost per SVR, these adverse events contribute substantially to higher costs. Based on lower real-world SVR rates than seen in phase 3 trials, the overall real-world cost per SVR was estimated to be $173,000 to $189,000 in these two single-center studies, and increased to $254,000 to $267,000 in patients with cirrhosis at baseline (Dieterich et al., 2012; Sethi et al., 2013).

In a real-world setting, early discontinuations often occur because of patient noncompliance, virologic failure, or adverse events. Nguyen and colleagues (2013) demonstrated in a large claims database analysis that treatment completion for both PegIFN/RBV therapy and PI-based triple therapy regimens is suboptimal in the real-world clinical setting. The steepest drop in dual therapy occurred between weeks 12 and 24: treatment completion rates declined by more than 35% during this time period. Interferon-related side effects, particularly depression and fatigue, tend to increase in severity over time, which may contribute to higher discontinuation rates observed at week 12 and after. Nguyen and colleagues (2013) also found that more than 50% of the patients receiving telaprevir- and boceprevir-based triple therapy did not complete the intended 24 weeks of therapy (Nguyen et al., 2013). The draft CTAF report did not mention the expected benefit of a regimen with a shorter duration of therapy or an interferon-free regimen that would lead to lower discontinuation rates.

2. Consideration of factors for progressing disease

Underlying risk factors can accelerate disease progression. Studies have shown that older age at time of infection, male gender, the degree of inflammation and fibrosis present on the liver biopsy, coinfection with HIV or HBV, and comorbid conditions such as immunosuppression, insulin resistance, nonalcoholic steatohepatitis, hemochromatosis, and schistosomiasis, as well as chronic alcohol use are risk factors for the progression of chronic hepatitis C to cirrhosis (Davis et al., 2010, Grebely and Dore, 2011). The median age of patients with HCV is increasing, as observed in a VA study where the median age was 59, suggesting these patients are more likely to present to health care systems with advanced fibrosis (Backus et al., 2013).

The draft CTAF model does not take into account the widespread prevalence of HCV co-infection in HIV patients. Prevalence rates for HCV co-infection in HIV patients are significant and may approach 30% in certain population (Soriano et al., 2002). Coinfection with HIV reduces the likelihood of spontaneously clearing HCV, increases HCV RNA levels in the blood, accelerates liver disease progression, and reduces the response to interferon-based therapies compared with HCV monoinfection (Grebely and Dore, 2011). HCV infection results in a significant increase in mortality in HIV infected individuals resulting in 14% to 18% of all deaths in HIV-infected patients from liver disease, making it the most common non–HIV-associated cause of death in this population (Price and Thio, 2010)

Another model of the long-term effects of HCV infection predicted that complications from chronic HCV continue to accumulate as patients continue to age and exhibit sequelae of disease (Davis et al., 2010). The

majority of baby boomers with HCV have had 20 to 30 years of chronic infection, and are the most at risk for advanced fibrosis. Cirrhosis in HCV-infected persons is expected to peak at 1 million persons in 2020 and decline slowly thereafter (Davis et al., 2010). In 2009, an estimated 11.7% of patients with HCV-related cirrhosis had decompensated liver disease (Davis et al., 2010). The total number with liver failure is expected to peak in 2022 at approximately 150,000 cases (Davis et al., 2010). Hepatocellular carcinoma occurs in approximately 1.3% of patients with chronic HCV infection (Kanwal et al., 2011) and the incidence of HCV-related HCC is expected to peak at 14,000 cases per year in 2019 (Davis et al., 2010). In the current model, disease progression estimates are assumed to be the same, regardless of any of the above risk factors.

3. The most costly liver disease sequelae are hepatocellular carcinoma (HCC), decompensated cirrhosis (DCC), and liver transplant, and these are not individually accounted for in the draft CTAF model.

   The CTAF model collapses all liver complications into one condition, regardless of severity, with an estimate of $25,728 per year based on a Florida Medicaid population (Menzin 2013). However, published costs of liver disease by severity show substantially higher costs in association with progression of liver disease (Gordon SC, et al. Hepatology 2012 and C McAdam-Marx et al. J Manag Care Pharm 2011).

McAdam-Marx et al. Per Patient Per Year Costs	**F0-F3**	**CC (F4)**	**DCC**	**HCC**	**Liver Transplant Year 1**	**Liver Transplant Year 2+**
All HCV Cost	$5,870	$5,330	$27,845	$43,671	$168,643	$38,015
N	26,977	1,521	4,249	959	891	891
Gordon et al. Per Patient Per Year Costs	**F0-F3**	**CC (F4)**	**DCC**	**HCC**	**Liver Transplant Year 1**	**All ESLD**
All HCV Cost	$7,804	$12,810	$42,824	$112,537	$145,045	$59,172
N	41,858	3,718	6,560	1,086	574	8,220

   In the CTAF model, the SVR vs. non-SVR costs are based on Manos 2013 study that evaluated a largely non-cirrhotic patient cohort (10% cirrhosis rate in Kaiser population) and the follow-up time was limited to 5 years. In contrast, another study by Gordon et al. found mean follow-up PPPM costs were around 29% lower in the treated non-cirrhotic vs. untreated end stage liver disease patients. Follow-up costs were >5-fold higher for untreated end stage liver disease patients vs. treated non-cirrhotic disease, suggesting that early intervention with successful treatment may prevent progression of liver disease and thus reduce costs. (Gordon S.C., et al. Aliment Pharmacol Ther. 2013).

   By utilizing more granular considerations of liver disease complications, updated transition probabilities and costs, SOF cost-effectiveness analyses show substantial reductions in cases of CC, HCC, DCC, liver transplant and HCV-related death when treating with SOF-based regimens versus other comparators. In the short-term, sofosbuvir is estimated to have the lowest cost per SVR in genotype 1 patients, including difficult-to-treat patients as shown in table 1.

Other model considerations include the following:

4. The budget impact model includes the assumption that 50% of patients with HCV who are aware of their disease will be treated; however, the clinical capacity to manage the treatment all these patients may not be feasible. Therefore, the real costs of managing these patients may be lower. In addition, the CTAF model

does not take into account the increased costs of following HCV-positive patients compared to non-infected patients.

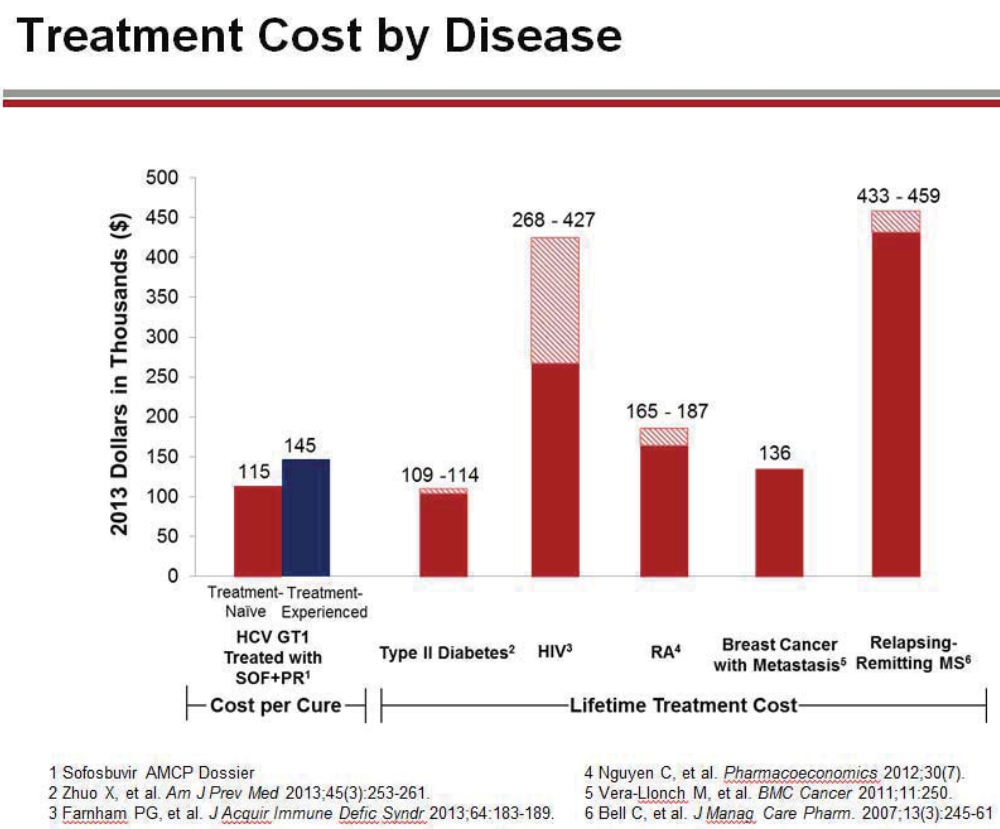
5. Patient perspective is not accounted for in the draft CTAF analysis. Therefore, it is important to consider the implications of patient-reported outcomes data on disability and adherence to treatment.

   The health-related quality of life (HRQoL) of patients treated with sofosbuvir-based regimens was evaluated from the Phase 3 studies FISSION, POSITRON, NEUTRINO, and FUSION by the Short Form-36 version 2 (SF-36v2). In FISSION, genotype 2 and 3 patients treated with SOF+RBV had better HRQoL scores at the end of treatment compared to patients receiving Peg-IFN+RBV. In POSITRON, at any time point, there was no significant difference in HRQoL scores between genotype 2 and 3 patients treated with SOF+RBV and those on placebo. In FUSION, an additional 4 weeks of SOF+RBV (16 weeks total) did not negatively impact HRQoL scores. In NEUTRINO, adding SOF to Peg-IFN+RBV for treatment of genotype 1 did not add further decrements to the HRQoL scores compared to historical scores with Peg-IFN+RBV. Achievement of SVR12 was associated with improvement in some domains of the SF-36. Therefore, shorter, highly effective, and more tolerable regimens provide HRQoL benefit to patients with chronic hepatitis C.

   The impact of sofosbuvir-based regimens on fatigue (measured by FACIT-F), HCV-specific quality of life (CLDQ), and work productivity (WPAI) was evaluated from the NEUTRINO and FUSION studies. The results were consistent with SF-36 score trends. The interferon-free regimen had significantly smaller decrements in fatigue scores, CLDQ-HCV, and work productivity scores, particularly presenteeism, than the interferon-containing regimen. Fatigue and receiving the interferon-containing regimen were independently associated with lower scores. By 4-12 weeks post-treatment, scores either returned to their baseline values or some domains improved in those achieving SVR-12. These studies show that achievement of SVR-12 has not only clinical benefits but also humanistic benefits. (Younossi ZM, et al. J Hepatol 2014. Article in Press).

6. A public health implication to consider with HCV is that unlike other disease areas, HCV can be cured, so the benefits of treatment are nearly instantaneous instead of the need for lifelong therapy as seen with HIV. This gives an opportunity to eradicate HCV from the entire population.

7. Lifetime treatment costs for chronic HCV should be placed into context of other disease areas.



1 Sofosbuvir AMCP Dossier
2 Zhuo X, et al. *Am J Prev Med* 2013;45(3):253-261.
3 Farnham PG, et al. *J Acquir Immune Defic Syndr* 2013;64:183-189.
4 Nguyen C, et al. *Pharmacoeconomics* 2012;30(7).
5 Vera-Llonch M, et al. *BMC Cancer* 2011;11:250.
6 Bell C, et al. *J Manag Care Pharm*. 2007;13(3):245-61

Of note, the ICER for treated HCV compared with no treatment was estimated to be $11,000/QALY by Hagan et al.

References

AASLD/IDSA HCV Guidance Recommendations for Testing, Managing, and Treating Hepatitis C; www.hcvguidelines.org ; January 29, 2014.

Backus L, Belperio P, Shahoumiam T, Cheung R, Mole L. Comparative Effectiveness of Boceprevir- and Telaprevir-Based Therapy in US Veterans. Poster presented at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013a. Washington, DC. Poster no. 1848.

Bichoupan K, Martel-Laferriere V, Ng M, Schonfeld EA, Pappas A, Crismale J, et al. Estimated costs of telaprevir-based triple therapy, including adverse event management at the Mount Sinai Medical Center, NY: $195,000 per SVR12. Poster presented at the 48th Annual Meeting of the European Association for the Study of the Liver; April 24-28, 2013b. Amsterdam, The Netherlands.

Bichoupan K, Martel-Laferriere V, Sachs D, Ng M, Schonfeld E, Pappas A, et al. Costs of telaprevir-based triple therapy including adverse event management at the Mount Sinai Medical Center, NY $189,000 per SVR. Oral presentation presented at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013a. Washington, DC. Presentation no. 244.

Curry MP, Forns X, Chung R, et al. Pretransplant Sofosbuvir and Ribavirin to Prevent Recurrence of HCV Infection After Liver Transplantation [Presentation 213]. Paper presented at: The Liver Meeting® 2013 The 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); November 1-5, 2013; Washington, D.C.

Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology. 2010 Feb;138(2):513-21, 521.e1-6.

FDA Antiviral Drugs Advisory Committee Meeting Background Package for NDA 205123: Simeprevir; October 24, 2013.

Gordon SC, Hamzeh FM, Pockros PJ, Hoop RS, Buikema AR, Korner EJ, Terrault NA. Hepatitis C virus therapy is associated with lower health care costs not only in noncirrhotic patients but also in patients with end-stage liver disease. Aliment Pharmacol Ther. 2013a;38:784-793.

Gordon SC, Muir AJ, Lim JK, Pearlman B, Argo CK, Neff GW, et al. The frequency and management of adverse events in chronic hepatitis C (HCV) treated with boceprevir or telaprevir: real world experience from HCV-TARGET Longitudinal Observational Study. Poster presented at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013b. Washington, DC. Poster no. 1866.

Gordon SC, Pockros PJ, Terrault NA, Hoop RS, Buikema A, Nerenz D, Hamzeh FM. Impact of disease severity on healthcare costs in patients with chronic hepatitis C (CHC) virus infection. Hepatology. 2012;56(5):1651-60.

Grebely J, Dore GJ. What is killing people with hepatitis C virus infection? Semin Liver Dis. 2011 Nov;31(4):331-9.

Hagan LM, Yang Z, Ehteshami M, Schinazi RF. All-oral, interferon-free treatment for chronic hepatitis C: cost-effectiveness analyses. J Viral Hepat. 2013 Dec;20(12):847-57.

Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med.* May 16 2013;368(20):1867-1877.

Jacobson IM, Ghalib R, Rodriguez-Torres M, et al. SVR results of a once-daily regimen of simeprevir (SMV, TMC435) plus sofosbuvir (SOF, GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naïve and prior null responder patients: The COSMOS study [Presentation LB-3]. Paper presented at: The Liver Meeting® 2013 The 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); November 1-5, 2013; Washington, D.C.

Kanwal F, Hoang T, Kramer JR, Asch SM, Goetz MB, Zeringue A, et al. Increasing prevalence of HCC and cirrhosis in patients with chronic hepatitis C virus infection. Gastroenterology. 2011 Apr;140(4):1182-8.

Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med.* May 16 2013;368(20):1878-1887.

Mangia A, Kugelmas M, Everson G, et al. Virologic Response Rates to Sofosbuvir-Containing Regimens Are Similar in Patients With and Without Traditional Negative Predictive Factors: a Retrospective Analysis of Phase 3 Data [Poster 1115]. Paper presented at: The Liver Meeting® 2013 The 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); November 1-5, 2013; Washington, D.C.

McAdam-Marx C, McGarry LJ, Hane CA, Biskupiak J, Deniz B, Brixner DI. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: a managed care perspective. J Manag Care Pharm. 2011;17(7):531-46.

McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009; 361(6):580-93.

Nguyen MH, Brooks L, Livornese RC. Suboptimal treatment rates and treatment completion rates of chronic hepatitis C virus therapy in patients with comorbidities: analysis of a large real-world US cohort. Poster presented at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013. Washington, DC. Poster no. 2040.

