Public Comments Received on "*Newest Treatments for Hepatitis C, Genotype 1"*

1. Rachel McLean, MPH, Viral Hepatitis Prevention Coordinator / STD Healthcare Policy Analyst, STD Control Branch, California Department of Public Health, Sacramento, CA
2. Folashade Naku, PharmD, MS, BCPS
3. Laura Bessen, MD, Vice President, Head of US Medical, Bristol-Myers Squibb Co., New York, NY
4. Emalie Huriaux, MPH, Director of Federal & State Affairs, Project Inform, San Francisco, CA
5. Connie Chiang, PharmD, Associate Director, Medical Information, Janssen Scientific Affairs, LLC, Titusville, NJ
6. Hans Reiser, MD, Senior Vice President, Medical Affairs, Gilead Sciences Inc., Foster City, CA
7. Nikil Patel, PharmD, Director, Healthcare Solutions, Global Medical Affairs, AbbVie, Inc, Mettawa, IL
8. Bill Remak, BSN, President and CEO, and Chairman of the Board, California Hepatitis C Task Force, Petaluma, CA
9. O.A.S.I.S. Clinic, Oakland, CA
10. Project Inform and the National Viral Hepatitis Roundtable, San Francisco, CA

Dear CTAF:

Thank you for the opportunity to provide comments on the draft report entitled "The Comparative Clinical Effectivenes and Value of Novel Combination Therapies for the Treatment of Patients with Genotype 1 Chronic Hepatitis C Infection."

Overall, I applaud CTAF for conducting a more robust analysis than for the previous report, such as by conducting analyses stratified by prior HCV treatment status and fibrosis score, and by partnering closely with a recognized hepatitis expert (Dr. Rena Fox).

Below are several comments for your consideration.

* Cost-Effectiveness--Exclusion of drugs pending FDA approval
It wasn't clear until I read the full body of the report that the cost-effectiveness analysis did not include AbbVie's 3D combination or BMS/Gilead's daclatasvir/sofosbuvir combination because these drugs have not been FDA-approved or priced in the U.S. Without that information in the Executive Summary, I mistakenly assumed the analysis had found ledipasvir/sofosbuvir more cost effective than the drugs currently pending FDA approval.

Suggestion: Make explicit in the Executive Summary that the cost-effectiveness analysis could not include 3D or DCV/SOF because the prices are not yet available for these drugs, and that the findings of subsequent analyses will be highly dependent on the prices of these drugs. This is implied in the statement re: the $34K-$42K price threshold mentioned in the last section of the Executive Summary, but a busy reader might miss this point.

* Cost-effectiveness--Assumption that 50% of persons with HCV genotype 1 will present for treatment
The report presents an analysis assuming 50% of persons with HCV genotype 1 will present for treatment. Historically, and as cited in your report, treatment rates have been <15%. It is unclear whether increasing treatment rates from <15% to 50% is realistic. There is limited capacity among hepatologists to manage patients with HCV who present for treatment, particularly given the complexities of navigating managed care prior authorization processes, patient assistance programs, and other hurdles even when patients are eligible for treatment. Also, many patients and providers remain unaware of the new treatments or have other competing health issues and concerns. For these reasons, it may be worth noting that it is unclear whether it is realistic for 50% of people with HCV to actually present for treatment in any given year, or even over the next 5-10 years.

Suggestion: Add a note in the Executive Summary and full body of the text that it may not be realistic for 50% of patients with HCV to present for tx. Thus, real-world cost projections may differ from those identified during this analysis.

* Secondary prevention
The full body of the report makes clear that the analysis did not take into consideration potential savings to health care systems with high HCV prevalence (such as Medi-Cal and state prisons) of HCV treatment as prevention. While this area requires further research, modeling studies have suggested that HCV treatment, particularly in combination with HCV prevention measures such as syringe exchange programs and opiate-replacement therapy, has the potential to substantially reduce HCV prevalence in high-risk populations, such as injection drug users (Martin, 2013). Given the high incidence (~25%/year) of HCV in young injection drug users (IDUS) (Hahn, 2002), and the evidence of HCV transmission in California state prisons associated with sharing of injection and/or tattoo equipment (Tsang, 2001), prevention strategies for high-risk populations will be critical for preventing future health care expenditures associated with incident infections, but this issue is not addressed in this report.

The report does not also address the potential cost-effectiveness, which has yet to be fully evaluated, of

HCV treatment as prevention for women of child-bearing age who have chronic HCV infection and who wish to become pregnant, a group recently recommended for treatment by AASLD/IDSA.

Suggestion: Mention in the Executive Summary that the analysis did not take into consideration potential cost savings / influence on cost-effectiveness models that could theoretically be realized through HCV treatment as prevention strategies with high-risk populations, such as prisoners and IDUs, or for women of child-bearing age who have chronic HCV infection and who wish to become pregnant.

References

Martin NK; et al. Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy. *Clin Infect Dis.* 2013;57(Suppl 2):S39-45.

Martin NK; et al. Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology.* 2013;58(5):1598-609.

Hahn JA. Hepatitis C virus seroconversion among young injection drug users: relationships and risks. J Infect Dis. 2002 Dec 1;186(11):1558-64.

Tsang TH, Horowitz E, Vugia D. Transmission of hepatitis C through tattooing in a United States prison. Am J Gastroenterol. 2001; 96(4):1304-5.

Thanks again for the opportunity to provide comments on the CTAF report. Please feel free to contact me with questions at (510) 620-3403 / Rachel.McLean@cdph.ca.gov.

Sincerely,

Rachel

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Comment on draft assessment of

Comparative Clinical Effectiveness and Value of Novel Combination therapies for patients with Genotype 1 Chronic Hepatitis C infection.

By Folashade Naku, Pharm.D.,MS,BCPS.

I cannot comment on the cost effectiveness model because the technical document is not available for review. I hope results of the cost effectiveness panes will be shown during the seminar to depict treatments that are dominant and dominated.

The Budget Impact Analysis (BIA) methodology does not follow the “Principles of Good Practice” for conducting budget impact analysis. The International Society for Pharmacoeconomics Outcomes Research (ISPOR) has published consensus guidelines and recommendations that serve as a framework for conducting BIA.A Budget Impact Analysis is a means of synthesizing available knowledge at the time of a coverage or formulary listing decision to estimate the likely financial consequences of that decision for a health care system. The ISPOR recommendations provide guidance on the acquisition and use of data, and offer a common reporting format that will promote standardization and transparency(1).