Price J, Thio C. Liver disease in the HIV-infected individual. Clin Gastroenterol Hepatol. 2010;8(12):1002-12.

Sethi N, Vong A, Firdoos S, Rourke M, and Afdhal NH. Analysis of direct and indirect costs of HCV care with PEG-Interferon triple therapy. Oral presentation presented at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013. Washington, DC. Presentation no. 1847.

Soriano V, Sulkowski M, Bergin C, Hatzakis A, Cacoub P, Katlama C, et al. Care of patients with chronic hepatitis C and HIV co-infection: recommendations from the HIV±HCV international panel. AIDS 2002;16:813-828.

SOVALDI (sofosbuvir) prescribing information. Foster City (CA): Gilead Sciences, Inc.; December 2013.

Sulkowski M, Rodriguez-Torres M, Lalezari J, et al. All-Oral Therapy With Sofosbuvir Plus Ribavirin For the Treatment of HCV Genotype 1, 2, and 3 Infection in Patients Co-infected With HIV (PHOTON-1) [Presentation 212]. Paper presented at: The Liver Meeting® 2013 The 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); November 1-5, 2013; Washington, D.C.

Younossi ZM, Gordon SC, Saab S, et al. A Decision-Analytic Markov Model to Evaluate the Health Outcomes of Sofsbuvir for Previously Untreated Patients with Hepatitis C Virus Genotype 1 Infection. Poster presented at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013a. Washington, DC. Poster no. 368.

Younossi ZM, Gordon SC, Saab S, et al. A decision-analytic markov model to evaluate the health outcomes of sofosbuvir for previously untreated patients and those without treatment options with chronic hepatitis C Virus genotype 2 infection. Poster presented at ISPOR 16th Annual European Congress; November 2-6, 2013c. Dublin, Ireland. Value Health. 2013;16(7) A341. Abstract no. PIN3.

Younossi ZM, Saab S, Gordon SC, et al. Evaluation of Long-Term Health Outcomes Associated with Earlier Versus Later Initiation of Treatment in Previously Untreated Patients with Chronic Hepatitis C Virus Genotype 1 Infection. Poster presented at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013b. Washington, DC. Poster no. 369.

Younossi ZM, Stepanova M, Henry L, Gane E, Jacobson IM, Lawitz E, Nelson D, Gerber L, Nader F, Hunt S. Effects of Sofosbuvir-Based Treatment, With and Without Interferon, on Outcome and Productivity of Patients With Chronic Hepatitis C. Clin Gastroenterol Hepatol. 2013 Dec 6.

Younossi ZM, Stepanova M, Henry L, Gane E, Jacobson IM, Lawitz E, Nelson D, Nader F, Hunt S. Minimal impact of sofosbuvir and ribavirin on health related quality of life in Chronic Hepatitis C (CH-C). J Hepatol. 2013 Dec 11. [Epub ahead of print]

Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir + Ribavirin for 12 or 24 Weeks for Patients With HCV Genotype 2 or 3: the VALENCE Trial [Poster 1085]. Paper presented at: The Liver Meeting® 2013 The 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); November 1-5, 2013; Washington, D.C.

To: **California Technology Assessment Forum**

From: **Hans Reiser, M.D.**
Senior Vice President, Medical Affairs
Gilead Sciences, Inc.

Date: **March 3, 2014**

Re: **Comments on " The Comparative Clinical Effectiveness and Value of Simeprevir and Sofosbuvir in the Treatment of Chronic Hepatitis C Infection" Draft Report**

We read with interest the draft CTAF report entitled "The Comparative Clinical Effectiveness and Value of Simeprevir and Sofosbuvir in the Treatment of Chronic Hepatitis C Infection", and appreciate the opportunity to provide clarification regarding the clinical effectiveness and cost effectiveness data that has been generated with SOVALDI (sofosbuvir).

The following commentary is structured according to the questions which will be posed to the panel at the March 10, 2014 public meeting in San Francisco.

Comparative Clinical Effectiveness

SOF is an HCV nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C in adults as a component of a combination antiviral treatment regimen. SOF efficacy has been established in subjects with HCV GT 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma (HCC) meeting Milan criteria (awaiting liver transplantation [LT]) and those with HCV/HIV-1 co-infection (SOVALDI package insert).

Gilead performed six Phase 3 clinical trials comprising 1,851 patients to demonstrate the effectiveness of SOF-based regimens. The real-world nature of HCV patients was reflected by expanded inclusion criteria that enrolled a proportionate number of non-white patients as in the general population, had no upper limit of age or BMI, allowed for opiate replacement therapy, and included approximately 20% cirrhotics (Jacobson et al, NEJM 2013; Lawitz et al, NEJM 2013; Sulkowski et al, AASLD 2013; Zeuzem et al, AASLD 2013).

Genotype 1

1. Among patients with genotype 1, is the evidence adequate to demonstrate that the combination of sofosbuvir with pegylated interferon and ribavirin (PegIFN + RBV) is equivalent or superior to triple therapy with telaprevir or boceprevir + PegIFN + RBV?

Based on clinical trial data, SOF+PegIFN+RBV for 12 weeks has many advantages for patients compared to regimens containing PI+PegIFN+RBV for 24-48 weeks:

- SOF+PegIFN+RBV achieved the highest overall SVR rates of an FDA-approved regimen (90%), the highest efficacy in GT1 with SVR rates of 89%, in GTs 4, 5 & 6 (97%), and the highest overall SVR rate in cirrhotics (80%)

- SOF+PegIFN+RBV was a well tolerated regimen, with few treatment discontinuations (<2%), no additional AEs in addition to PEG-IFN+RBV, no increase in anemia or neutropenia, and no need for bone marrow stimulating agents such as erythopoetin, filgrastim or eltrombopag
- High barrier to resistance - no resistance in any Phase 3 trial
- SOF+PegIFN+RBV is administered orally, once daily, without regard to food, for a finite 12 week duration vs 24-48 weeks of Response Guided Therapy with protease inhibitors
- SOF is renally cleared, with a lower potential for drug-drug interactions (DDIs) than protease inhibitors with numerous CYP450 interactions

NEUTRINO is a phase 3, open-label, historical control, single-arm trial that evaluated SOF + PegIFN + RBV for 12 weeks of treatment in 327 treatment-naïve (TN) subjects infected with HCV GT 1, 4, 5 or 6, with no response guided algorithm (Lawitz et al, NEJM 2013). SVR was the primary endpoint, defined as HCV RNA < 25 IU/mL, at 12 weeks after the end of treatment. The primary endpoint was compared to a predetermined historical control response rate of 60% for protease inhibitor + PegIFN + RBV triple therapy based on discussions with the FDA, modeled to reflect the characteristics of patients in NEUTRINO with a target of 20% cirrhotics. A sample size of 300 subjects provided 90% power to detect a 9% improvement in SVR12 rate from 60% to 69% using a two-sided one-sample binomial test at the 0.05 significance level.

Treated subjects had a median age of 54 years; 89% had HCV GT 1 and 11% had HCV GT 4, 5 or 6; 17% had cirrhosis; 29% had the *IL28B* CC allele, 55% had the CT allele, and 16% had the TT allele; 64% were male; 79% were White; 17% were Black; 14% were Hispanic or Latino; mean BMI was 29 kg/m^2; and 78% had baseline HCV RNA > 6 $\log_{10}$ IU/mL. Because of the expanded inclusion criteria, NEUTRINO had a large number of patients with traditional negative predictors of response to PegIFN + RBV regimens, due to cirrhosis, older age, high BMI and non-white patients.

The overall SVR12 rate (90% [295/327]) was superior to historical control SVR rate of 60% ($P < 0.001$). SVR12 was achieved by 89% (261/292) of subjects with HCV GT 1 (GT 1a- 92% [206/225]; GT 1b-82% [54/66]). The difference in GT1a and GT1b response rates is accounted for by a lower proportion of *IL28B* CC genotype in the GT1b subjects (20%) than among GT 1a subjects (32%). The SVR12 rate in cirrhotic patients was 80% overall and 81% in GT1 patients, which is the highest efficacy published in a phase 3 clinical trial to date.

High SVR12 rates were achieved across all GT 1, 4, 5, and 6 subjects despite the presence of traditional negative predictive factors [91% SVR in non-Black vs. 87% SVR in Black subjects; 90% SVR in BMI <35 kg/m^2 vs. 91% SVR for BMI ≥35 kg/m^2; 91% SVR in *IL28B* non-TT vs. 86% SVR in *IL28B* TT] (Mangia et al, AASLD 2013).

No subject experienced virologic breakthrough on-treatment. No resistance-associated mutations, including *S282T*, were observed by population or deep sequencing (1% cut-off) among subjects who did not achieve SVR.

The safety assessment of the short duration of SOF + PegIFN + RBV for 12 weeks is based on the overall population of GT 1, 4, 5, and 6 subjects. The safety profile was consistent with that of PegIFN + RBV alone, with 1.5% (5/327) discontinuations due to AEs, which is lower than historically been seen with longer durations (24-48 weeks) of response guided therapy with PegIFN + RBV + PIs (13-14%).

For the purposes of determining a control SVR rate for the network meta-analysis, based on the calculated historical control SVR rate of 60% for PI + PegIFN + RBV triple therapy in NEUTRINO, any estimate of an SVR rate for double therapy with PegIFN + RBV must be lower than 60%. Historical SVR rates for PegIFN + RBV have consistently been in the low 40% range (McHutchison, et al.). Recent PegIFN + RBV control arms from QUEST-1 and QUEST-2 containing a lower proportion (11-13%) of cirrhotic patients and a higher proportion of GT1b subjects yielded SVR rates of 50% (FDA Antiviral Drugs Advisory Committee Meeting Background Package). Thus, the SVR input to the network meta-analysis of 57% based on 26 patients from the PROTON study is spuriously high, and the inputs to the CTAF network meta-analysis require downward revision.

The recent AASLD/IDSA HCV Guidance Recommendations for Testing, Managing, and Treating Hepatitis C recommend SOF + PegIFN + RBV x 12 weeks regardless of subtype, with Class I/Level A evidence and strength, indicating that it is "Optimal treatment favored for most patients". The combination of PegIFN + RBV ± TVR or BOC x 24-48 weeks is specifically not recommended, meaning that the "Treatment is clearly inferior or is deemed harmful. Unless otherwise indicated, such regimens should not be administered to patients with HCV infection" (AASLD/IDSA HCV Guidance, 2014).

2. Among patients with genotype 1, is the evidence adequate to demonstrate that simeprevir + PR is equivalent or superior to triple therapy with telaprevir or boceprevir + PR?

No comment.

3. Among patients with genotype 1, is the evidence adequate to demonstrate that sofosbuvir + PR is equivalent or superior to simeprevir + PR?

NEUTRINO (SOF + PegIFN + RBV x 12 weeks, no response guided therapy) and QUEST-1 and QUEST-2 (SMV + PegIFN + RBV x 24-48 weeks, with response guided therapy) were studies conducted contemporaneously in HCV subjects infected with GT1 virus, however with different Inclusion and Exclusion criteria, and different patient Baseline Characteristics. The FDA combined QUEST-1 and QUEST-2 due to identical study designs, and reference is made to the FDA Antiviral Drugs Advisory Committee Meeting Background Package for NDA 205123: Simeprevir; October 24, 2013.

NEUTRINO specifically targeted increased enrollment of patients with cirrhosis (17%), had no upper age or BMI limits, permitted opiate replacement therapy, and had lower limits of platelets (≥ 90,000/mm) and neutrophils (≥ 1500/mm^3 or 1000/mm^3 in Black subjects). This is represented in the table below, illustrating that the NEUTRINO trial enrolled more patients with historical negative predictors of SVR than the QUEST-1 and QUEST-2 trials.

Comparison of baseline characteristics between NEUTRINO and QUEST-1/QUEST-2

Inclusion criterion	**NEUTRINO**	**QUEST-1/QUEST-2**
Median age, years	54	46-48
Median BMI, kg/m^2	29	26-27
Genotype 1a/1b/4,5,6	69%/20%/11%	41-56%/44-58%/0%
% Caucasian/% Black	79%/17%	89%/8%
IL28B CC %	29%	29%
% cirrhotic	17%	7-12%

The overall SVR rate from NEUTRINO for GT1 subjects was 89%, compared to the overall SVR rates from the combined QUEST-1 and QUEST-2 trials of 80%. Among cirrhotic patients, the GT1 SVR rate in NEUTRINO was 81%, compared to 58-65% in QUEST-1 and QUEST-2.

The Q80K mutation is present in 40-50% of HCV patients infected with GT1a virus. In the pooled QUEST-1 and QUEST-2 trials, the SVR12 rate in GT1a subjects with the Q80K polymorphism was 58% in the SMV+PegIFN+RBV group, and 55% in the PegIFN+RBV Group (p=NS). The Q80K mutation does not affect viral sensitivity to sofosbuvir, and the SVR rate for GT1a patients in NEUTRINO was 92%.

The SVR rates for other historical negative predictive factors are shown below:

SVR	**NEUTRINO**	**QUEST-1/QUEST-2**
Black subjects	87%	67%
IL28B non-CC	87%	66%
Baseline HCV RNA > 800,000	89%	77%
Age > 50 (NEUTRINO) or Age >45 (QUEST 1 and 2)	88%	75%
Combination of *IL28B* non-CC alleles, HCV RNA >800,000 IU/mL and Metavir F3/F4 fibrosis	71%	51%

4. Among patients with genotype 2, is the evidence adequate to demonstrate that the combination of sofosbuvir and ribavirin (R) is equivalent or superior to pegylated interferon and ribavirin (PR)?

See responses below to both Questions 4 and 5.

5. Among patients with genotype 3, is the evidence adequate to demonstrate that sofosbuvir + R is equivalent or superior to PR?

SOF + RBV has been studied for the treatment of HCV GT 2 or 3 in five phase 3 studies comprised of treatment-naïve (TN) subjects (FISSION), subjects previously treated with interferon (IFN)-based regimen (FUSION), IFN-ineligible, -intolerant, or –unwilling (POSITRON) and in both TN and treatment-experienced (TE) subjects (VALENCE). PHOTON-1, a phase 3 study, evaluated TN or TE subjects with HCV/HIV-1 co-infection due to any genotype.

FISSION: SOF + RBV vs. PegIFN + RBV in TN Subjects with HCV GT 2 or 3

FISSION is a non-inferiority, phase 3, randomized, open-label, active-controlled trial that evaluated 12 weeks of SOF + RBV therapy compared to 24 weeks of PegIFN + RBV therapy in TN subjects infected with HCV GT 2 or 3 (Lawitz et al, NEJM 2013). The RBV dose used in the SOF + RBV arm was weight-based (1000–1200 mg daily) and in the PegIFN + RBV arm was 800 mg daily regardless of weight (consistent with approved labeling in the United States), administered in two divided doses in both treatment groups. Subjects were randomized in a 1:1 ratio and stratified by cirrhosis (presence vs. absence), HCV GT (2 vs. 3), and baseline HCV RNA level (< 6 $\log_{10}$ IU/mL vs. ≥ 6 $\log_{10}$ IU/mL). Treated subjects (N = 499) had a median age of 50 years; 72% had HCV GT 3 and 20% had cirrhosis; 66% of the subjects were male; 87% were White; 3% were Black; 14% were Hispanic or Latino; mean body mass index (BMI) was 28 kg/m^2; and 57% had baseline HCV RNA levels > 6 $\log_{10}$ IU/mL.

SVR in GT 2 subjects was 95% on SOF + RBV and 78% on PegIFN + RBV, favoring SOF+RBV with non-overlapping 95% confidence intervals. In GT 3 subjects, SVR was 56% on SOF + RBV and 63% on PegIFN + RBV, which was non-inferior. *IL28B* genotype did not make a difference in response rates for the SOF + RBV arm**.**

SOF + RBV was associated with significantly fewer AEs than PegIFN + RBV, and the SOF + RBV safety profile was consistent with that of RBV alone. Discontinuation due to AEs occurred in 1% of subjects in the SOF + RBV arm vs. 11% in the PegIFN + RBV arm. The influenza-like symptoms and fever that are characteristic of interferon treatment were reported in 18% and 16% of subjects receiving PegIFN, respectively, but in only 3% of subjects receiving SOF. Treatment-emergent depression or worsening depression, occurred in 17% of subjects receiving PegIFN, as compared with 6% of subjects receiving SOF + RBV.