The methodology in the draft is flawed because there should be no “cost offsets” in a budget impact analysis. As the term BIA suggests, the purpose is to determine the immediate affordability of a treatment during a budgetary year or years. The cost data presented in March and included in this draft is a Cost Benefit Analysis, which is a beneficial analysis only from the perspective of the drug manufacturer as a marketing tool. The budget impact analysis needs to be from the perspective of the payer or insurance companies. The use of “fluff” terms such as “Care Value Analysis” and “Health System Value Analysis” are not standard terminologies in health economic evaluations but I must admit that these terms evoke an emotional response from the reader, if that is what it is intended to do.

AASLD and USPSTF recommend HCV testing and linkage to care for the following groups : At least once for persons born between 1945 and 1965 (Birth cohort) and for other persons with risk factors for HCV infection- behaviors, exposures, and conditions associated with an increased risk of HCV infection-(Risk cohort)(2,3). One estimation for the US population, of the impact on persons tested using a one-time birth-cohort (1945 to 1965) screening performed over a single year estimated that approximately 60,400,000 persons would undergo HCV antibody testing compared with 14,800,000 using traditional risk-based testing. A model which assumed full implementation of testing with intention to treat similar to what has occurred with colorectal cancer screening provided a more realistic estimate of approximately 12 million persons

undergoing HCV antibody testing in the first 3 years of implementation of these recommendation(4). Since these are current treatment recommendations the size and characteristics of the eligible population should be properly accounted for in the economic analysis.

A time horizon of more than one year for a BIA in the hepatitis C domain is currently unrealistic because of the dynamic nature of the field. There is always some degree of uncertainty surrounding new medical technologies after their initial introduction. This is because the effectiveness and the cost vary over the lifetime of the technology. A good example is the introduction of Boceprevir and Telaprevir in 2011. By late 2013 with the arrival of Sofosbuvir, these drugs were removed from the treatment guideline because of the advent of more effective therapy. The most usual reason for the demise of medical products after an initial period of dominance is the appearance of adverse events or contraindication in use. The treatment guidelines could look very different when other pipeline drugs arrive on the market and a more crowded market space may encourage competition and thus lower prices.

References.

1. http://www.ispor.org/budget-impact-health-study-guideline.pdf
2. U.S. Preventive Services Task Force > Topic Index > Screening for Hepatitis C Virus Infection

3. AASLD/IDSA/IAS-USA. Recommendations for testing, managing, and treating hepatitis C.

4. Rein DB, Smith BD, Wittenborn JS, Lesesne SB, Wagner LD, Roblin DW, et al. The Cost-Effectiveness of Birth-Cohort Screening for Hepatitis C Antibody in U.S. Primary Care Settings. Ann Intern Med. 2012;156:263-270. doi:10.7326/0003-4819-156-4-20120221Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ Ann The prevalence of hepatitis C virus infection in the United States, 1999 through 2002.Armstrong GL1, Intern Med. 2006 May 16;144(10):705-14

Bristol-Myers Squibb Company

December 5, 2014

Dear California Technology Assessment Forum:

On behalf of Bristol-Myers Squibb, US Medical we appreciate the opportunity to comment on the draft report **"The Comparative Clinical Effectiveness and Value of Novel Combination Therapies for the Treatment of Patients with Genotype 1 Chronic Hepatitis C Infection".** We greatly acknowledge and thank you for your time, consultation, and consideration in the preparation of the draft, as well.

We found this assessment timely, comprehensive and relevant given the significant changes and evolving landscape in Hepatitis C. As compared to the March 2014 report, this report provides greater transparency with regards to methods used to conduct the literature analysis, as well as the measures and methods used to assess the cost-effectiveness and value of treatment regimens.

Our detailed comments for consideration are provided below:

1. Page ES2, Table ES2 – Please note Daklinza is not a branded name in the United States market, as it has yet to be approved. Please change to daclatasvir.

2. Page ES4, Figure ES1 – For this figure and other comparator tables, we would caution the limitations of making side-by-side comparisons between clinical trials with different patient populations and different trial designs. For example, Study-040 is a Phase II trial versus other Phase III trials presented here. In addition, Figure ES1 is labeled with both Fibrosis status and cirrhosis status but may not necessarily be agreement in terminology. For example, for the treatment naïve or treatment experienced cirrhotic data sets, it should be noted that although patients were enrolled in Study-040 (DCV/SOF) with F4 fibrosis by FibroTest, the patient inclusion criteria further required patients to be non-cirrhotic based on a biopsy. Therefore, there were no cirrhotic patients (by biopsy) enrolled. Attributing patients as cirrhotic in the figure may be construed as misleading.

3. Page ES4, Figure ES1 – Please consider including data from the DCV+SOF+RBV arm in Study-040. Although this is consistent with data presented in the figure from the ION studies (as data from SOF+LDV+RBV group were also not included), including these patients would increase the sample size of patients while not impacting efficacy with this combination due to the high SVR rates in all arms.

4. Page ES6 – The inclusion of the March 2014 CTAF review of genotypes 2 and 3 in the Health System Value Analysis contradicts the stated scope of work and does not incorporate any emerging study results which are notable. Furthermore, the resultant Health Systems Value Analysis and the potential budgetary impact of HCV therapy in Genotype 3 could change significantly with the advent of new therapies in HCV and shifting to shorter (12 vs. 24 week) treatment durations (e.g., 12 weeks was shown in Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week combination treatment with daclatasvir (DCV) and sofosbuvir (SOF) in patients infected with HCV genotype (GT) 3: ALLY-3 phase 3 study.

Hepatology. 2014;60(1)(suppl)). The last paragraph states that new HCV treatments would increase costs by $1.6 billion, $545 million and $901million, please include which specific HCV treatment regimens are being referenced in this sentence. The PMPM calculation is unclear. Please provide total population details in the Executive Summary.

5. Page 3 - The last paragraph lists the most common causes of death among patients with chronic hepatitis as being drug overdose, HIV, and liver disease. These statements are referenced with papers in specific populations (Citation 28, opioid abusers; Citation 30, Inner City residents) and not reflecting the overall population (Citation 47) chronically infected in the US. This is one of the reasons why CDC took the birth cohort approach beyond the risk based approach. These statements contribute to the stigma of HCV identifying people with chronic HCV as drug abusers, which is far from the reality. Of note, more data is pending from the CDC on the evaluation of death certificates. HCV is largely underreported in death certificates.

6. Page 4, Table 1 - This table is missing two key publications (Aging of HCV population, (http://dx.doi.org/10.1053/j.gastro.2009.09.067) and Increasing mortality from hepatic and extrahepatic diseases in HCV (J Infect Dis. (2012) 206 (4): 469-477. http://dx.doi.org/10.1093/infdis/jis385))

7. Page 4 - Please consider adding genotype to the list of factors associated with cirrhosis (Source: AASLD Guidelines)

8. Page 7 – While recent real world data from a CVS/Caremark report suggest treatment discontinuation rates higher than reported in clinical trials, it should be noted that this report was not peer-reviewed and methods were not clearly stated. In contrast, the HCV-TARGET (which was funded through unrestricted grants not “a consortium of pharmaceutical companies” as the report states, which implies a bias of the investigators and is inaccurate) real-world registry findings were initially similar to observed clinical trial rates. In addition, more recent and complete data has been presented at the 2014 AASLD conference, which reported a discontinuation rate of 3% overall (out of 2063 patients who initiated therapy). Early discontinuation due to lack of efficacy (0.4%), loss to follow-up (0.3%), or death (0.6%) was rare. Of note, the HCV-TARGET registry had a higher percentage of cirrhotic and liver transplant patients than the general HCV population and is therefore biased towards more difficult to treat patient types.

9. Page 9 – Bristol-Myers Squibb is misspelled. It should be noted that daclatasvir will NOT be approved by the FDA before the end of 2014 as stated in the report, please delete this statement.

10. Page 10, Table 2 – Under non-nucleoside polymerase inhibitor, the generic name beclabuvir should be inserted under the column “Generic Name” for BMS-791325.

11. Page 10 – Within the table, please remove the Brand names Sunvepra and Daklinza as these not approved in the US yet. Please consider restating the first paragraph below the tables with the following statements that would be more accurate: The European Commission approved the use of daclatasvir as part of combination therapy in August 2014, but it has not yet been approved in the United States. Bristol-Myers Squibb submitted two New Drug Applications in the US in April 2014. One

for daclatasvir and one for asunaprevir. The basis for both applications was the combination of daclatasvir and asunaprevir in a 24 week regimen for genotype 1b HCV infection. Given the rapidly evolving hepatitis C treatment landscape in the U.S., BMS decided to not pursue FDA approval for this regimen and therefore withdrew the asunaprevir NDA in October 2014, while pursuing FDA approval of daclatasvir in other treatment regimens. The daclatasvir/asunaprevir combination was approved in Japan in July 2014. BMS also has three phase 3 studies of the combination of daclatasvir, asunaprevir, and beclabuvir (BMS-791325) in progress (UNITY 1, 2, and 3).

12. Page 21, Table – For ALLY-2, recommend adding under column "Comparator" DCV+SOF for 8 weeks vs. DCV+SOF for 12 weeks.

13. Page 24 – Please note Daklinza is a brand name used in Japan and parts of the EU, where the use and marketing of daclatasvir is approved, and should be removed from this list as it is not currently approved or marketed in the US.

14. Page 24 – A fixed-effects meta-analysis model was used in the analysis. A random-effects model may be more appropriate to account for heterogeneity in study populations.

15. Page 26 – The ICER Evidence Rating Matrix is used to evaluate the evidence for each therapy. Please provide more information on this reference and how it was validated.

16. Pages 27 & 28 – According to the report, the key patient outcome is SVR24 as the standard primary outcome of HCV studies with SVR12 representing an "intermediate outcome", and further states that this is a limitation of these studies. However, it should be noted that the SVR12 is now the preferred efficacy outcome recommended by the FDA (See FDA draft guidance details provided at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm225333.pdf).

17. Page 28 – Again, it should be noted that DCV is NOT expected to launch by end of 2014.

18. Page 31 – Withdrawal of NDA for DCV+ASV is mentioned, however it should be noted that only the NDA for asunaprevir was withdrawn in October 2014. See item 11 above for further details

19. Page 33, Table 5 – DCV+SOF x 12 weeks shows N=35 for treatment duration of 12 weeks. However, it should reflect N=41 since all patients in study were technically non-cirrhotic. All F4 patients were ruled out as having no cirrhosis based on biopsy. For patients treated with DCV+SOF x 24 weeks, N=14 to reflect those GT 1 patients treated for 24 weeks that are treatment naive. Please consider adding the DCV+SOF+RBV arm results as including these patients would increase the sample size of patients while not impacting efficacy with this combination due to the high SVR rates in all arms.

20. Page 35, Table 6 – DCV+SOF x 12 weeks shows N=6 for treatment duration of 12 weeks. However, it should reflect N=0 since all patients in study were technically non-cirrhotic by biopsy. For patients treated with DCV+SOF x 24 weeks, N=0 should also be reflect for the same reasons as mentioned above. Essentially there is no data with DCV+SOF from Study-040.

21. Page 36, Table 7 – DCV+SOF x 24 weeks in GT 1 Treatment Experienced shows N=18, however, the correct N=21 since all patients were non-cirrhotic based on biopsy that ruled out F4 by FibroTest. Please consider adding the DCV+SOF+RBV arm results as including these patients would increase the sample size of patients while not impacting efficacy with this combination due to the high SVR rates in all arms.

22. Page 38, Table 8 – DCV+SOF x 24 weeks in GT 1 Treatment Experienced Cirrhotic shows N=3, however, it should be N=0 since all patients were technically not cirrhotic as patients were further ruled out by biopsy if FibroTest showed F4.

23. Page 39, Table 9 – DCV+SOF x 12 weeks Fatigue shows 37%. This should be corrected to 39%. Headache shows 22%. This should be corrected to 34%.

24. Page 50, Table 11 – With regards to the annual cost of CHC-related health care by disease state (Mc-Adam Marx article), if all costs are converted to 2014 dollars, model appears to use incremental costs vs. all-cause costs for disease state costs. May want to consider using all-cause costs since the patient is not being compared to someone without HCV but incurring the cost of the disease over a year. For example, instead of $188,671 for the reported cost of year one liver transplant this would instead be $218,758 ($190,995 of the all-cause cost inflated to 2014). Also, with regards to the Cost of CHC related health care, it doesn't appear that the costs were adjusted to 2014 dollars. This has an effect, albeit limited, on the reported cost-offsets.

25. Page 64 - It would be helpful to see the data and calculations for the cost to avoid one HCV-related death ($24 million at 1-yr). Showing the cost to avoid other complications (HCC, transplant, etc) may be of interest as well.

26. Page 66 & Appendix G – Stated base PMPM is $611. It would be helpful to have a detailed description of how this was calculated (population included, costs included, SOF cost included). When using a 0.5 – 1% acceptability for PMPM increases, what is the baseline? And is this true regardless of baseline? As mentioned previously, as time goes on the likely regimen will be dynamic as will be the duration of treatment, which would impact baselines.