Summary of Commonly Reported AEs (≥ 15% in Either Arm) in FISSION

AEs, n (%)	**SOF + RBV 12 weeks n = 256**	**PegIFN + RBV 24 weeks n = 243**	***P*-value***
Fatigue	92 (36)	134 (55)	< 0.0001
Headache	64 (25)	108 (44)	< 0.0001
Nausea	46 (18)	70 (29)	0.0057
Insomnia	31 (12)	70 (29)	< 0.0001
Depression	16 (6)	42 (17)	< 0.001
Rash	23 (9)	43 (18)	0.0052
Diarrhea	23 (9)	42 (17)	0.0075
Irritability	25 (10)	40 (16)	0.0328
Decreased appetite	17 (7)	44 (18)	0.0001
Myalgia	21 (8)	40 (16)	0.0060
Pruritus	19 (7)	42 (17)	0.0009
Flu-like symptoms	7 (3)	44 (18)	< 0.0001
Chills	7 (3)	43 (18)	< 0.0001

**P*-value from 2-sided Fisher exact Test

VALENCE: SOF + RBV in TN or TE Subjects with HCV GT 2 or 3

VALENCE is a phase 3 study conducted to evaluate SOF + RBV for 12 weeks in HCV GT 2 subjects or 24 weeks in HCV GT 3 subjects who were either TN or TE (did not achieve SVR with prior IFN-based treatment), including subjects with compensated cirrhosis. Treated subjects (N = 419) had a median age of 51 years; 60% male; median BMI 25 kg/m^2; mean baseline HCV RNA level 6.4 $\log_{10}$IU/ml; 78% had HCV GT 3; and 65% were prior relapsers (Zeuzem et al, AASLD 2013).

The overall SVR rate was 93% among HCV GT 2 subjects treated with 12 weeks of SOF + RBV and 84% among HCV GT 3 subjects treated with 24 weeks of SOF + RBV. The table below presents additional response rates for the treatment groups. No resistance-associated mutations, including *S282T*, were observed by population or deep sequencing (1% cut-off) among subjects who did not achieve SVR.

Response Rates in VALENCE[4]

	GT 2 **SOF + RBV 12 Weeks** **n = 73**	**GT 3** **SOF + RBV 24 Weeks** **n = 250**
Overall SVR	93% (68/73)	84% (210/250)
TN	97% (31/32)	93% (98/105)
Non-cirrhotic	97% (29/30)	93% (86/92)
Cirrhotic	100% (2/2)	92% (12/13)
TE	90% (37/41)	77% (112/145)
Non-cirrhotic	91% (30/33)	85% (85/100)
Cirrhotic	88% (7/8)	60% (27/45)
Outcome for Subjects without SVR		
On-Treatment Virologic Failure	0% (0/73)	<1% (1/250)
Relapse	7% (5/73)	14% (34/249)
Other*	0% (0/73)	2% (5/250)

*Other includes subjects who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow up)

The safety profile of SOF + RBV was consistent with that of RBV alone. No additional AEs were observed when treatment was extended from 12 to 24 weeks. Discontinuation due to AEs was low and occurred in 1 subject in each treatment arm.

The recent AASLD/IDSA HCV Guidance Recommendations for Testing, Managing, and Treating Hepatitis C recommend SOF + RBV x 12 weeks (GT2) or SOF+RBV x 24 weeks (GT3), with Class I/Level A or Level B evidence and strength, indicating that it is "Optimal treatment favored for most patients". The combination of PegIFN + RBV x 24-48 weeks is specifically not recommended, meaning that the "Treatment is clearly inferior or is deemed harmful. Unless otherwise indicated, such regimens should not be administered to patients with HCV infection"

6. Among patients who are ineligible for or intolerant to interferon, is the evidence adequate to demonstrate that sofosbuvir + R is equivalent or superior to no treatment?

The SVR rate is zero for interferon-ineligible or –intolerant chronic HCV patients who do not receive treatment. All currently approved HCV regimens, with the exception of SOF + RBV, require PegIFN, and are therefore contraindicated in interferon-ineligible or –intolerant patients. SOF+RBV provides treatment options to HCV infected patients who would not otherwise receive treatment, and whose liver disease would progress unchecked.

POSITRON is a phase 3, randomized, double-blind, PBO-controlled trial that evaluated 12 weeks of treatment with SOF + RBV (n = 207) compared to PBO (n = 71) in IFN-intolerant, -ineligible, or -unwilling subjects infected with HCV GT 2 or 3 (Jacobson et al, NEJM 2013). Subjects were randomized in 3:1 ratio and stratified by cirrhosis (presence vs. absence). Treated subjects (N = 278) had a median age of 54 years; 49% had HCV GT 3; 16% had cirrhosis; 54% were male; 91% were White; 5% were Black; 11% were Hispanic or Latino; mean BMI was 28 kg/m^2; and 70% had baseline HCV RNA levels > 6 $\log_{10}$ IU/mL.

The proportions of subjects who were IFN-intolerant, -ineligible, or -unwilling were 9%, 44%, and 47%, respectively. Most subjects (81%) had no prior HCV treatment.[3]

The overall SVR12 rate was 78% with SOF + RBV and 0% with PBO *(P* < 0.001). SVR in GT 2 subjects was 93% on SOF + RBV and 0% on PBO. SVR in GT 3 subjects was 61% on SOF + RBV and 0% on PBO.

No subject experienced virologic breakthrough on-treatment. No resistance-associated mutations, including *S282T*, were observed by population or deep sequencing (1% cut-off) among subjects who did not achieve SVR.

The safety profile of SOF + RBV was consistent with that of RBV alone. The most commonly reported AEs were fatigue, nausea, headache and insomnia. Discontinuation due to AEs occurred in 2% of subjects in the SOF + RBV arm vs. 4% in the PBO arm.

Additional data, from HCV/HIV-1 co-infected patients further support that SOF + RBV is an effective and well-tolerated regimen. PHOTON-1 is a phase 3, open-label study conducted to evaluate 12 or 24 weeks of SOF + RBV in subjects with HCV/HIV-1 co-infection (Sulkowski et al, AASLD 2013). Many HCV/HIV-co-infected patients are considered IFN-ineligible.

Because of the lower chance of drug-drug interactions, SOF + RBV was effectively co-administered with multiple ARV agents including inhibitors of HIV-1 protease, reverse transcriptase (non-nucleoside/nucleoside) and integrase. Among GT 1 subjects, 76% achieved SVR12 following 24 weeks of SOF + RBV. SVR rates in subjects with HCV GT 1 were 80% (24/30) in subjects with baseline IL28B CC allele and 75% (62/83) in subjects with baseline IL28B non-CC alleles.

The safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects. SOF was well-tolerated, with a low rate of treatment discontinuations due to AEs overall of approximately 3%. The most commonly reported AEs were fatigue, insomnia, headache, and nausea.

7. Among patients who are ineligible for or intolerant to interferon, is the evidence adequate to demonstrate that the combination of sofosbuvir + simeprevir is equivalent or superior to sofosbuvir + R?

COSMOS is an ongoing, phase 2a, open-label study evaluating the use of SOF 400 mg daily + SMV 150 mg daily ± weight-based RBV for 12 or 24 weeks in GT 1 prior null responders with METAVIR scores of F0-F2 (Cohort 1, n = 80), and treatment-naïve and prior null responders with METAVIR scores of F3-F4 (Cohort 2, n = 87). Prior null response was defined as a failure to achieve a > 2 $\log_{10}$ decline in HCV RNA by Week 12 of a Peg-IFN + RBV regimen (Jacobson et al, AASLD 2013).

Subjects were randomized 2:1:2:1 to SOF + SMV + RBV 12 weeks, SOF + SMV 12 weeks, SOF + SMV + RBV 24 weeks and SOF + SMV 24 weeks. In Cohort 1, 78% of subjects had GT1a, 50% had Q80K baseline polymorphism, 94% had *IL28B* CT or TT haplotype, and 59% had METAVIR score F2. In Cohort 2, 78% of subjects had GT1a, 40% had Q80K baseline polymorphism, 79% had *IL28B* CC or TT haplotype, 47% had METAVIR score F4 and 54% were prior null responders.

Due to the complexity of the COSMOS study design, the SVR results of the subgroups are presented in the table below for Cohort 1 (SVR12 pooled for 12 and 24 weeks arms) and SVR4 rates in Cohort 2 (12

weeks arms only; 24 week data have not been presented) among GT 1a with Q80K and without Q80 K and for GT 1b subjects. Q80K at baseline reduced SVR rates by 10% in SMV-based regimens.

Virologic Response in Cohort 1 and Cohort 2 from the COSMOS Study

	Cohort 1 **SOF + SMV ± RBV** **Pooled 12 and 24 weeks**	**Cohort 2** **SOF + SMV ± RBV** **12 weeks**
SVR 4		
GT1a with Q80K	-	91% (10/11)[b]
GT1a without Q80K	-	100% (21/21)
GT1b	-	100% (8/8)
SVR12		
GT1a with Q80K	89% (24/27)[a]	-
GT1a without Q80K	100% (30/30)	-
GT1b	100% (17/17)	-

[a] 3 relapsed (with baseline Q80K); [b] 1 relapsed (with baseline Q80K)

SOF + SMV ± RBV was generally safe and well-tolerated across both Cohorts 1 and 2. AEs leading to treatment discontinuation were reported in 4 subjects (2%). The most common AEs were fatigue (30%), headache (20%) and nausea (14%). Serious AEs were reported in 3 subjects (anemia, injury, retinal tear). Anemia and hyperbilirubinemia occurred mainly in the RBV-containing arms.

The recent AASLD/IDSA HCV Guidance Recommendations for Testing, Managing, and Treating Hepatitis C recommend SMV+ SOF ± RBV x 12 weeks for interferon-ineligible GT1 patients, with Class I/Level B evidence and strength, indicating that it is "Optimal treatment favored for most patients". The combination of SOF + RBV x 24 weeks, regardless of GT 1 subtype, is an alternative regimen for these patients.

Cost-effectiveness

The draft CTAF report concludes that for the majority of patients, the downstream medical cost benefit of treating most hepatitis C patients with sofosbuvir (SOF) is not outweighed by the upfront cost of treatment. Any cost offsets downstream of treatment with SOF (from fewer liver-related complications) would represent less than 10%-20% of upfront treatment expenditures after 5 years, and only recoup about 66% of upfront treatment costs after 20 years. However, the report finds a stronger value proposition after 20 years for the use of SOF in patients with advanced liver fibrosis.

These findings are in contrast to several recent publications supporting the cost-effectiveness of SOF-based regimens vs. other comparators. (Younossi ZM, et al. AASLD 2013. #368, Younossi ZM, et al. AASLD 2013. #369, Younossi ZM, et al. ISPOR EU 2013, Abstracts accepted to DDW and ISPOR 2014). When evaluated by ICER (incremental cost-effectiveness ratio) or the cost per SVR, SOF-based therapies were shown to be the most cost-effective treatment option for patients infected with HCV GT 1, including those who are difficult to treat (Table 1). These analyses were based on a decision-analytic model that projected health and economic outcomes for patients with chronic HCV infection treated with SOF-based regimens compared with currently available comparators. The state-transition model

had six health states with annual transitions: without cirrhosis, compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), liver transplant and death.

Table 1. Genotype 1 Short-term Base-Case Results: 1-Year Total Cost per Sustained Virologic Response

	Cost per SVR	Increase From Sofosbuvir-based Regimen	Percentage Difference
Treatment naïve			
All patients			
SOF + PegIFN2a/RBV	$116,068	—	—
SMV + PegIFN2a/RBV	$125,950	$9,882	9%
TVR + PegIFN2a/RBV	$136,644	$20,576	18%
BOC + PegIFN2b/RBV	$133,644	$17,576	15%
Without cirrhosis			
SOF + PegIFN2a/RBV	$113,148	—	—
SMV + PegIFN2a/RBV	$119,878	$6,730	6%
TVR + PegIFN2a/RBV	$132,114	$18,966	17%
BOC + PegIFN2b/RBV	$129,803	$16,655	15%
With cirrhosis			
SOF + PegIFN2a/RBV	$132,592	—	—
SMV + PegIFN2a/RBV	$166,165	$33,573	25%
TVR + PegIFN2a/RBV	$163,394	$30,802	23%
BOC + PegIFN2b/RBV	$155,460	$22,868	17%
HIV-coinfected			
SOF + PegIFN2a/RBV	$135,830	—	—
SMV + PegIFN2a/RBV	$155,868	$20,038	15%
TVR + PegIFN2a/RBV	$175,551	$39,721	29%
BOC + PegIFN2b/RBV	$193,096	$57,266	42%
Treatment experienced			
All patients			
SOF + PegIFN2a/RBV	$145,628	—	—
SMV + PegIFN2a/RBV	$161,485	$15,857	11%
TVR + PegIFN2a/RBV	$206,626	$60,998	42%
BOC + PegIFN2b/RBV	$234,592	$88,964	61%

BOC = boceprevir; HIV = human immunodeficiency virus; PegIFN2a = peginterferon alfa-2a; PegIFN2b = peginterferon alfa-2b; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response; TVR = telaprevir.

When considering the lifetime incremental cost per QALY gained, sofosbuvir + PegIFN/RBV was shown to be the most cost-effective treatment option for genotype 1 patients. The sofosbuvir regimen

dominated (i.e., is less costly and more effective than) simeprevir + PegIFN/RBV, telaprevir + PegIFN/RBV and boceprevir + PegIFN/RBV.

Furthermore, initiation of HCV therapy at an earlier disease stage (i.e., in patients without cirrhosis, with METAVIR fibrosis scores F0-F3) yielded substantially fewer cases of CC, DCC, HCC, liver transplant, and HCV-related death, stemming from higher SVR rates among non-cirrhotic patients than cirrhotic patient. Consequently, the downstream total cost of care associated with advanced disease will be reduced substantially with earlier initiation of treatment. For patients infected with HCV genotype 1, cases of liver disease complications were threefold lower, and total costs of care were 38% to 46% lower when therapy was initiated at the non-cirrhotic stage than at the cirrhotic stage.

Several assumptions and model inputs may explain the discrepancies between these analyses and the CTAF report, which are outlined below:

1. Clinical considerations represented in model

   The most sensitive drivers in any HCV cost-effectiveness model are drug costs and SVR rates of the various regimens. The CTAF network analysis for SOF estimated an SVR of 83% among GT 1 treatment-naïve patients, whereas clinical studies with SOF showed SVR rates of 89-91%. Among GT 1 treatment-experienced patients, the CTAF model estimated an SVR rate of 67%; however, 71% is the estimated response rate based on analysis conducted by the FDA utilizing multiple baseline factors traditionally associated with lower response to interferon-based treatment that would predict the response rate in patients who previously failed pegylated interferon and ribavirin therapy (SOF US Prescribing Information). To ensure consistency of the analysis, it is important to understand the details of how the patient populations were defined (ie. proportions of nulls/partials/relapsers in the treatment-experienced population). For example, 90% was quoted as simeprevir's SVR12 in treatment-experienced trials, which reflects the SVR in relapsers and not null or partial responders. The FDA analysis estimated an SVR rate of 51% for SMV + PegIGN + RBV for patients with the combination of *IL28B* non-CC alleles, HCV RNA >800,000 IU/mL and Metavir F3/F4 fibrosis.

   In addition, the draft CTAF report did not provide estimates of SVR rates for SOF in certain subpopulations vs. comparators (e.g., SOF in cirrhotic vs. non-cirrhotic or HIV/HCV co-infection) for GT 1 patients. These data are provided in the response to Question 3, above.

   Sofosbuvir phase 3 clinical trials had expanded inclusion criteria that reflected patient characteristics in real-world settings. The sofosbuvir trials overall included 20% of patients with cirrhosis and also patients who were older than 65 years, and had no restrictions for body weight, depression, or methadone use. The efficacy of sofosbuvir has been established in patients HCV across all genotypes, including those with HCC meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 coinfection. Based on registrational trial data and described in the new AASLD/IDSA guidelines, sofosbuvir-based regimens are expected to result in the following clinical benefits to the overall treatment goal of SVR. High SVR rates with a 12- or 24-week duration of therapy across HCV genotypes 1, 2, 3, 4, 5, and 6:

   - Improved safety and tolerability, with no incremental adverse events, resulting in low discontinuation rates (1%-3%)
   - High barrier to resistance, with no patients developing resistance to sofosbuvir when used in combination with ribavirin ± peginterferon and no baseline resistance screening required
   - Simplified dosing (once daily, no food requirements, no response-guided therapy, minimal drug-drug interactions)

- Efficacy in the real-world setting across a broad spectrum of patients with HCV, including those who have compensated cirrhosis, are elderly, have a high BMI, receive methadone, have psychiatric comorbidities, are awaiting a liver transplant, are reinfected with HCV post-transplant, or are coinfected with HIV

The draft CTAF report utilized adverse event rates based on clinical trials, and reports of adverse events and discontinuations from real world studies were not mentioned.

In the HCV-TARGET cohort, an observational analysis of patients treated with protease inhibitors s at 103 academic and community centers, serious adverse events occurred in 8% of telaprevir-treated patients and 13% of boceprevir-treated patients. As in the French cohort, hepatic decompensation events occurred in 5% of patients in the HCV-TARGET cohort, and early discontinuation of all HCV drugs due to an adverse event occurred in 10% of patients. Respectively, 33% and 40% of telaprevir-treated patients and boceprevir-treated patients used epoetin-alfa to manage anemia (Gordon et al., 2013b). As noted in studies by Bichoupan and colleagues (2013a; 2013b) and Sethi colleagues (2013) evaluating cost per SVR, these adverse events contribute substantially to higher costs. Based on lower real-world SVR rates than seen in phase 3 trials, the overall real-world cost per SVR was estimated to be $173,000 to $189,000 in these two single-center studies, and increased to $254,000 to $267,000 in patients with cirrhosis at baseline (Dieterich et al., 2012; Sethi et al., 2013).

In a real-world setting, early discontinuations often occur because of patient noncompliance, virologic failure, or adverse events. Nguyen and colleagues (2013) demonstrated in a large claims database analysis that treatment completion for both PegIFN/RBV therapy and PI-based triple therapy regimens is suboptimal in the real-world clinical setting. The steepest drop in dual therapy occurred between weeks 12 and 24: treatment completion rates declined by more than 35% during this time period. Interferon-related side effects, particularly depression and fatigue, tend to increase in severity over time, which may contribute to higher discontinuation rates observed at week 12 and after. Nguyen and colleagues (2013) also found that more than 50% of the patients receiving telaprevir- and boceprevir-based triple therapy did not complete the intended 24 weeks of therapy (Nguyen et al., 2013). The draft CTAF report did not mention the expected benefit of a regimen with a shorter duration of therapy or an interferon-free regimen that would lead to lower discontinuation rates.

2. Consideration of factors for progressing disease

Underlying risk factors can accelerate disease progression. Studies have shown that older age at time of infection, male gender, the degree of inflammation and fibrosis present on the liver biopsy, coinfection with HIV or HBV, and comorbid conditions such as immunosuppression, insulin resistance, nonalcoholic steatohepatitis, hemochromatosis, and schistosomiasis, as well as chronic alcohol use are risk factors for the progression of chronic hepatitis C to cirrhosis (Davis et al., 2010, Grebely and Dore, 2011). The median age of patients with HCV is increasing, as observed in a VA study where the median age was 59, suggesting these patients are more likely to present to health care systems with advanced fibrosis (Backus et al., 2013).

The draft CTAF model does not take into account the widespread prevalence of HCV co-infection in HIV patients. Prevalence rates for HCV co-infection in HIV patients are significant and may approach 30% in certain population (Soriano et al., 2002). Coinfection with HIV reduces the likelihood of spontaneously clearing HCV, increases HCV RNA levels in the blood, accelerates liver disease progression, and reduces the response to interferon-based therapies compared with HCV monoinfection (Grebely and Dore, 2011). HCV infection results in a significant increase in mortality in HIV infected individuals resulting in 14% to 18% of all deaths in HIV-infected patients from liver

disease, making it the most common non–HIV-associated cause of death in this population (Price and Thio, 2010)

Another model of the long-term effects of HCV infection predicted that complications from chronic HCV continue to accumulate as patients continue to age and exhibit sequelae of disease (Davis et al., 2010). The majority of baby boomers with HCV have had 20 to 30 years of chronic infection, and are the most at risk for advanced fibrosis. Cirrhosis in HCV-infected persons is expected to peak at 1 million persons in 2020 and decline slowly thereafter (Davis et al., 2010). In 2009, an estimated 11.7% of patients with HCV-related cirrhosis had decompensated liver disease (Davis et al., 2010). The total number with liver failure is expected to peak in 2022 at approximately 150,000 cases (Davis et al., 2010). Hepatocellular carcinoma occurs in approximately 1.3% of patients with chronic HCV infection (Kanwal et al., 2011) and the incidence of HCV-related HCC is expected to peak at 14,000 cases per year in 2019 (Davis et al., 2010). In the current model, disease progression estimates are assumed to be the same, regardless of any of the above risk factors.

3. The most costly liver disease sequelae are hepatocellular carcinoma (HCC), decompensated cirrhosis (DCC), and liver transplant, and these are not individually accounted for in the draft CTAF model.

   The CTAF model collapses all liver complications into one condition, regardless of severity, with an estimate of $25,728 per year based on a Florida Medicaid population (Menzin 2013). However, published costs of liver disease by severity show substantially higher costs in association with progression of liver disease (Gordon SC, et al. Hepatology 2012 and C McAdam-Marx et al. J Manag Care Pharm 2011).

McAdam-Marx et al. Per Patient Per Year Costs	**F0-F3**	**CC (F4)**	**DCC**	**HCC**	**Liver Transplant Year 1**	**Liver Transplant Year 2+**
All HCV Cost	$5,870	$5,330	$27,845	$43,671	$168,643	$38,015
N	26,977	1,521	4,249	959	891	891
Gordon et al. Per Patient Per Year Costs	**F0-F3**	**CC (F4)**	**DCC**	**HCC**	**Liver Transplant Year 1**	**All ESLD**
All HCV Cost	$7,804	$12,810	$42,824	$112,537	$145,045	$59,172
N	41,858	3,718	6,560	1,086	574	8,220

In the CTAF model, the SVR vs. non-SVR costs are based on Manos 2013 study that evaluated a largely non-cirrhotic patient cohort (10% cirrhosis rate in Kaiser population) and the follow-up time was limited to 5 years. In contrast, another study by Gordon et al. found mean follow-up PPPM costs were around 29% lower in the treated non-cirrhotic vs. untreated end stage liver disease patients. Follow-up costs were >5-fold higher for untreated end stage liver disease patients vs. treated non-cirrhotic disease, suggesting that early intervention with successful treatment may prevent progression of liver disease and thus reduce costs. (Gordon S.C., et al. Aliment Pharmacol Ther. 2013).

By utilizing more granular considerations of liver disease complications, updated transition probabilities and costs, SOF cost-effectiveness analyses show substantial reductions in cases of CC, HCC, DCC, liver transplant and HCV-related death when treating with SOF-based regimens versus other comparators. In the short-term, sofosbuvir is estimated to have the lowest cost per SVR in genotype 1 patients, including difficult-to-treat patients as shown in table 1.

Other model considerations include the following:

4. The budget impact model includes the assumption that 50% of patients with HCV who are aware of their disease will be treated; however, the clinical capacity to manage the treatment all these patients may not be feasible. Therefore, the real costs of managing these patients may be lower. In addition, the CTAF model does not take into account the increased costs of following HCV-positive patients compared to non-infected patients.

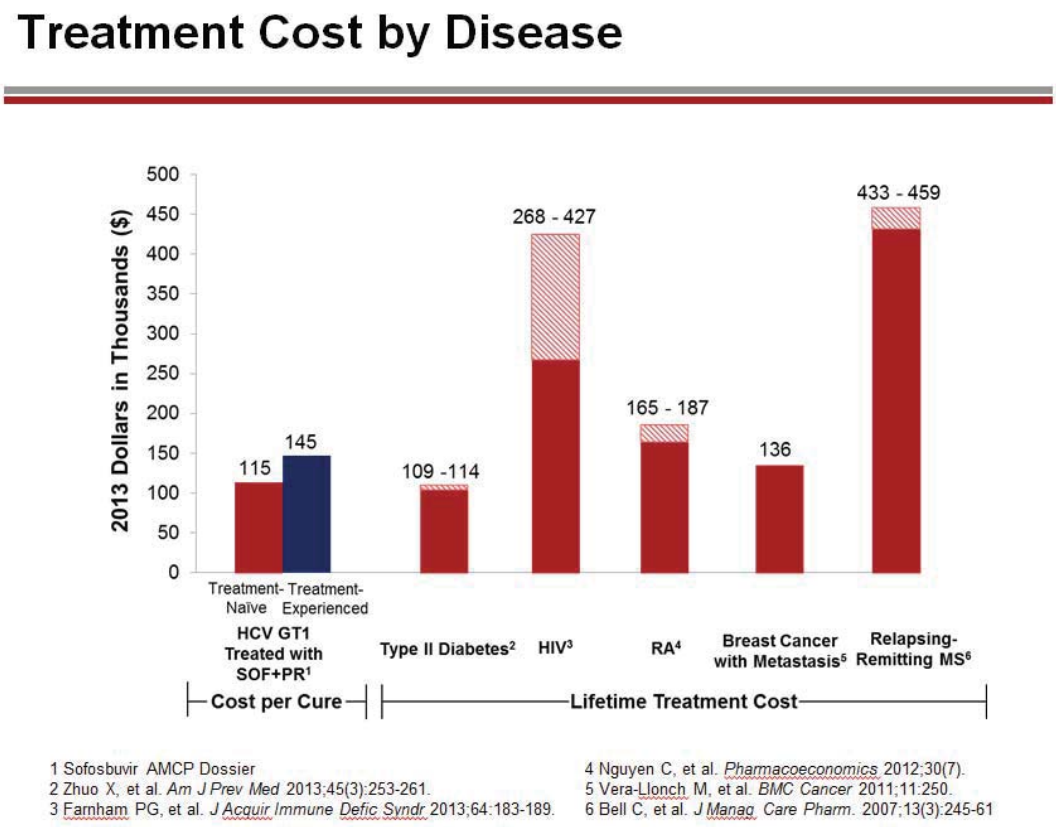
5. Patient perspective is not accounted for in the draft CTAF analysis. Therefore, it is important to consider the implications of patient-reported outcomes data on disability and adherence to treatment.

   The health-related quality of life (HRQoL) of patients treated with sofosbuvir-based regimens was evaluated from the Phase 3 studies FISSION, POSITRON, NEUTRINO, and FUSION by the Short Form-36 version 2 (SF-36v2). In FISSION, genotype 2 and 3 patients treated with SOF+RBV had better HRQoL scores at the end of treatment compared to patients receiving Peg-IFN+RBV. In POSITRON, at any time point, there was no significant difference in HRQoL scores between genotype 2 and 3 patients treated with SOF+RBV and those on placebo. In FUSION, an additional 4 weeks of SOF+RBV (16 weeks total) did not negatively impact HRQoL scores. In NEUTRINO, adding SOF to Peg-IFN+RBV for treatment of genotype 1 did not add further decrements to the HRQoL scores compared to historical scores with Peg-IFN+RBV. Achievement of SVR12 was associated with improvement in some domains of the SF-36. Therefore, shorter, highly effective, and more tolerable regimens provide HRQoL benefit to patients with chronic hepatitis C.

   The impact of sofosbuvir-based regimens on fatigue (measured by FACIT-F), HCV-specific quality of life (CLDQ), and work productivity (WPAI) was evaluated from the NEUTRINO and FUSION studies. The results were consistent with SF-36 score trends. The interferon-free regimen had significantly smaller decrements in fatigue scores, CLDQ-HCV, and work productivity scores, particularly presenteeism, than the interferon-containing regimen. Fatigue and receiving the interferon-containing regimen were independently associated with lower scores. By 4-12 weeks post-treatment, scores either returned to their baseline values or some domains improved in those achieving SVR-12. These studies show that achievement of SVR-12 has not only clinical benefits but also humanistic benefits. (Younossi ZM, et al. J Hepatol 2014. Article in Press).

6. A public health implication to consider with HCV is that unlike other disease areas, HCV can be cured, so the benefits of treatment are nearly instantaneous instead of the need for lifelong therapy as seen with HIV. This gives an opportunity to eradicate HCV from the entire population.

7. Lifetime treatment costs for chronic HCV should be placed into context of other disease areas.



Of note, the ICER for treated HCV compared with no treatment was estimated to be $11,000/QALY by Hagan et al.

Summary

Sofosbuvir, the first FDA approved NS5B nucleotide polymerase inhibitor, provides an interferon-limiting or interferon-free regimen for patients infected with HCV genotypes 1 and 4, interferon-free for genotypes 2 and 3, and treatment options for interferon-ineligible and -intolerant patients.

- Highest efficacy rates, shortest treatment duration regimen (12 weeks) in combination with RBV +/- PegIFN for patients infected with genotype 1, 4, 5, or 6.
- Excellent safety and tolerability profile
- No response guided therapy
- First all oral regimen for patients who have no treatment options because they are they are interferon-unwilling, -ineligible, or –intolerant
- The only approved DAA available for patients of all genotypes with HCC meeting Milan criteria (awaiting liver transplantation)
- The only approved DAA available for patients with HCV/HIV-1 coinfection, with SVR rates and a safety/tolerability profile similar to those observed for HCV monoinfected patients
- Lack of food effect, once daily administration, very limited drug-drug interactions

Sofosbuvir brings significant value to payers, providers, patients and society above currently available agents by providing the following:

- Economic analysis shows that, compared with current treatment regimens, sofosbuvir-based regimens yield the most favorable future health outcomes and the fewest cases of liver disease complications and HCV-related deaths across patients infected with all HCV genotypes (1, 2, 3, and 4), levels of treatment experience, fibrosis and cirrhosis stages, as well as patients with or without HIV coinfection.
- In the 1-year analysis, the cost per SVR for the sofosbuvir-based regimen is lowest of all currently approved regimens due to higher efficacy rates, a high barrier to resistance, and improved tolerability. In the long-term, the sofosbuvir-based regimens are the most cost-effective treatment options for patients infected with HCV genotype 1, because of averted liver-disease costs.
- Earlier initiation of the more effective sofosbuvir-based treatment yields better health and economic outcomes compared with later initiation, reducing advanced liver disease complications and the downstream costs associated with advancing disease.

References

AASLD/IDSA HCV Guidance Recommendations for Testing, Managing, and Treating Hepatitis C; www.hcvguidelines.org ; January 29, 2014.

Backus L, Belperio P, Shahoumiam T, Cheung R, Mole L. Comparative Effectiveness of Boceprevir- and Telaprevir-Based Therapy in US Veterans. Poster presented at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013a. Washington, DC. Poster no. 1848.

Bichoupan K, Martel-Laferriere V, Ng M, Schonfeld EA, Pappas A, Crismale J, et al. Estimated costs of telaprevir-based triple therapy, including adverse event management at the Mount Sinai Medical Center, NY: $195,000 per SVR12. Poster presented at the 48th Annual Meeting of the European Association for the Study of the Liver; April 24-28, 2013b. Amsterdam, The Netherlands.