27. Page 68 – The Budgetary Impact to Medi-Cal specifically is addressed in 1, 5, and 20-year intervals using standard WAC pricing for drugs. We would like to point out that this assessment omits the federally mandated rebates that a pharmaceutical manufacturer pays to the State Medicaid programs (http://www.medicaid.gov/medicaid-chip-program-information/by-topics/benefits/prescription-drugs/medicaid-drug-rebate-program.html). This is public information and applies to all medications within the Medicaid program. The Mandated Rebates begin at 23.1% off of the Average Manufacturers Price (AMP). These rebates often increase over time, the longer a drug is on the market. Built into the Mandated Rebate amount is a CPI penalty that is cumulative by quarter. This is paid on top of the 23.1%. In addition, another requirement, the best price penalty ensures that Medicaid programs receive the best commercially-available discount. Over the time intervals used in this analysis with Medi-Cal, the 23.1% rebate can grow within 1, 5, and more significantly, within a 20-year interval. While looking at a time period of 5 through 20 years, it should also be noted that the mandated rebate has

historically increased from 10%, to 15.1%, to 23.1% since it was passed by the United States Congress. Furthermore, the mandated rebate may be enhanced by a supplemental rebate offered by the manufacturer. Therefore, a simplistic reliance on publicly available pricing of a particular product(s) fails to reflect actual costs incurred and over estimates the drug impact on the model by a State Medicaid program.

28. Page 111, Appendix D – Disease transition rates used in the model are referenced from Thein, Hagan, and Coffin Please consider including Martin article as well.(Martin et al., Hepatology 2012;55:49-57).

29. Page 107, Appendix Table C13. In the paragraph below this table, it states that ASV dose was reduced from 600mg BID to 200mg BID due to elevations in liver enzymes. The sentence preceding this statement indicates that the likely recommended dosing schedule for asunaprevir would have been 100mg BID. This implies that the further dose reduction was also due to liver enzyme elevations; however, it was due to a change in the formulation from tablet to soft gel capsule. This is important to clarify because the future DCV/ASV/Beclabuvir regimen will include the 200mg dose of asunaprevir BID as a tablet formulation (and 100mg ASV soft gel capsules will no longer be available). So as not to confuse the reader, CTAF may consider removing the discussion on 100mg dosing as it is no longer relevant.

In conclusion, we value this report as a timely and important analysis related to the HCV Epidemic, where HCV is a leading cause of cirrhosis, liver cancer, and advanced or end-stage liver disease, possibly leading to the need for a liver transplant. Successful treatment of HCV infection would lower the risk of transmitting HCV, prevent new infection, and reduce the burden to the healthcare system. Societal benefits of treatment, both direct and indirect, are vital considerations for policy makers when weighing public health options.

This draft report recommends a pricing range of $36,000 - $42,000 for these new and more effective HCV treatments (pages 14, 70 and 72). The amount suggested is no greater than the quoted $42,000 cost of current treatment regimens (price cited from page 70). In our opinion, any pricing recommendation should take into account the advancement of these new-to-market products, and their associated cost-effectiveness given an associated offset of other treatment costs, while also encouraging future innovative development.

The information provided is in response to the public comment period and is not intended as an endorsement of any products mentioned. We welcome the opportunity to discuss any of the material contained within this reply and thank you, in advance, for your consideration.

Sincerely,

Laura Bessen, MD
Vice President, Head of US Medical
Bristol-Myers Squibb

To Whom It May Concern:

Thank you for the opportunity to comment on CTAF's draft report "The Comparative Clinical Effectiveness and Value of Novel Combination Therapies for the Treatment of Patients with Genotype 1 Chronic Hepatitis C Infection."

Below are Project Inform's comments for your consideration.

- The report fails to examine infections averted through various treatment strategies and the implications of "cure as prevention", particularly among people who inject drugs, women of childbearing age, and people in prison. This omission leaves the cost-effectiveness analysis woefully inadequate to truly assess the implications of the various treatment strategies outlined in the report. We highly recommend that you include this analysis in the final cost-effectiveness analysis, since infections averted through a "cure as prevention" model is a critical component of understanding the value of novel hepatitis C treatment medications, both from a public health perspective and for payers, such as Medicaid programs and prison health systems.

- There is nothing in the report that examines quality of life or patient-related outcomes. There are reports, papers, and conference presentations that show the value of achieving an SVR. We think this information should be considered, as it is critical to providing the full picture of the value of treatments.

- The AbbVie regimen will likely be approved in the next two weeks. At that time the price will be announced. Will CTAF revise this analysis to include the price of this regimen? The inclusion of an analysis based on the price of this regimen is critical to providing the most useful and applicable document for policy makers.

- Page 12 – Clarify that the AASLD/IDSA/IAS-USA guidelines section on in when and in whom to initiate therapy provides prioritization that is meant for clinicians to use, not payers, and is not meant to exclude anyone from treatment. The document states that, "Evidence clearly supports treatment in all HCV-infected persons, except those with limited life expectancy (less than 12 months) due to non-liver-related comorbid conditions."

- Throughout the report there are references to outdated data, which is understandable since this draft was developed prior to AASLD's annual "Liver Meeting", at which a great deal of new data was presented.

    - For example, on page 31 the report references the NIH ERADICATE trial that assessed Harvoni in HIV/HCV co-infected persons. The report states that SVR12 was only available for 10, which was data from EASL in April. At the Liver Meeting data was presented that 49 of 50 achieved an SVR12. Similarly, there was good data presented at the Liver Meeting on post-transplant treatment and cost-effectiveness. We suggest that an analysis of data presented at the Liver Meeting be conducted and the draft report updated as appropriate.

- It is vital to draw data from the HCV TARGET study, which looks at real-world HCV treatment outcomes. Much of this data to date was presented at the Liver Meeting.

- The assumption in the report that 50% of genotype 1 patients will be treated in a year seems wildly unrealistic given that current treatment rates are 15% or less. The history of addressing HIV, a similar chronic infectious disease, provides a useful analogy to addressing HCV. Even with the significant investment in HIV testing, care, and treatment over the last 30 years, only 33% of Americans living with HIV are prescribed antiretroviral therapy and only 25% are virally suppressed. Given this history, Dr. John Ward, the Director of the Division of Viral Hepatitis at the Centers for Disease Control & Prevention, stated at a meeting on July 29th (hosted by the National Viral Hepatitis Roundtable and the National Alliance of State & Territorial AIDS Directors) that it will take at least 15 years to successfully test and treat everyone living with hepatitis C. There are significant provider shortages, as the number of hepatologists is inadequate to treat everyone living with hepatitis C. There are also significant barriers patients and providers must manage in order to get through lengthy prior authorization and patient assistance program processes. In addition, there are many patients who are not engaged with a health care provider or who have competing priorities that make it difficult for them to access treatment. We recommend re-evaluating the assumption that 50% of genotype 1 patients will be treated in a year and use a more realistic number.

- In the report the WAC price is used for prisons. Prisons never pay the WAC price and often pay at or lower than the 340B price. We realize that these price reductions are likely to remain secret, but a failure to mention this seems dishonest at best.

We appreciate your careful consideration of public comment and look forward to the final draft of the report. Please do not hesitate to contact me if you have any questions or require additional information.

Sincerely,

Emalie Huriaux on behalf of Project Inform

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December 8, 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 Novel Combination Therapies for the Treatment of Patients with Genotype 1 Chronic Hepatitis C Infection".

We found this updated assessment timely given the recent significant changes and evolving landscape in Hepatitis C.

Comments in relation to OLYSIO® (simeprevir) are provided below:

- As noted in the draft CTAF report, the simeprevir/sofosbuvir (SMV/SOF) regimen was recently approved by the FDA. This approval was based on efficacy and safety results from the phase 2 COSMOS study. Based on this clinical evidence and lack of head-to-head trials, it would be helpful to understand how the conclusion that SMV/SOF is "less effective" than ledipasvir/sofosbuvir (LDV/SOF) was determined as noted on pages 53 and 77.
    - Tables 14 – 17 show differences in effectiveness rates between LDV/SOF and SMV/SOF of 0.07, 0.09, 0.14, and 0.08, respectively. While there are small numerical differences, it is unclear if these calculated or modeled differences support the conclusion that SMV/SOF is "less effective". Providing the thresholds used for this comparison would be helpful.
- Suggest including context into the report that the SVR rates reported for the SMV+PR regimen are based on data without the exclusion of genotype 1a patients with baseline Q80K polymorphism and are underestimated. As noted in the OLYSIO prescribing information, SMV+PR efficacy is substantially reduced in patients with baseline Q80K polymorphism and alternative therapy should be considered for these patients.

In summary, there is currently insufficient evidence to conclude SMV/SOF is less effective than other interferon-free HCV regimens. The phase 3 SMV/SOF OPTIMIST trials (page 20) are currently ongoing and will provide additional data next year.

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 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

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Inquiry #: 00097424

To: **California Technology Assessment Forum**

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

Date: **December 8, 2014**

Re: **Comments in response to " The Comparative Clinical Effectiveness and Value of Novel Combination Therapies for the Treatment of Patients with Genotype 1 Chronic Hepatitis C Infection" Draft Report (November 17, 2014)**

Gilead commends the California Technology Assessment Forum (CTAF) and the Institute for Clinical and Economic Review (ICER) for conducting a thorough, timely and comprehensive review of the available information regarding treatments for chronic HCV infection.

We appreciate the opportunity to provide our perspective, and to respond to specific details and concepts discussed within the draft CTAF/ICER report dated November 17, 2014. There are five areas of focus for your consideration:

a. Unmet medical needs of HCV patients
b. Suggestions for additional analyses on cost-effectiveness analysis and budget impact model
c. Comments on specific data points within the report
d. Benefits of HCV treatment beyond achieving sustained virologic response, such as patient reported outcomes, decreased viral transmission and its impact on public health, and extrahepatic manifestations of infection
e. Lifetime treatment costs for chronic HCV should be placed into context of other disease areas.

A. Unmet Medical Needs

The American Association for the Study of Liver Disease (AASLD) and Infectious Diseases Society of America (IDSA) have described four attributes of an optimal HCV regimen – that it be highly efficacious, well tolerated, of short duration with simple dosing, and displays efficacy in special subpopulations.[1]

The development of ledipasvir/sofosbuvir (LDV/SOF) during the past 3 years resulted in the FDA approval of HARVONI, which fulfills all of these attributes:

- the first daily single-tablet regimen that is interferon-, ribavirin- and ritonavir-free for GT1 HCV
- sustained virologic response (SVR) rates between 94-100%, depending on patients' treatment experience and stage of fibrosis/cirrhosis
- improved tolerability and minimal side effects due to the elimination of interferon and ribavirin
- short duration of treatment (eight or twelve weeks for over 90% of patients)

- limited drug interactions requiring modification of co-administered medications, and no CYP450 interactions, which are associated with protease inhibitors and ritonavir

The efficacy and safety of LDV/SOF has been studied in a broad range of patients representing the diversity of the HCV-infected population in the United States:

- patients with traditional negative predictors of outcome: age over 65 years, high BMI, IL28B non-CC haplotype, African Americans and Asians, glucose intolerance, and opiate replacement therapy
- nineteen studies, with more than 1000 compensated or decompensated cirrhotic patients
- HIV/HCV co-infected patients
- pre-and post- liver transplant patients
- patients who failed previous treatments, including protease inhibitor (PI) + pegylated interferon + ribavirin (P/R) failures
- patients infected with genotypes 3, 4, and 6, with additional clinical trials underway in genotypes 2, 5 and 6

The clinical trial programs for both SOVALDI and HARVONI enrolled difficult-to-treat patients, and, more recently, real-world experience with sofosbuvir-containing regimens indicates effectiveness similar to outcomes observed in clinical trials. Data presented in November at AASLD 2014 for more than 4000 patients from the HCV-TARGET and TRIO cohorts treated with sofosbuvir-based regimens demonstrated similar efficacy and tolerability as in phase 2 and 3 clinical trials, despite the fact that these real-world patient cohorts were comprised of sicker patients (more advanced fibrosis and cirrhosis, and inclusion of patients with decompensated cirrhosis, liver transplants and HCC). In addition, real-world patient population analyses have shown that most HCV patients have one or more comorbidities (92%), which increase with age, and that 21% of patients were prescribed two or more medications with CYP450 drug interactions. [2,3]

Gilead concurs with the draft CTAF report conclusions that LDV/SOF is very cost effective (regardless of treatment naïve or experience or treatment comparisons), producing ICERs of $\leq$ $20,000 per QALY gained. Treating all HCV patients, beyond those with advanced fibrosis/cirrhosis (F3/F4), will increase cost. Yet treating earlier (F0-F2) yields substantial health benefits and still meets the cost-effectiveness threshold of ~$50,000 per QALY gained.