Bichoupan K, Martel-Laferriere V, Sachs D, Ng M, Schonfeld E, Pappas A, et al. Costs of telaprevir-based triple therapy including adverse event management at the Mount Sinai Medical Center, NY $189,000 per SVR. Oral presentation presented at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013a. Washington, DC. Presentation no. 244.

Curry MP, Forns X, Chung R, et al. Pretransplant Sofosbuvir and Ribavirin to Prevent Recurrence of HCV Infection After Liver Transplantation [Presentation 213]. Paper presented at: The Liver Meeting® 2013 The 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); November 1-5, 2013; Washington, D.C.

Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology. 2010 Feb;138(2):513-21, 521.e1-6.

FDA Antiviral Drugs Advisory Committee Meeting Background Package for NDA 205123: Simeprevir; October 24, 2013.

Gordon SC, Hamzeh FM, Pockros PJ, Hoop RS, Buikema AR, Korner EJ, Terrault NA. Hepatitis C virus therapy is associated with lower health care costs not only in noncirrhotic patients but also in patients with end-stage liver disease. Aliment Pharmacol Ther. 2013a;38:784-793.

Gordon SC, Muir AJ, Lim JK, Pearlman B, Argo CK, Neff GW, et al. The frequency and management of adverse events in chronic hepatitis C (HCV) treated with boceprevir or telaprevir: real world experience from HCV-TARGET Longitudinal Observational Study. Poster presented at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013b. Washington, DC. Poster no. 1866.

Gordon SC, Pockros PJ, Terrault NA, Hoop RS, Buikema A, Nerenz D, Hamzeh FM. Impact of disease severity on healthcare costs in patients with chronic hepatitis C (CHC) virus infection. Hepatology. 2012;56(5):1651-60.

Grebely J, Dore GJ. What is killing people with hepatitis C virus infection? Semin Liver Dis. 2011 Nov;31(4):331-9.

Hagan LM, Yang Z, Ehteshami M, Schinazi RF. All-oral, interferon-free treatment for chronic hepatitis C: cost-effectiveness analyses. J Viral Hepat. 2013 Dec;20(12):847-57.

Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med.* May 16 2013;368(20):1867-1877.

Jacobson IM, Ghalib R, Rodriguez-Torres M, et al. SVR results of a once-daily regimen of simeprevir (SMV, TMC435) plus sofosbuvir (SOF, GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naïve and prior null responder patients: The COSMOS study [Presentation LB-3]. Paper presented at: The Liver Meeting® 2013 The 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); November 1-5, 2013; Washington, D.C.

Kanwal F, Hoang T, Kramer JR, Asch SM, Goetz MB, Zeringue A, et al. Increasing prevalence of HCC and cirrhosis in patients with chronic hepatitis C virus infection. Gastroenterology. 2011 Apr;140(4):1182-8.

Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med.* May 16 2013;368(20):1878-1887.

Mangia A, Kugelmas M, Everson G, et al. Virologic Response Rates to Sofosbuvir-Containing Regimens Are Similar in Patients With and Without Traditional Negative Predictive Factors: a Retrospective Analysis of Phase 3 Data [Poster 1115]. Paper presented at: The Liver Meeting® 2013 The 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); November 1-5, 2013; Washington, D.C.

McAdam-Marx C, McGarry LJ, Hane CA, Biskupiak J, Deniz B, Brixner DI. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: a managed care perspective. J Manag Care Pharm. 2011;17(7):531-46.

McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009; 361(6):580-93.

Nguyen MH, Brooks L, Livornese RC. Suboptimal treatment rates and treatment completion rates of chronic hepatitis C virus therapy in patients with comorbidities: analysis of a large real-world US cohort. Poster presented at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013. Washington, DC. Poster no. 2040.

Price J, Thio C. Liver disease in the HIV-infected individual. Clin Gastroenterol Hepatol. 2010;8(12):1002-12.

Sethi N, Vong A, Firdoos S, Rourke M, and Afdhal NH. Analysis of direct and indirect costs of HCV care with PEG-Interferon triple therapy. Oral presentation presented at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013. Washington, DC. Presentation no. 1847.

Soriano V, Sulkowski M, Bergin C, Hatzakis A, Cacoub P, Katlama C, et al. Care of patients with chronic hepatitis C and HIV co-infection: recommendations from the HIV±HCV international panel. AIDS 2002;16:813-828.

SOVALDI (sofosbuvir) prescribing information. Foster City (CA): Gilead Sciences, Inc.; December 2013.

Sulkowski M, Rodriguez-Torres M, Lalezari J, et al. All-Oral Therapy With Sofosbuvir Plus Ribavirin For the Treatment of HCV Genotype 1, 2, and 3 Infection in Patients Co-infected With HIV (PHOTON-1) [Presentation 212]. Paper presented at: The Liver Meeting® 2013 The 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); November 1-5, 2013; Washington, D.C.

Younossi ZM, Gordon SC, Saab S, et al. A Decision-Analytic Markov Model to Evaluate the Health Outcomes of Sofsbuvir for Previously Untreated Patients with Hepatitis C Virus Genotype 1 Infection. Poster presented at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013a. Washington, DC. Poster no. 368.

Younossi ZM, Gordon SC, Saab S, et al. A decision-analytic markov model to evaluate the health outcomes of sofosbuvir for previously untreated patients and those without treatment options with chronic hepatitis C Virus genotype 2 infection. Poster presented at ISPOR 16th Annual European Congress; November 2-6, 2013c. Dublin, Ireland. Value Health. 2013;16(7) A341. Abstract no. PIN3.

Younossi ZM, Saab S, Gordon SC, et al. Evaluation of Long-Term Health Outcomes Associated with Earlier Versus Later Initiation of Treatment in Previously Untreated Patients with Chronic Hepatitis C Virus Genotype 1 Infection. Poster presented at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013b. Washington, DC. Poster no. 369.

Younossi ZM, Stepanova M, Henry L, Gane E, Jacobson IM, Lawitz E, Nelson D, Gerber L, Nader F, Hunt S. Effects of Sofosbuvir-Based Treatment, With and Without Interferon, on Outcome and Productivity of Patients With Chronic Hepatitis C. Clin Gastroenterol Hepatol. 2013 Dec 6.

Younossi ZM, Stepanova M, Henry L, Gane E, Jacobson IM, Lawitz E, Nelson D, Nader F, Hunt S. Minimal impact of sofosbuvir and ribavirin on health related quality of life in Chronic Hepatitis C (CH-C). J Hepatol. 2013 Dec 11. [Epub ahead of print]

Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir + Ribavirin for 12 or 24 Weeks for Patients With HCV Genotype 2 or 3: the VALENCE Trial [Poster 1085]. Paper presented at: The Liver Meeting® 2013 The 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); November 1-5, 2013; Washington, D.C.

To Whom It May Concern at CTAF (per http://ctaf.org/contact-us) - A hopefully-simple question.

We at the California Public Employees' Retirement System (CalPERS) have been following the CTAF deliberations on hepatitis C treatments with some interest. Today I noticed that Figures 6 and 7 in the draft report posted on the Web were quite different from Figures 6 and 7 in the slides for the 3/10 meeting. See attached Word file. What happened?

Were the draft report's Figures in error? If so, I would recommend that an Erratum be placed in the PDF file http://ctaf.org/sites/default/files/assessments/CTAF_Hep_C_Draft_021214.pdf to prevent any possible confusion.

Thanks in advance.

Richard KP Sun, MD, MPH, Medical Consultant II
Chief, Clinical Programs, Policies, and Procedures Unit
Health Plan Administration Division
California Public Employees' Retirement System (CalPERS)
P.O. Box 1953, Sacramento CA 95812-1953
Email: Richard.Sun@CalPERS.ca.gov Voice: 916-795-1288 Fax: 916-795-1513

Figures 6 & 7 Different - Why?

Source: http://ctaf.org/sites/default/files/assessments/CTAF_Hep_C_Draft_021214.pdf, "The Comparative Clinical Effectiveness and Value of Simeprevir and Sofosbuvir in the Treatment of Chronic Hepatitis C Infection | A Technology Assessment | Draft Report for March 10, 2014 Meeting," pages 75 and 76

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).

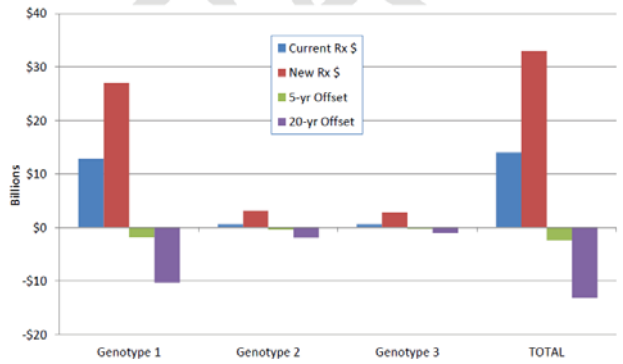
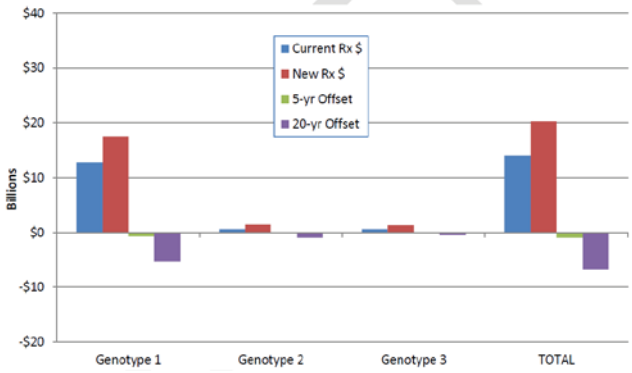


Figure 7. Total Budgetary Impact and Potential Cost Offsets from Use of Newer Drug Regimens in the Chronic Hepatitis C Population with Advanced Fibrosis in California: 50% of Infected Patients Are Treated (n=217,839).



Source: http://ctaf.org/sites/default/files/u119/handout_tables_031014_posted.pdf ("Key tables from draft assessment"), last slide

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=270,525).

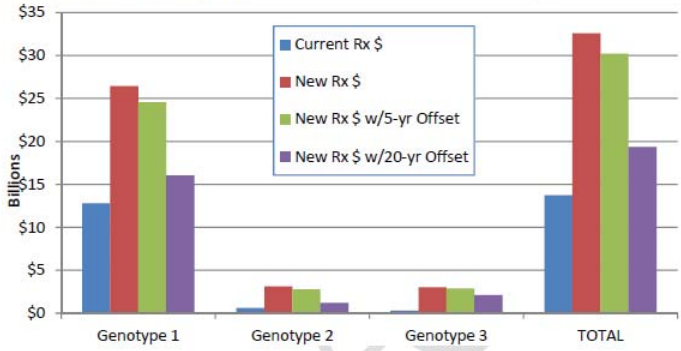
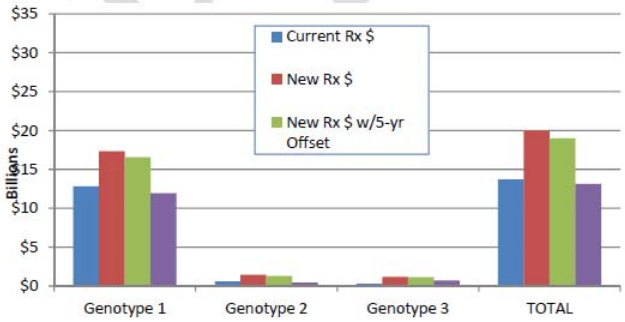


Figure 7. Total Budgetary Impact and Potential Cost Offsets from Use of Newer Drug Regimens Only in the Chronic Hepatitis C Population with Advanced Fibrosis in California: 50% of Infected Patients Are Treated (n=89,544).



March 3, 2014

Dear California Technology Assessment Forum:

On behalf of Janssen Scientific Affairs, LLC, we appreciate the opportunity to comment on the draft report "The Comparative Clinical Effectiveness and Value of Simeprevir and Sofosbuvir in the Treatment of Chronic Hepatitis C Infection".

We found this assessment timely, thorough and relevant given the significant changes and evolving landscape in Hepatitis C. Our detailed comments for consideration are provided in the attached document while a brief summary is also provided below:

- Differences in response rates and treatment approaches, including length of treatment, vary based on different subpopulations/patient characteristics and can have a substantial impact on the network meta-analysis (NMA) results and subsequent modeling findings contained in the report. Examples include genotype subtypes 1a (absence of Q80K) vs 1b, relapsers vs non-responders in treatment-experienced, cirrhotic vs non-cirrhotic, and RGT elgibility. When choosing the treatment approaches and response rates included in the NMA and models, factors such as these should be considered.

- As model cost findings from the report appear highly sensitive to the assumptions for drug costs used by the authors, use of drug references from a single source and point in time would be recommended. In addition, implications to the model results regarding inclusion/exclusion of available treatment regimens and durations as well as other elements (e.g., costs of adverse events, monitoring and discontinuation) and assumptions made regarding drug formulations, patient types, and treatment/retreatment algorithms should be described and discussed.

The most important changes we would recommend are the following:

    - Consider including SVR rates for SMV+ PR without Q80K. Based on label and AASLD/IDSA Guideline recommendations for excluding patients with Q80K, using these SVR rates in patients with G1a without Q80K and G1b would impact the NMA and overall model results.

- Incorporate durations of therapy for all patient types and all regimens into the model
    - Naïve and Relapsers to PR: telaprevir+PR treatment is based on RGT and can have 24-week or 48-week dosing of PR. For example in the ADVANCE trial, 58% of the telaprevir treatment-naïve patients were eligible to receive 24 weeks of total treatment. For simeprevir+PR, all naïve and relapser patients including those with cirrhosis receive 24 weeks of PR therapy
    - Non-Responders (partial and null) to PR: for telaprevir+PR and simeprevir+PR, all patients receive 48 weeks of PR therapy
    - Cirrhotics: As noted in the telaprevir full prescribing information, patients with cirrhosis may benefit from 48 weeks of PR therapy including naïve and relapsers
- Use of drug cost references from a single source and point in time
- Evaluate model sensitivity to cost assumptions including choices of brand versus generic ribavirin costs

The information provided is because of your specific unsolicited request and is not intended as an endorsement of any usage not contained in the OLYSIO™ (simeprevir) Prescribing Information. For complete information, please refer to the full Prescribing Information, including the following sections: INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS.

We welcome the opportunity to discuss any of the material contained within this reply and thank you, in advance, for your consideration.