Furthermore, initiation of LDV/SOF treatment at earlier stage (F0-F2) substantially decreases cases of compensated cirrhosis, decompensated cirrhosis, liver transplant, and HCV-related death. The downstream total cost of care associated with advanced disease will be reduced substantially with earlier initiation of treatment. Costs per SVR for LDV/SOF for F0-F1 and F2 patients was almost 10% lower than the cost per SVR for F3/F4 patients.[4]

B. Suggestions for additional analyses on cost-effectiveness analysis and budget impact model

Gilead has also conducted CEA models with LDV/SOF in consultation with hepatologists and health economic experts and would like to propose the following amendments to the CTAF model:

- Amend SVR inputs to reflect recent data for 12 week treatment with LDV/SOF+RBV for treatment-experienced cirrhotics who achieved SVR rates of 96% to 97%.[5,6]

- Amend cost inputs for HCC. The CTAF model used a value of $47,525, which is lower than that observed in other studies. A recent abstract at AASLD 2014 found a mean cost of $218,120 per HCC patient.[7]
- Modify utilities used in the CTAF model to reflect patient reported outcomes (PRO) data reported by Younossi on ION studies, in which patients on LDV/SOF experienced a gain in utility while on treatment.[8]

To best inform Medi-Cal and DoC decision makers, Gilead would like to propose updating the Budget Impact Model in order to more accurately estimate the incremental budget impact of LDV/SOF specific to the Medi-Cal and DoC systems:

- Model for a population that has characteristics similar to those currently enrolled in Medi-Cal and DoC. For example, the following could be incorporated:
    - Simulate a cohort of younger patients (i.e. 50 year-olds rather than 60 year-olds)
    - Include 10-14% HIV/HCV coinfection (using coinfection transitional probability) and other comorbidities that would accelerate HCV disease progression
- Reflect actual Medicaid drug costs (e.g., mandatory and supplemental rebates that result in sub-WAC pricing) rather than utilizing WAC
- Model patient treatment flow that mirrors the NIH-sponsored eradication study or use historical data using a range of 10-15 percent of the diagnosed population treated in year one rather than 100% of the diagnosed population treated in Year one.
- Determine the budget impact of LDV/SOF incremental to the current therapies (e.g., SOF+SMV, SOF+RBV, SOF+PR, SMV+PR) utilized in the Medi-Cal and DoC population. It is also important to account for actual cost per SVR of different regimens. Cost per SVR should include all drug and medical costs for those who achieve SVR.
- Incorporate a sensitivity analysis using a range of 50-80% of treatment-naïve patients eligible for LDV/SOF eight-week regimen
    - According to a survey of 2,570 GT1 treatment-naïve and treatment-experienced HCV patients under physician care between 2013-2014, 53% would eligible to receive the LDV/SOF 8-week regimen.[26]

C. Comments on specific data within the report

CTAF Report - Executive Summary

Figure ES1: SVR and 95% CIs for the Primary DAA Regimens in Four Clinical Subgroups

The SVR depicted for the combination of LDV/SOF in treatment-naïve, cirrhotic patients (89.2%) differs from the 94% figure in the HARVONI label and the Gilead database. The reason for this disparity is discussed below in Section 6.3, and involves the inclusion of decompensated cirrhotic patients into the 89.2% calculation.

Section 6.1

Page 31:

It is noted that in the sub-section entitled "HIV co-infection" that "the ERADICATE trial treated 50 patients [with LDV/SOF], but SVR12 results were only available for 10 [patients]." The final data from ERADICATE were presented at AASLD 2014 by Kotillil et al from the NIAID, and SVR was achieved by 98% of subjects (49/50), further confirming that HIV-HCV co-infected patients respond similarly to DAA

therapy as HCV mono-infected patients.[9] Gilead requests that the report be updated to reflect these updated data.

Gilead is currently evaluating a 12-week regimen of LDV/SOF in the ION-4 trial of 335 HIV-HCV co-infected subjects. Enrollment is complete, and data are expected to be presented at a major scientific congress in 1Q2015.[10]

Section 6.2 SVR Outcomes of Treatment of HCV GT1 in Treatment-naïve, Cirrhotic Patients
Page 35, Table 6 and Figure ES1 cited above
The 89.2% SVR depicted for the combination of LDV/SOF in 57 treatment-naïve, cirrhotic patients differs from the HARVONI label and the Gilead database. Upon inspection of Appendix Table C10 (page 105), it is evident that treatment-experienced patients with decompensated Child-Turcotte-Pugh (CTP) Class B cirrhosis enrolled in the ELECTRON-2 study were included in the calculation of overall SVR.[11] This is in contrast to the remainder of the data depicted in Table 6 which are derived from studies in treatment-naïve patients with Child-Turcotte-Pugh Class A compensated cirrhosis.

It is well recognized that patients with decompensated cirrhosis exhibit lower SVR rates than patients with compensated cirrhosis, so Gilead proposes that the ELECTRON-2 data in CTP-B decompensated cirrhosis be removed from this calculation of SVR, resulting in an SVR rate of 94.6% (35/37) based on the SYNERGY and ION-1 studies.[12,13]

A larger dataset of 57 subjects from the SOLAR-1 study with decompensated CTP-B cirrhosis treated with LDV/SOF+RBV were presented at AASLD, and SVR rates of 87% (26/30) and 89% (24/27) were observed with 12 and 24 weeks of treatment, respectively.[14]

In addition, results from subjects in the SOLAR-1 study with more advanced, decompensated CTP-C cirrhosis treated with LDV/SOF+RBV were presented at AASLD, and SVR rates of 86% (19/22) and 90% (18/20) were observed with 12 and 24 weeks of treatment, respectively.[14]

Section 6.3 SVR Outcomes of Treatment of HCV GT1 in Treatment-experienced, Cirrhotic Patients
Page 37:
The data in the draft report for treatment-experienced, cirrhotic population describe the responses for LDV/SOF for 24 weeks, however, two presentations at AASLD 2014 described the results of shortening the course of LDV/SOF treatment to 12 weeks with the addition of RBV to LDV/SOF.[5,6] Gilead requests that these data be included in the report.