Thank you,

Connie Chiang, PharmD

Associate Director, Medical Information
Janssen Scientific Affairs, LLC
609-730-2984
cchiang3@its.jnj.com

Inquiry #: 1-1842884457

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

A Technology Assessment

Draft Report for March 10, 2014 Meeting

Completed by:

Institute for Clinical and Economic Review

AUTHORS: Jeffrey A. Tice, MD
Associate Professor of Medicine
Division of General Internal Medicine
Department of Medicine
University of California San Francisco

Daniel A. Ollendorf, MPH, ARM
Chief Review Officer, Institute for Clinical and Economic Review

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review

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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 N=109	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

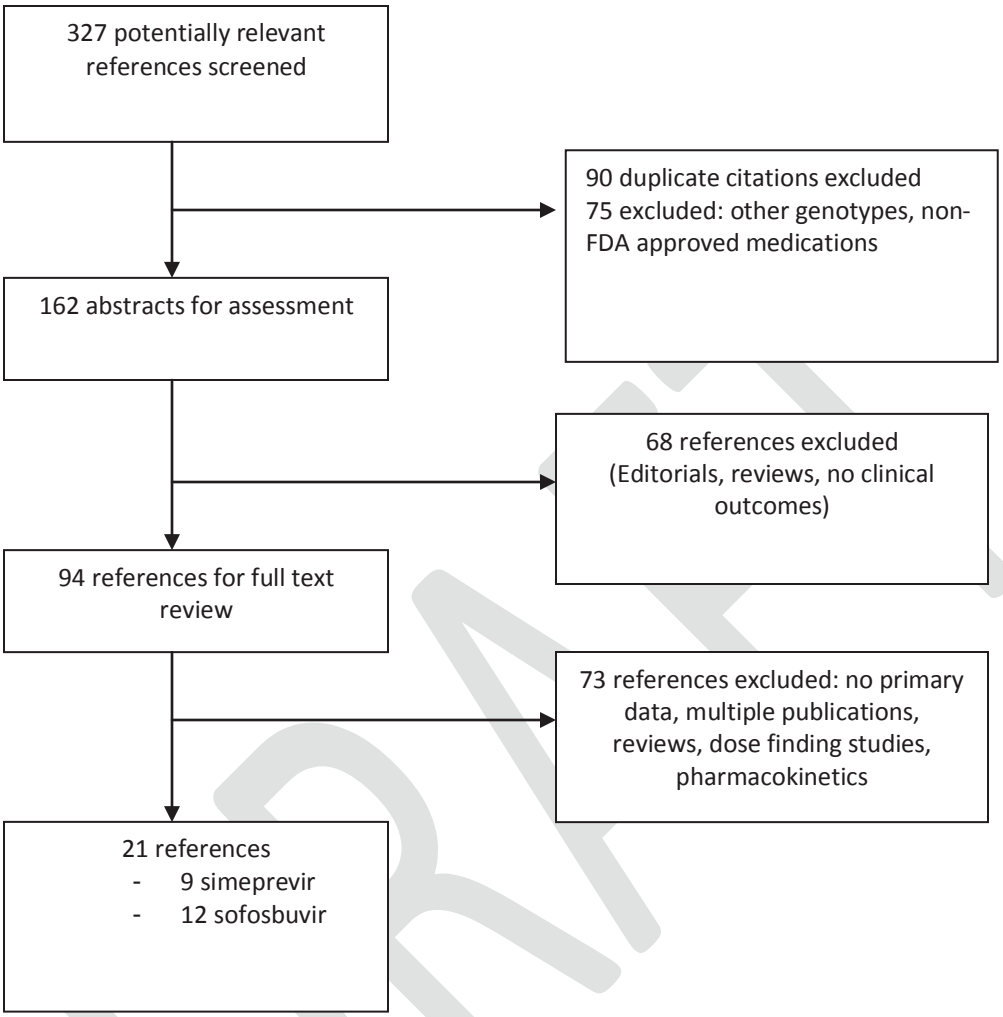
6. Evidence Review (Methods & Results)

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 + PR	~~TVR~~	1	Experienced	Yes	

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.

80% - 81%

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				

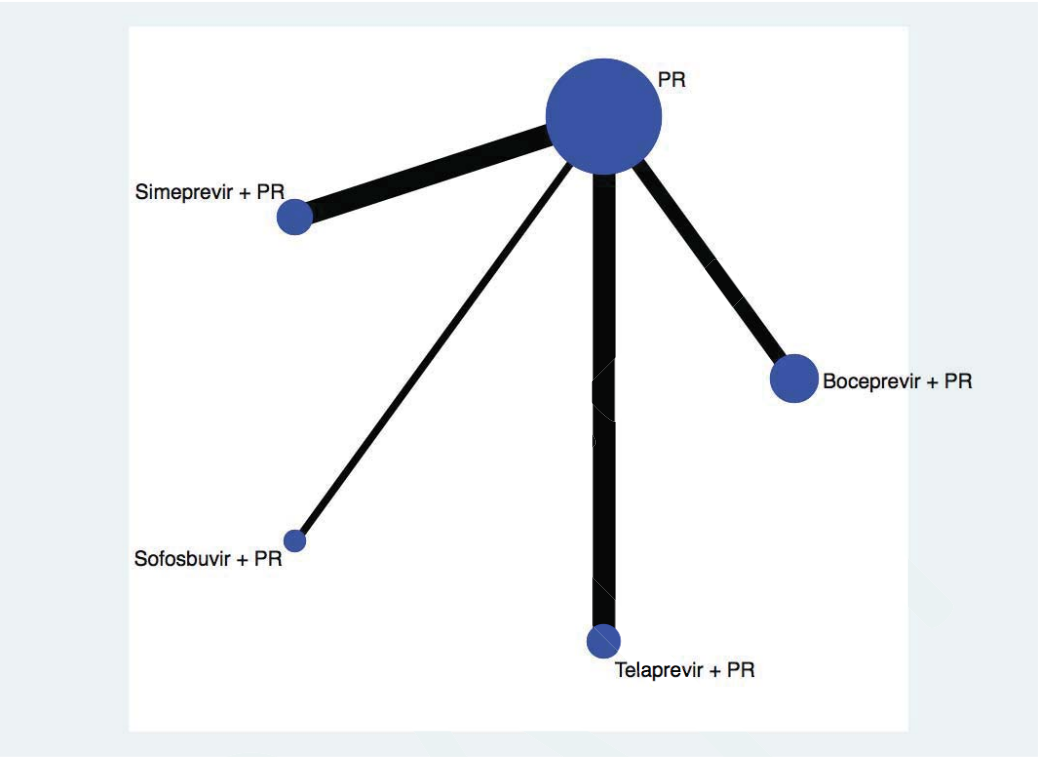
The one exception was the presence of the Q80K polymorphism. Among the 128 patients with the Q80K polymorphism, the SVR12 was only 58% for simeprevir and 52% for PR (difference NS). The prevalence of the Q80K polymorphism was 16% and it occurred almost exclusively in HCV genotype 1a.

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

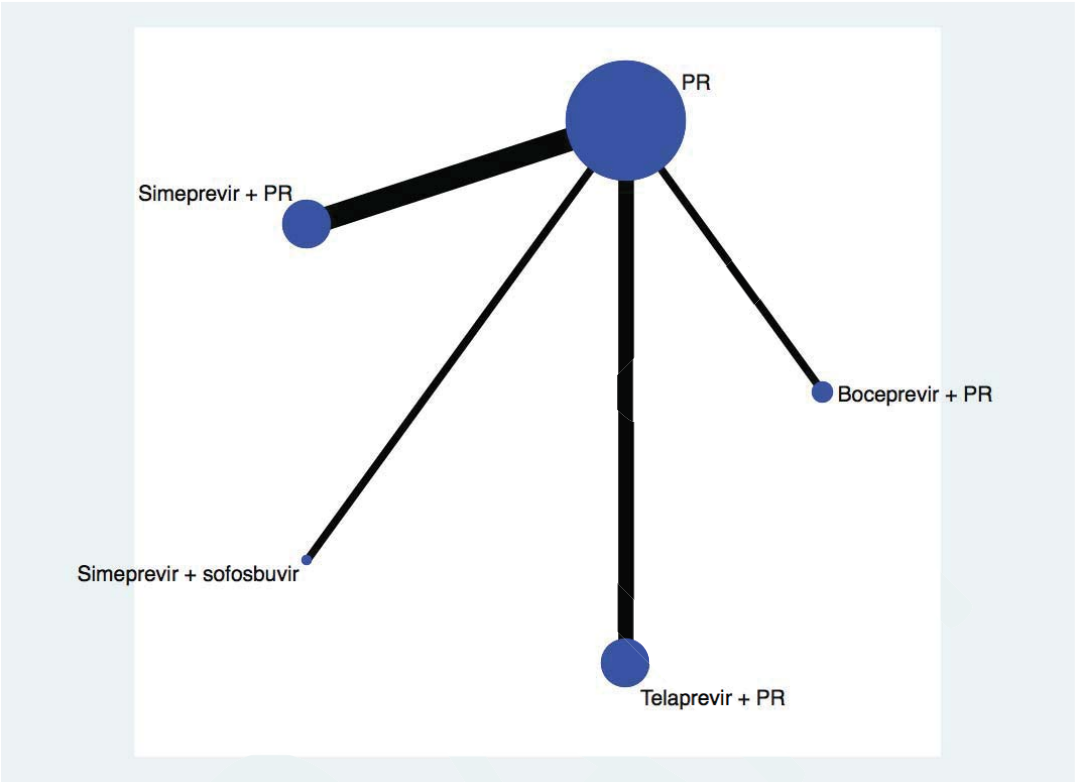
accepted, that this would be a reasonable estimate for the SVR12 for treatment-experienced patients retreated with sofosbuvir + PR. The SVR12 for the 52 patients in NEUTRINO with "poor prognostic factors" was 71%.

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

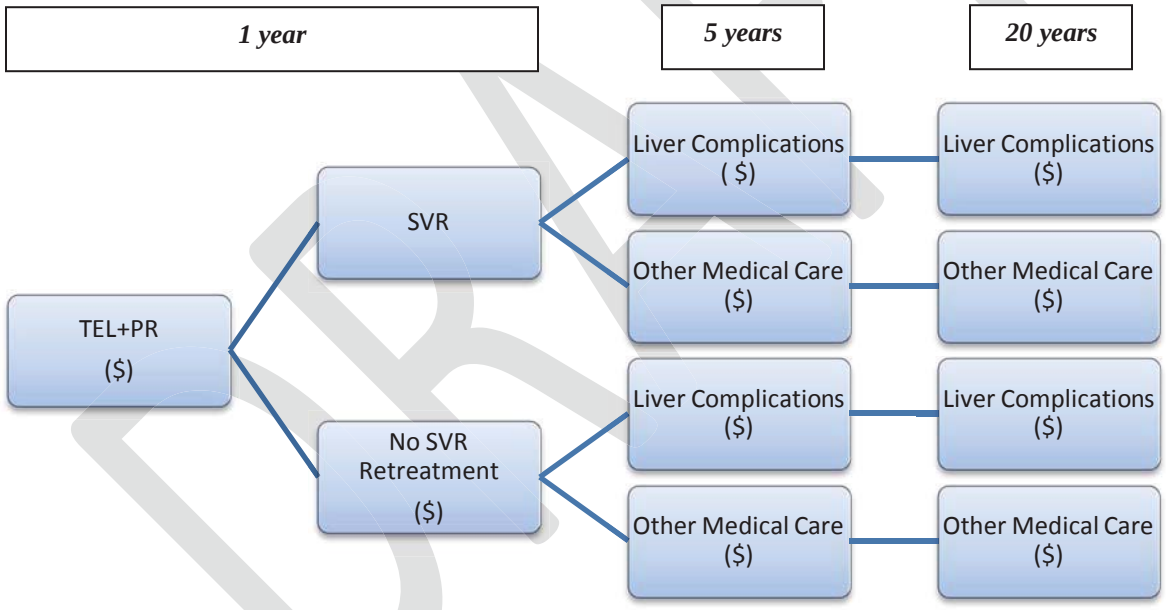
Cost-Effectiveness of Telaprevir and/or Boceprevir

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

Patient Outcomes

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*			
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)**		**Total Estimated Cost Offset† (per 1000, vs. pre-DAA)**	
								5 years	**20 years**	**5 years**	**20 years**
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)**		**Total Estimated Cost Offset† (per 1000, vs. pre-DAA)**	
								5 years	**20 years**	**5 years**	**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).

	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)**		**Total Estimated Cost Offset† (per 1000, vs. pre-DAA)**	
								5 years	**20 years**	**5 years**	**20 years**
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*			
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)**		**Total Estimated Cost Offset† (per 1000, 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)**		**Total Estimated Cost Offset† (per 1000, vs. pre-DAA)**	
								5 years	**20 years**	**5 years**	**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*			
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)**		**Total Estimated Cost Offset† (per 1000, 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

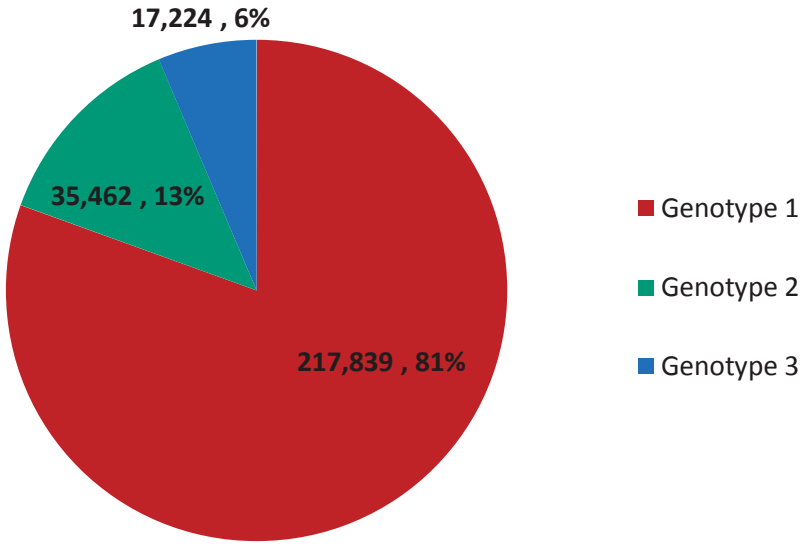
As mentioned above, we also applied estimates of the budgetary impact as well as 5- and 20-year clinical benefits and cost offsets to the California hepatitis C population. In this case, the budgetary impact was compared for the previous standard of care and the most effective regimen in each genotype/prior 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).

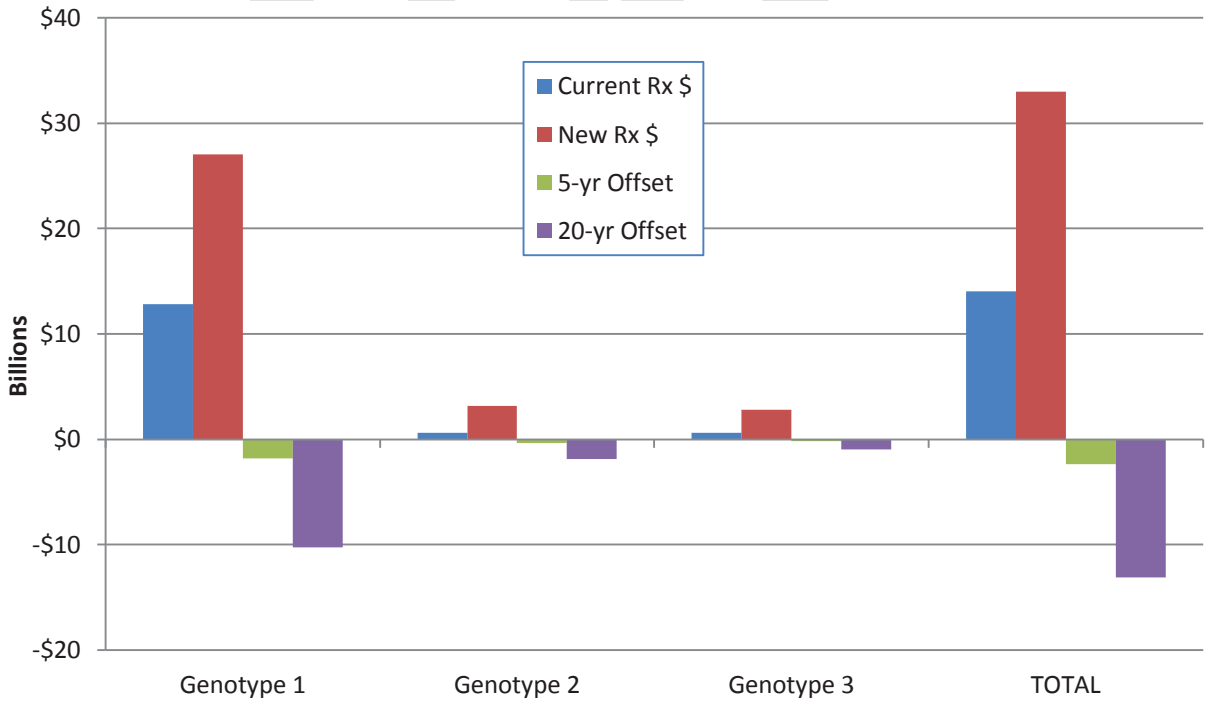
For the California population of hepatitis C patients, we evaluated two different treatment scenarios. In Scenario 1, all patients with known hepatitis C infection are treated. In Scenario 2, only those patients with advanced liver fibrosis (METAVIR scores of F3 or F4) receive treatment. The proportion 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

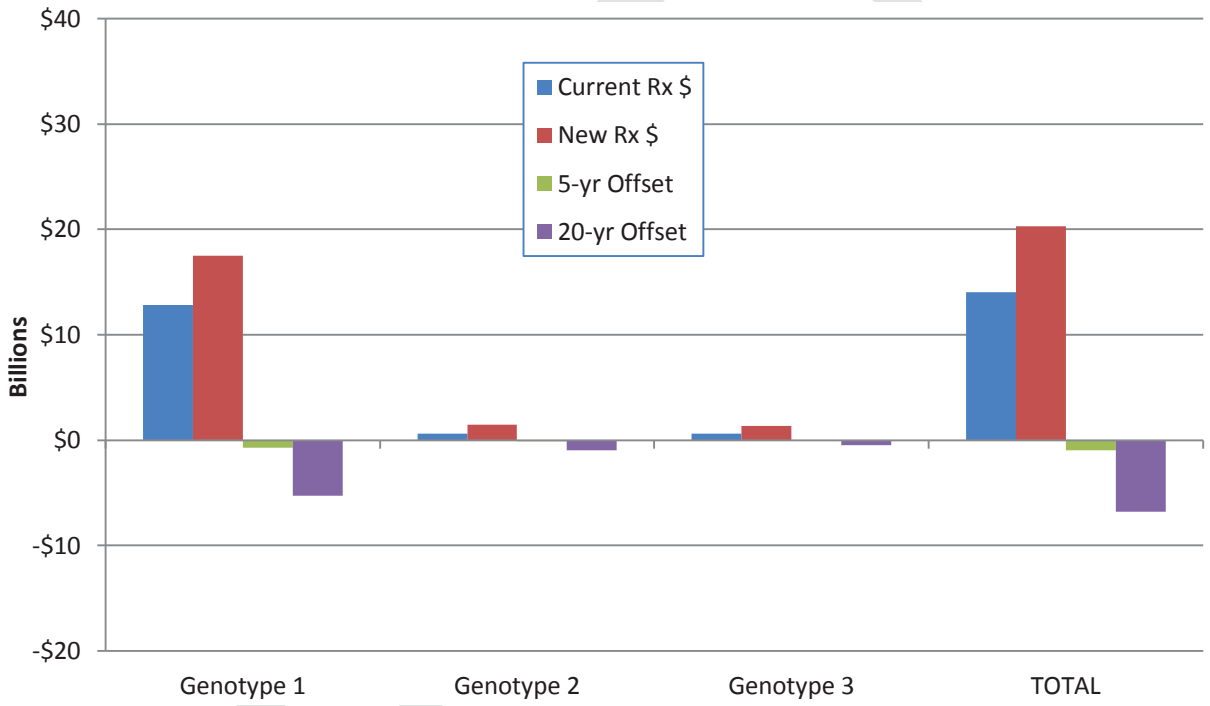
Figure 6 below depicts the budgetary impact and potential cost offsets if 50% of the estimated total California chronic hepatitis C population were to be treated (n=217,839). Drug costs to treat all these patients with the previous standard of care are estimated to total approximately $14 billion across 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).

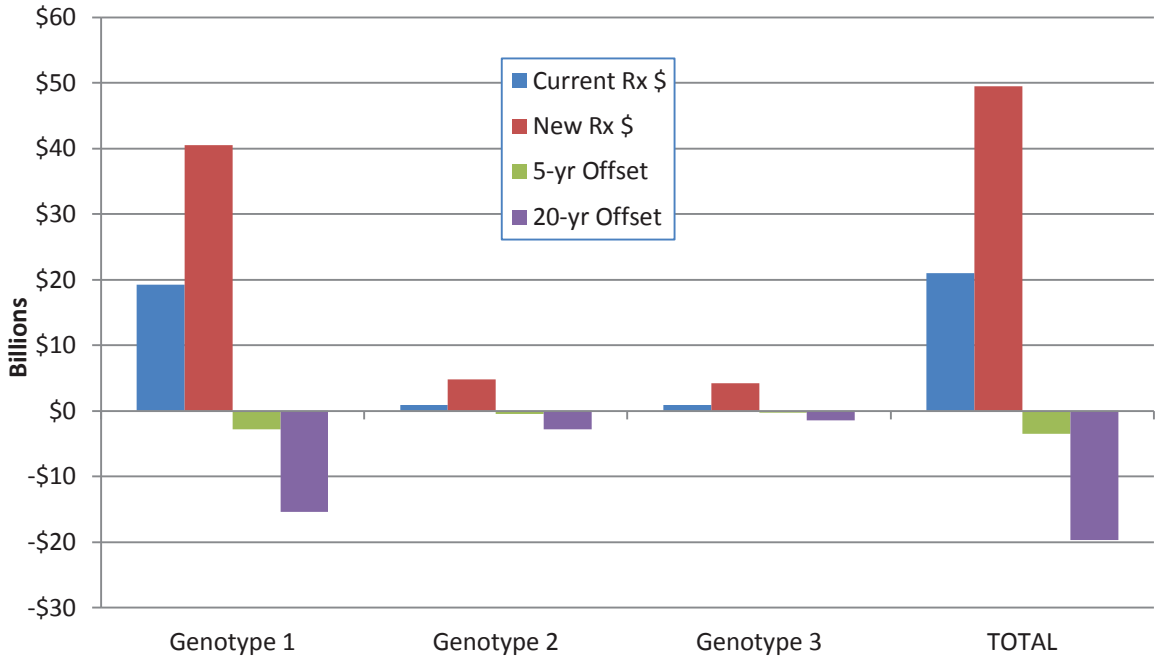
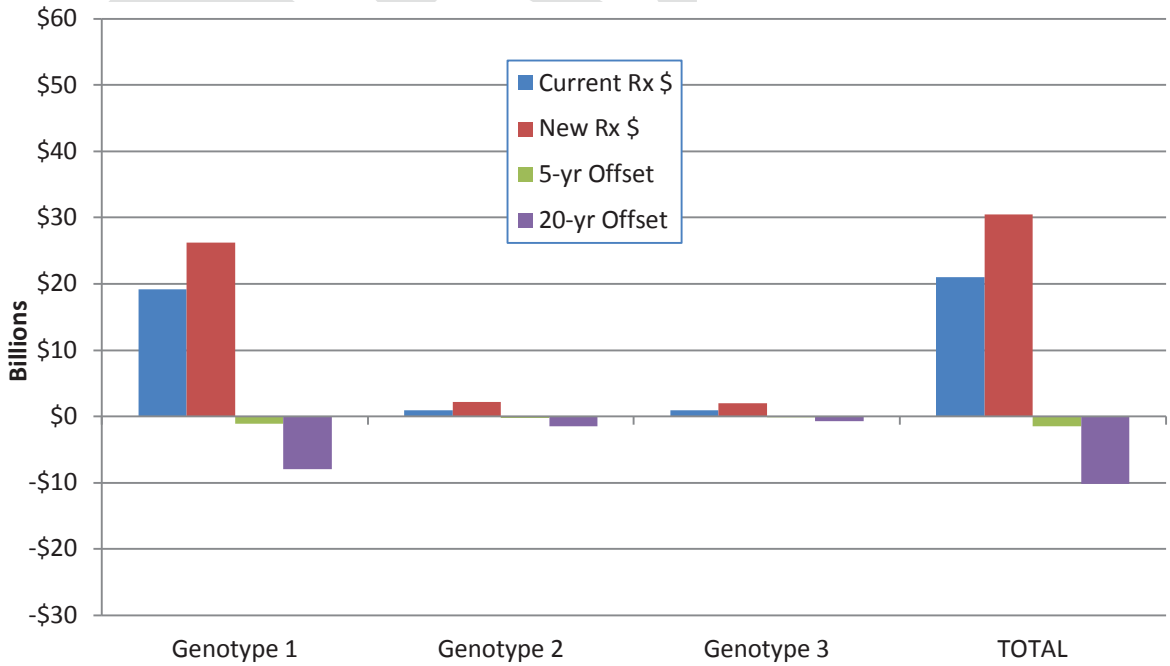


Figure 9. Total Budgetary Impact and Potential Cost Offsets from Use of Newer Drug Regimens in the Chronic Hepatitis C Population with Advanced Fibrosis in California: 75% of Infected Patients Are Treated (n=326,759).



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.**

References

1. Kim WR. The burden of hepatitis C in the United States. *Hepatology.* Nov 2002;36(5 Suppl 1):S30-34.

2. United States Department of Veterans Affairs. National Hepatitis C Program Office. Interferon and Ribavirin Treatment Side Effects. http://www.hepatitis.va.gov/provider/reviews/treatment-side-effects.asp. Accessed January 8, 2014.

3. Butt AA, Kanwal F. Boceprevir and telaprevir in the management of hepatitis C virus-infected patients. *Clin Infect Dis.* Jan 1 2012;54(1):96-104.

4. Hagan LM, Yang Z, Ehteshami M, Schinazi RF. All-oral, interferon-free treatment for chronic hepatitis C: cost-effectiveness analyses. *Journal of viral hepatitis.* Dec 2013;20(12):847-857.

5. Reau NS, Jensen DM. Sticker shock and the price of new therapies for hepatitis C: Is it worth it? *Hepatology.* Feb 3 2014.

6. Hepatitis C--global prevalence (update). *Releve epidemiologique hebdomadaire / Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record / Health Section of the Secretariat of the League of Nations.* Dec 10 1999;74(49):425-427.

7. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Annals of internal medicine.* May 16 2006;144(10):705-714.

8. Chak E, Talal AH, Sherman KE, Schiff ER, Saab S. Hepatitis C virus infection in USA: an estimate of true prevalence. *Liver international : official journal of the International Association for the Study of the Liver.* Sep 2011;31(8):1090-1101.

9. Holmberg SD, Spradling PR, Moorman AC, Denniston MM. Hepatitis C in the United States. *The New England journal of medicine.* May 16 2013;368(20):1859-1861.

10. Kershenobich D, Razavi HA, Cooper CL, et al. Applying a system approach to forecast the total hepatitis C virus-infected population size: model validation using US data. *Liver international : official journal of the International Association for the Study of the Liver.* Jul 2011;31 Suppl 2:4-17.

11. Chinnadurai R, Velazquez V, Grakoui A. Hepatic transplant and HCV: a new playground for an old virus. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons.* Feb 2012;12(2):298-305.

12. Simmonds P, Holmes EC, Cha TA, et al. Classification of hepatitis C virus into six major genotypes and a series of subtypes by phylogenetic analysis of the NS-5 region. *The Journal of general virology.* Nov 1993;74 (Pt 11):2391-2399.

13. Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* Jun 2011;9(6):509-516.e501.

14. Blatt LM, Mutchnick MG, Tong MJ, et al. Assessment of hepatitis C virus RNA and genotype from 6807 patients with chronic hepatitis C in the United States. *Journal of viral hepatitis.* May 2000;7(3):196-202.

15. Germer JJ, Mandrekar JN, Bendel JL, Mitchell PS, Yao JD. Hepatitis C virus genotypes in clinical specimens tested at a national reference testing laboratory in the United States. *Journal of clinical microbiology.* Aug 2011;49(8):3040-3043.

16. Manos MM, Shvachko VA, Murphy RC, Arduino JM, Shire NJ. Distribution of hepatitis C virus genotypes in a diverse US integrated health care population. *Journal of medical virology.* Nov 2012;84(11):1744-1750.

17. Nainan OV, Alter MJ, Kruszon-Moran D, et al. Hepatitis C virus genotypes and viral concentrations in participants of a general population survey in the United States. *Gastroenterology.* Aug 2006;131(2):478-484.

18. Zein NN, Rakela J, Krawitt EL, Reddy KR, Tominaga T, Persing DH. Hepatitis C virus genotypes in the United States: epidemiology, pathogenicity, and response to interferon therapy. Collaborative Study Group. *Annals of internal medicine.* Oct 15 1996;125(8):634-639.

19. Farci P, Alter HJ, Wong D, et al. A long-term study of hepatitis C virus replication in non-A, non-B hepatitis. *The New England journal of medicine.* Jul 11 1991;325(2):98-104.

20. Alter MJ, Margolis HS, Krawczynski K, et al. The natural history of community-acquired hepatitis C in the United States. The Sentinel Counties Chronic non-A, non-B Hepatitis Study Team. *The New England journal of medicine.* Dec 31 1992;327(27):1899-1905.

21. Barrera JM, Bruguera M, Ercilla MG, et al. Persistent hepatitis C viremia after acute self-limiting posttransfusion hepatitis C. *Hepatology.* Mar 1995;21(3):639-644.

22. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology.* Aug 2008;48(2):418-431.

23. Freeman AJ, Dore GJ, Law MG, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology.* Oct 2001;34(4 Pt 1):809-816.

24. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature.* Oct 8 2009;461(7265):798-801.

25. Grebely J, Petoumenos K, Hellard M, et al. Potential role for interleukin-28B genotype in treatment decision-making in recent hepatitis C virus infection. *Hepatology.* Oct 2010;52(4):1216-1224.

26. Tillmann HL, Thompson AJ, Patel K, et al. A polymorphism near IL28B is associated with spontaneous clearance of acute hepatitis C virus and jaundice. *Gastroenterology.* Nov 2010;139(5):1586-1592, 1592.e1581.

27. Suppiah V, Moldovan M, Ahlenstiel G, et al. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nature genetics.* Oct 2009;41(10):1100-1104.

28. Chen Y, Xu HX, Wang LJ, Liu XX, Mahato RI, Zhao YR. Meta-analysis: IL28B polymorphisms predict sustained viral response in HCV patients treated with pegylated interferon-alpha and ribavirin. *Alimentary pharmacology & therapeutics.* Jul 2012;36(2):91-103.

29. Denniston MM, Klevens RM, McQuillan GM, Jiles RB. Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: National Health and Nutrition Examination Survey 2001-2008. *Hepatology.* Jun 2012;55(6):1652-1661.

30. Moorman AC, Gordon SC, Rupp LB, et al. Baseline characteristics and mortality among people in care for chronic viral hepatitis: the chronic hepatitis cohort study. *Clin Infect Dis.* Jan 2013;56(1):40-50.

31. Moyer VA. Screening for hepatitis C virus infection in adults: U.S. Preventive Services Task Force recommendation statement. *Annals of internal medicine.* Sep 3 2013;159(5):349-357.

32. Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Ward JW. Hepatitis C virus testing of persons born during 1945-1965: recommendations from the Centers for Disease Control and Prevention. *Annals of internal medicine.* Dec 4 2012;157(11):817-822.

33. Bonis PA, Tong MJ, Blatt LM, Conrad A, Griffith JL. A predictive model for the development of hepatocellular carcinoma, liver failure, or liver transplantation for patients presenting to clinic with chronic hepatitis C. *The American journal of gastroenterology.* Jun 1999;94(6):1605-1612.

34. Ghany MG, Kim HY, Stoddard A, Wright EC, Seeff LB, Lok AS. Predicting clinical outcomes using baseline and follow-up laboratory data from the hepatitis C long-term treatment against cirrhosis trial. *Hepatology.* Nov 2011;54(5):1527-1537.

35. Ghany MG, Lok AS, Everhart JE, et al. Predicting clinical and histologic outcomes based on standard laboratory tests in advanced chronic hepatitis C. *Gastroenterology.* Jan 2010;138(1):136-146.

36. Tong MJ, el-Farra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis C. *The New England journal of medicine.* Jun 1 1995;332(22):1463-1466.

37. Fried MW, Buti M, Dore GJ, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naive genotype 1 hepatitis C: The randomized PILLAR study. *Hepatology.* Dec 2013;58(6):1918-1929.