The SIRIUS study was a phase 2, randomized, double-blind, placebo-controlled study which evaluated LDV/SOF + RBV for 12 weeks (including a 12-week start placebo phase) compared with LDV/SOF for 24 weeks in HCV GT 1 subjects with compensated cirrhosis who previously failed 2 prior treatments with both PegIFN + RBV and also PI + PegIFN + RBV regimens. SVR12 was achieved in 96% (74/77) of subjects in the 12-week LDV/SOF + RBV arm and 97% (75/77) of subjects in the 24-week LDV/SOF treatment arm.[5]

In addition, a cross-study analysis of 7 phase 2 or 3 clinical trials comprising 513 subjects with compensated cirrhosis found that LDV/SOF + RBV for 12 weeks achieved 96% SVR, compared with 100% SVR in subjects treated with 24 weeks of LDV/SOF.[6]

Section 6.6 Harms of Treatment

We agree with the conclusion in this section that "elimination of interferon from the treatment regimen markedly decreases the risk for several adverse events including fatigue, flu-like illness, anemia, pruritis, nausea and rashes", however, no mention is made of the benefit of the elimination of RBV from the vast majority of LDV/SOF regimens.

The safety and tolerability data from 1952 subjects (no RBV, n=1080; RBV, n=872) treated in the ION studies were presented in the original NEJM publications and summarized at AASLD 2014. Sixteen percent were African American, 11% had compensated cirrhosis, 26% had a BMI ≥ 30 kg/m^2, and 23% were treatment-experienced, including prior protease inhibitor failures.[13,14]

Treatment-related AEs occurred more frequently in RBV arms (71%) than non-RBV arms (45%). Fatigue, insomnia, nausea, irritability, and rash were approximately twice as common in RBV-containing arms compared to LDV/SOF alone. In particular, anemia (Hgb <10 g/dL) was observed in 7% (n=58) of patients receiving RBV and <0.01% (n=1) of patients taking LDV/SOF alone.[15]

With the exception of the 12 week course for treatment-experienced cirrhotic patients as noted above, the use of HARVONI in treatment-naïve and treatment-experienced GT1 patients eliminates the need for ribavirin and its associated adverse effects.

Real-world data

Page ES3:

CTAF recognizes that "High-quality observational data from real world settings will be essential for evaluating the comparative effectiveness of the combination DAA therapies and to see if the SVR rates achieved in clinical trials are replicated in usual care settings."

The interim results from two large observational real world databases (HCV-TARGET and TRIO), describing the outcomes of HCV treatment with SOF+PegIFN+RBV, SOF+RBV or SOF+SMV±RBV were presented at AASLD 2014.[2,3]

HCV-TARGET is a real-world observational study of >2000 patients treated with DAAs at academic (n=38) and community medical centers (n=15) in the U.S., Germany, and Canada:

- 68% of GT 1 patients received off-label SOF+SIM ± RBV, 23% SOF+PegIFN+RBV, and 9% SOF+RBV
- 99% of patients with GT 2, and 92% of patients with GT3 were treated with SOF+RBV regimen
- Across arms, 31-60% of patients have cirrhosis, 11-51% had a history of liver decompensation, 36-56% are treatment-naive, 8-31% are prior DAA failures, and 7-14% are liver transplant recipients
- Interim SVR4 data:
    - GT1: SOF+PegIFN+RBV 85% overall (90% no cirrhosis, 70% cirrhosis)
    - GT1: SOF+SMV±RBV 89% overall (92% no cirrhosis, 87% cirrhosis)
    - GT2: SOF+RBV 90% overall (91% no cirrhosis, 88% cirrhosis); GT 3 data pending
- Overall, low discontinuation rates due to adverse events were reported (2.1% overall). AEs with all-oral regimens were much lower than those which utilized PegIFN.

TRIO is a real-world observational database derived primarily from specialty pharmacy records of 1,211 patients who started treatment prior to April 1, 2014 in 150 practices (31 academic centers; 119 community practices):

- Genotype distribution reflected prior epidemiology: 73% GT 1, 22% GT 2, 1% GT 3, 2% GT 4, <1% GT 6.

- 57% of patients were treatment-naive and 43% were treatment-experienced and had failed an IFN-based regimen, including 20% 1st generation PI failures; cirrhosis was present in 30% of patients.
- GT 1 regimens were 52% SOF+PegIFN+RBV and 46% SOF+SMV±RBV for 12 weeks; GT 2 and 3 patients used RBV+SOF for 12 or 24 weeks.
- SVR12 data in SOF+PegIFN+RBV was 81% in TN, and 72% in TE patients. SVR12 in SOF+SMV±RBV was 83% in TN, and 81% in TE patients.
- Discontinuation due to AEs in GT 1 patients on SOF+PegIFN+RBV was 2% and SOF+SIM±RBV was 1.4%; discontinuation in GT2 patients on SOF+RBV was 0%. AEs were characterized as general intolerance and rash.

These data collectively demonstrate that the patients treated in real-world settings tend to have more advanced liver disease than those studied in phase 3 clinical trials; however, the SVR rates were much closer to those observed in the SOF-based regimens than previously reported for PI-based real-world studies.[16-18]

Cost Effectiveness Analysis (CEA) / Care Value Analysis

Gilead concurs with the draft CTAF report conclusions that LDV/SOF is very cost effective (regardless of treatment naïve or experience or treatment comparisons), producing ICERs of $\leq$ $20,000 per QALY gained. Treating all HCV patients rather than just those with advanced fibrosis/cirrhosis (F3/F4) will increase cost. But treating earlier (F0-F2) yields substantial health benefits and treating all stages (F0-F4) still meets the threshold for cost-effectiveness of ~$50,000 per QALY gained. CTAF concludes that the cost of LDV/SOF is justified for F3-F4 patients based on a conservative willingness-to-pay threshold of ~$50,000 per QALY gained and on the CTAF threshold of <0.5% annual increase in per-patient per-month (PMPM) costs. Gilead agrees with these conclusions as the findings from the cost-effectiveness analysis from CTAF were consistent with many published reports on the cost-effectiveness of SOF+PR analyses[19-23] and most recently with LDV/SOF[24].

Cost per SVR has recently been reported in the literature[19,20,24] as a short term (1-year) economic outcome of cost-effectiveness analysis. In contrast to previous regimens, LDV/SOF demonstrates a high cure rate, as well as excellent intermediate and long-term health and economic outcomes (i.e., cost per SVR, ICERs).

Moreover, initiation of LDV/SOF at earlier stages (i.e., F0-F2) resulted in substantially fewer cases of CC, DCC, liver transplant, and HCV-related death, stemming from higher SVR rates among F0-F2 than F3/F4 patients. See Appendix C. The total lifetime cost of care associated with advanced disease will be reduced substantially with earlier initiation of treatment. Cost per SVR for LDV/SOF for F0-F1 and F2 patients were close to 10% lower than the cost per SVR for F3/F4 patients.[4]

Gilead would like to propose the following CEA model considerations:

a. Age of CHC cohort: CTAF modeled a cohort with a standard age of 60 years underestimating the cost-effectiveness of LDV/SOF. Previous models have estimated the median age of CHC cohort between 50 to 52.[19-23] The mean age reported in the ION studies was 53 years (n=1952; range 18-80). In this model, when the age of cohort was modified to 50 years, it generated more QALYs and the cost-effectiveness of the "treat all" v. "treat at F3, F4' improved.