38. Ng V, Saab S. Effects of a sustained virologic response on outcomes of patients with chronic hepatitis C. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* Nov 2011;9(11):923-930.

39. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *The New England journal of medicine.* Sep 26 2002;347(13):975-982.

40. Kramer JR, Kanwal F, Richardson P, Mei M, El-Serag HB. Gaps in the achievement of effectiveness of HCV treatment in national VA practice. *Journal of hepatology.* Feb 2012;56(2):320-325.

41. Zeuzem S, Hultcrantz R, Bourliere M, et al. Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. *Journal of hepatology.* Jun 2004;40(6):993-999.

42. Gaetano JN, Reau N. Hepatitis C: management of side effects in the era of direct-acting antivirals. *Current gastroenterology reports.* Jan 2013;15(1):305.

43. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology.* Oct 2011;54(4):1433-1444.

44. Myers RP, Ramji A, Bilodeau M, Wong S, Feld JJ. An update on the management of hepatitis C: consensus guidelines from the Canadian Association for the Study of the Liver. *Canadian journal of gastroenterology = Journal canadien de gastroenterologie.* Jun 2012;26(6):359-375.

45. Ramachandran P, Fraser A, Agarwal K, et al. UK consensus guidelines for the use of the protease inhibitors boceprevir and telaprevir in genotype 1 chronic hepatitis C infected patients. *Alimentary pharmacology & therapeutics.* Mar 2012;35(6):647-662.

46. Hezode C. Boceprevir and telaprevir for the treatment of chronic hepatitis C: safety management in clinical practice. *Liver international : official journal of the International Association for the Study of the Liver.* Feb 2012;32 Suppl 1:32-38.

47. Hezode C, Fontaine H, Dorival C, et al. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. *Journal of hepatology.* Sep 2013;59(3):434-441.

48. Reesink HW, Zeuzem S, Weegink CJ, et al. Rapid decline of viral RNA in hepatitis C patients treated with VX-950: a phase Ib, placebo-controlled, randomized study. *Gastroenterology.* Oct 2006;131(4):997-1002.

49. Susser S, Welsch C, Wang Y, et al. Characterization of resistance to the protease inhibitor boceprevir in hepatitis C virus-infected patients. *Hepatology.* Dec 2009;50(6):1709-1718.

50. Hill A, Khoo S, Fortunak J, Simmons B, Ford N. Minimum costs for producing Hepatitis C Direct-acting Antivirals, for use in large-scale treatment access programs in developing countries. *Clin Infect Dis.* Jan 6 2014.

51. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *The New England journal of medicine.* Mar 31 2011;364(13):1207-1217.

52. Hezode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *The New England journal of medicine.* Apr 30 2009;360(18):1839-1850.

53. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *The New England journal of medicine.* Jun 23 2011;364(25):2405-2416.

54. Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *Lancet.* Aug 28 2010;376(9742):705-716.

55. McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *The New England journal of medicine.* Apr 30 2009;360(18):1827-1838.

56. McHutchison JG, Manns MP, Muir AJ, et al. Telaprevir for previously treated chronic HCV infection. *The New England journal of medicine.* Apr 8 2010;362(14):1292-1303.

57. Poordad F, McCone J, Jr., Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *The New England journal of medicine.* Mar 31 2011;364(13):1195-1206.

58. Sulkowski M, Pol S, Mallolas J, et al. Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomised, double-blind, controlled phase 2 trial. *The Lancet infectious diseases.* Jul 2013;13(7):597-605.

59. Hayashi N, Seto C, Kato M, Komada Y, Goto S. Once-daily simeprevir (TMC435) with peginterferon/ribavirin for treatment-naive hepatitis C genotype 1-infected patients in Japan: the DRAGON study. *Journal of gastroenterology.* Sep 5 2013.

60. Jacobson I, Dore GJ, Foster GR, et al. Simeprevir (Tmc435) with Peginterferon/Ribavirin for Chronic Hcv Genotype-1 Infection in Treatment-Naive Patients: Results from Quest-1, a Phase Iii Trial. *Journal of Hepatology.* Apr 2013;58(Suppl. 1):S574-S574.

61. Jacobson IM, Dore GJ, Foster G, et al. Simeprevir (TMC435) with peginterferon/ribavirin for chronic hcv genotype-1 infection in treatment-nai;auve patients: Results from quest-1, a phase III trial. *Gastroenterology.* 2013;144(5):S374.

62. Jacobson IM, Ghalib RH, Rodriguez-Torres M, et al. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naive and prior null responder patients: The COSMOS study. *Hepatology.* Dec 2013;58(6):1379A-1380A.

63. Lawitz E, Forns X, Zeuzem S, et al. Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic hcv genotype 1 infection in patients who relapsed after previous interferon-based therapy: Results from promise, a phase III trial. *Gastroenterology.* 2013;144(5):S151.

64. Manns M, Marcellin P, Poordad FPF, et al. Simeprevir (Tmc435) with Peginterferon/Ribavirin for Treatment of Chronic Hcv Genotype-1 Infection in Treatment-Naive Patients: Results from Quest-2, a Phase Iii Trial. *Journal of Hepatology.* Apr 2013;58(Suppl. 1):S568-S568.

65. Poordad F, Manns MP, Marcellin P, et al. Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic hcv genotype-1 infection in treatment-naive patients: Results from quest-2, a phase III trial. *Gastroenterology.* 2013;144(5):S151.

66. Scott J, Gilles L, Fu M, et al. Patients with chronic hepatitisc virus treated with simeprevir added to peginterferon and ribavirin experienced less time with fa tigue, depressive symptoms, and functional limitations: Results from patients in the quest-1, quest-2, and promise studies. *Value in Health.* 2013;16(7):A362.

67. Scott JA, Gilles L, Fu M, et al. Adding simeprevir to peginterferon/ribavirin for HCV shortens time with patient-reported symptoms and impairment in quality of life: Results from the simeprevir Phase III QUEST 1, QUEST 2 and PROMISE studies. *Hepatology.* 2013;58(4):753A.

68. Zeuzem S, Berg T, Gane E, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. *Gastroenterology.* Feb 2014;146(2):430-441 e436.

69. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *The New England journal of medicine.* Jan 3 2013;368(1):34-44.

70. Gane EJ, Stedman CA, Hyland RH, et al. All-Oral Sofosbuvir-Based 12-Week Regimens for the Treatment of Chronic Hcv Infection: The Electron Study. *Journal of Hepatology.* Apr 2013;58:S6-S7.

71. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *The New England journal of medicine.* May 16 2013;368(20):1867-1877.

72. Kowdley KV, Lawitz E, Crespo I, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. *Lancet.* Jun 15 2013;381(9883):2100-2107.

73. Lawitz E, Lalezari JP, Hassanein T, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *The Lancet infectious diseases.* May 2013;13(5):401-408.

74. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *The New England journal of medicine.* May 16 2013;368(20):1878-1887.

75. Osinusi A, Meissner EG, Lee YJ, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. *Jama.* Aug 28 2013;310(8):804-811.

76. Sulkowski M, Rodriguez-Torres M, Lalezari JP. All-oral therapy with sofosbuvir plus ribavirin for the treatment of HCV genotype 1, 2, and 3 infections in patients co-infected with HIV (PHOTON-1). 64th Annual Meeting of the Amercian Association for the Study of Liver Diseases; November 1-5, 2013, 2013; Washington, D.C.

77. Younossi Z, Stepanova M, Gerber L, et al. Successful treatment with sofosbuvir (SOF) regimen improves patient-reported outcomes (PROS) in patients with chronic Hepatitis c (CH-C). *American Journal of Gastroenterology.* 2013;108:S144.

78. Younossi ZM, Stepanova M, Lawitz E, et al. Successful treatment with sofosbuvir regimen improves fatigue scores in patients with chronic hepatitis C (CHC). *Hepatology.* 2013;58(4):1277A.

79. Zeuzem S, Dusheiko G, Salupere R. Sofosbuvir + ribavirin for 12 or 24 weeks for patients wtih HCV genotype 2 or: the VALENCE trial. 64th Annual Meeting of the Amercian Association for the Study of Liver Diseases; November 1-5, 2013, 2013; Washington, D.C.

80. Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *Journal of hepatology.* May 2010;52(5):652-657.

81. George SL, Bacon BR, Brunt EM, Mihindukulasuriya KL, Hoffmann J, Di Bisceglie AM. Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: a 5-year follow-up of 150 patients. *Hepatology.* Mar 2009;49(3):729-738.

82. Giannini EG, Basso M, Savarino V, Picciotto A. Sustained virological response to pegylated interferon and ribavirin is maintained during long-term follow-up of chronic hepatitis C patients. *Alimentary pharmacology & therapeutics.* Feb 15 2010;31(4):502-508.

83. Trapero-Marugan M, Mendoza J, Chaparro M, et al. Long-term outcome of chronic hepatitis C patients with sustained virological response to peginterferon plus ribavirin. *World journal of gastroenterology : WJG.* Jan 28 2011;17(4):493-498.

84. Koh C, Heller T, Haynes-Williams V, et al. Long-term outcome of chronic hepatitis C after sustained virological response to interferon-based therapy. *Alimentary pharmacology & therapeutics.* May 2013;37(9):887-894.

85. Marcellin P, Boyer N, Gervais A, et al. Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alpha therapy. *Annals of internal medicine.* Nov 15 1997;127(10):875-881.

86. Arora S, O'Brien C, Zeuzem S, et al. Treatment of chronic hepatitis C patients with persistently normal alanine aminotransferase levels with the combination of peginterferon alpha-2a (40 kDa) plus ribavirin: impact on health-related quality of life. *Journal of gastroenterology and hepatology.* Feb 2006;21(2):406-412.

87. Spiegel BM, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. *Hepatology.* Apr 2005;41(4):790-800.

88. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. *Annals of internal medicine.* Mar 5 2013;158(5 Pt 1):329-337.

89. Morgan TR, Ghany MG, Kim HY, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. *Hepatology.* Sep 2010;52(3):833-844.

90. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *Jama.* Dec 26 2012;308(24):2584-2593.

91. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Annals of internal medicine.* Nov 20 2007;147(10):677-684.

92. McCombs J, Matsuda T, Tonnu-Mihara I, et al. The Risk of Long-term Morbidity and Mortality in Patients With Chronic Hepatitis C: Results From an Analysis of Data From a Department of Veterans Affairs Clinical Registry. *JAMA internal medicine.* Nov 5 2013.

93. Ferreira Sda C, Carneiro Mde V, Souza FF, et al. Long-term follow-up of patients with chronic hepatitis C with sustained virologic response to interferon. *The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases.* Jul-Aug 2010;14(4):330-334.

94. Florian J, Jadhav PR, Amur S, et al. Boceprevir dosing for late responders and null responders: the role of bridging data between treatment-naive and -experienced subjects. *Hepatology.* Mar 2013;57(3):903-907.

95. Liu J, Florian J, Birnkrant D, Murray J, Jadhav PR. Interferon responsiveness does not change in treatment-experienced hepatitis C subjects: implications for drug development and clinical decisions. *Clin Infect Dis.* Sep 2012;55(5):639-644.

96. Liu J, Jadhav PR, Amur S, et al. Response-guided telaprevir therapy in prior relapsers? The role of bridging data from treatment-naive and experienced subjects. *Hepatology.* Mar 2013;57(3):897-902.

97.

98. Petta S, Cabibbo G, Enea M, et al. Cost-effectiveness of Sofosbuvir-based triple therapy for untreated patients with genotype 1 chronic hepatitis C. *Hepatology.* 2014:n/a-n/a.

99. Younossi ZM, Singer ME, Mir HM, Henry L, Hunt S. Impact of interferon-free regimens on clinical and cost outcomes for chronic hepatitis C genotype 1 patients. *Journal of hepatology.* Nov 19 2013.

100. Chan K, Lai MN, Groessl EJ, et al. Cost effectiveness of direct-acting antiviral therapy for treatment-naive patients with chronic HCV genotype 1 infection in the veterans health administration. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* Nov 2013;11(11):1503-1510.

101. Liu S, Cipriano LE, Holodniy M, Owens DK, Goldhaber-Fiebert JD. New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. *Annals of internal medicine.* Feb 21 2012;156(4):279-290.

102. Camma C, Petta S, Cabibbo G, et al. Cost-effectiveness of boceprevir or telaprevir for previously treated patients with genotype 1 chronic hepatitis C. *Journal of hepatology.* Oct 2013;59(4):658-666.

103. Camma C, Petta S, Enea M, et al. Cost-effectiveness of boceprevir or telaprevir for untreated patients with genotype 1 chronic hepatitis C. *Hepatology.* Sep 2012;56(3):850-860.

104. Cure S, Bianic F, Gavart S, Curtis S, Lee S, Dusheiko G. Cost-effectiveness of telaprevir in combination with pegylated interferon alpha and ribavirin in previously untreated chronic hepatitis C genotype 1 patients. *Journal of medical economics.* Jan 2014;17(1):65-76.

105. Ferrante SA, Chhatwal J, Brass CA, et al. Boceprevir for previously untreated patients with chronic hepatitis C Genotype 1 infection: a US-based cost-effectiveness modeling study. *BMC Infect Dis.* Apr 27 2013;13(1):190.

106. AASLD/IDSA/IAS. Recommendations for Testing, Managing, and Treating Hepatitis C. 2014; http://www.hcvguidelines.org/full-report-view. Accessed 2014, 2014.

107. Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* Mar 2010;8(3):280-288, 288.e281.

108. Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. *Clin Infect Dis.* Apr 1 2011;52(7):889-900.

109. Xu KY, Petti F. HCV Protease Sales/ Vertex ALS2200 Future. 2012; http://www.natap.org/2012/HCV/102312_02.htm. Accessed January, 2014.

110. Menzin J, White LA, Nichols C, Deniz B. The economic burden of advanced liver disease among patients with Hepatitis C Virus: a large state Medicaid perspective. *BMC Health Services Research.* 2012;12:459.

111. Manos MM, Darbinian J, Rubin J, et al. The effect of hepatitis C treatment response on medical costs: a longitudinal analysis in an integrated care setting. *J Manag Care Pharm.* 2013;19(6):438-447.

112. Red Book® Online. Thomson Reuters (Healthcare) Inc.; 2013.

113. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *JAMA.* 1996;276(15):1253-1258.

114. Fox RK, Currie SL, Evans J, et al. Hepatitis C virus infection among prisoners in the California state correctional system. *Clin Infect Dis.* 2005;41(2):177-186.

115. Gelberg L, Robertson MJ, Arangua L, et al. Prevalence, distribution, and correlates of hepatitis C virus infection among homeless adults in Los Angeles. *Public health reports.* Jul-Aug 2012;127(4):407-421.

116. Bini EJ, Brau N, Currie S, et al. Prospective multicenter study of eligibility for antiviral therapy among 4,084 U.S. veterans with chronic hepatitis C virus infection. *The American journal of gastroenterology.* Aug 2005;100(8):1772-1779.

117. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. *The Lancet.* 1997;349(9055):825-832.

118. Bichoupan K, Martel-Laferriere V, Sachs D, et al. Costs of Telaprevir-based Triple Therapy Including Adverse Event Management at the Mount Sinai Medical Center, NY: $189,000 per SVR. Paper presented at: 64th Annual Meeting of the American Association for the Study of Liver Diseases; 2013/11/05, 2013; Washington, DC.

119. Buti M, Casado MA, Esteban R. Evaluating the cost of sustained virologic response in naive chronic hepatitis C patients treated a la carte. *Alimentary pharmacology & therapeutics.* Sep 1 2007;26(5):705-716.

120. Hill AM, Clotet B, Johnson M, Stoll M, Bellos N, Smets E. Costs to Achieve Undetectable HIV RNA with Darunavir-Containing Highly Active Antiretroviral Therapy in Highly Pretreated Patients: the POWER Experience. *Pharmacoeconomics.* 2010;28 Suppl 1:69-81.

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.