   Costs and outcomes of the 60-year-old cohort were utilized in the Budget Impact Model to determine potential "return on investment". Older patients may not live long enough to

experience the benefits of achieving a cure (i.e., reduced CC, DCC, HCC, transplants, HCV-related deaths) due to background mortality secondary to other causes.

b. SVR inputs: As described in the Clinical Response, recent data regarding 12 week treatment with LDV/SOF+RBV for treatment-experienced cirrhotics suggests the importance of revising the CTAF model using SVR rates of 96% to 97%.[5,6] This will further improve the cost-effectiveness ratio of LDV/SOF+RBV vs. comparators and provide a more favorable return on investment with the Budget Impact Model.

c. Cost inputs: The cost of HCC incorporated in the CTAF model (HCC: $47,525) is lower than that observed in other studies. A recent abstract at AASLD 2014 found a mean cost of $218,120 per HCC patient (mean of $395,000 per transplanted patient compared to a mean cost of $100,299 for a patient who does not receive a transplant).[7]

d. Utilities: Regarding utilities used in the model, CTAF included a disutility on treatment for LDV/SOF due to AEs incurred rather than referring to PRO data reported by Younossi on ION studies, in which patients on LDV/SOF actually experience a gain in utility while on treatment.[8]

Budget Impact Model (BIM)/ Health-System Value Analysis

Gilead concurs with a major finding of the CTAF Budget Impact Model/Health System Value Analysis. LDV/SOF produces incremental clinical benefits shortly after treatment initiation, as early as year one in preventing cases of cirrhosis, decompensated cirrhosis, HCC, liver transplant and HCV-related deaths. The Budget Impact Calculations used the costs and outcomes of the 60-year-old cohort from the Markov model described in the previous section.

Gilead recommends recasting the following assumptions in the Budget Impact Model:

a. Cost assumptions: The standard wholesale acquisition costs of LDV/SOF (approximately $63,000 and $95,000 for 8 and 12 weeks, respectively) were used in the Budget Impact model. For state Medicaid programs, the federally-mandated 23.1% discount should be applied, in addition to supplemental rebates that vary by state. Similarly, the discounts that California Department of Corrections received should also be reflected in the budget impact analysis. Budget impact should be based on the actual net costs paid by the systems rather than on WAC pricing.

b. Treatment flow assumptions: It appears that CTAF assumed that approximately 45,000 Medi-Cal patients will present themselves for treatment in the base case during one year. This would represent almost 100% of diagnosed Medi-Cal patients (assuming a diagnosis rate of 50% of infected population). This treatment rate is inconsistent with historical trends, including the recent SOF+PR launch in the US during 2014. In the U.S., approximately 150,000 patients will have been treated by the end of 2014. This is about 7.5% of approximately 2 million HCV diagnosed patients nationally.

c. Clinical capacity assumptions: Experience show that there is a practical limit to the number of HCV patients who can be seen in a year. Even if the number of HCV patients seen in a clinic were to double, at most 15% of *diagnosed* patients would be treated in 2015. In this regard, the draft report is also inconsistent with the most recently published NIH sponsored study, in which the authors concluded that even in the ideal case scenario, where there were no limits on budgets

and clinical capacity, it would take the U.S. healthcare system over 10 years to reduce the prevalence of HCV infections to a rare disease.[25] Applying a treatment assumption to 2015 based on actual treatment rates from 2014 sharply decrease the PMPM cost. A more realistic patient flow model would also improve the accepted payment threshold results and raise the number of patients, regardless of level of fibrosis and treatment experience, who could access LDV/SOF treatment.

d. Comparators: Medi-Cal and DoC incurred costs of PR+PIs (e.g., telaprevir, boceprevir or simeprevir) and SOF+PR or SOF+SMV in the healthcare systems in 2014. Based on HCV-TARGET and TRIO, around 50% of regimens used in 2014 were the al-oral combination of SOF+SMV, with costs almost twice as high as the blended cost of LDV/SOF for 12 weeks. LDV should be compared to the HCV therapies currently being utilized by MediCal and DoC in 2014 to determine the *incremental* PMPM impact, and not be compared to PR solely.

    - Real world effectiveness should also be considered in the Budget Impact Model. Recent real world studies suggest that SVR and discontinuation rates for SOF-based regimens closely approximate clinical trials data. There is extensive evidence that this is not the case with the PR regimen or PI+ PR regimens. Real world cost per SVR should also be considered in the Budget Impact Model. [17,18]

e. Patient demographics: The modeled population should reflect actual Medi-Cal and DoC patient demographics – including age, comorbidities and underlying fibrosis stages (e.g., F3/F4). Simulating a cohort of 60-year-old is appropriate for this targeted population. Liu et al conducted a cost-effectiveness analysis of SOF+PR regimen in incarcerated population and he simulated a cohort of 40 year old.[23] Up to 14% of the HCV-infected incarcerated population also is co-infected with HIV, which is a known factor for accelerated disease progression. Other factors to include in this analysis should include alcoholism/substance abuse, obesity, diabetes and cardiovascular disease.

f. Annual Medical Expenditures: The figures the authors use for annual CHC-related healthcare costs seem unrealistically low--$810 for F0-F2, $2,150 for F3, $2,516 for compensated cirrhosis.. By contrast, Gordon et al. (2012) find healthcare costs around $7,800 for F0-F3, and $12,000 for compensated cirrhosis. The references should be compared to determine the basis for this large discrepancy, which has myriad implications.
    - Some of the CTAF estimates come from a study by Backx et al. (CTAF citation # 150), a British study of resource utilization among 193 HCV patients from five centers in the UK. It is inappropriate to use such a study to measure US healthcare costs due to the widely recognized differences in patterns of care, and prices, among international health systems.

Drug Pricing to Meet Per-Member Per-Month Benchmarks

The CTAF report stated that PMPM increases of 0.5%-1% in a given year were used in this report as a range of potential budget impact that, when exceeded, is likely to drive specific efforts to manage the costs of a new health care intervention. The rationale for this range is unclear; it would be helpful to clarify how the 1% threshold was determined. CTAF report concluded that all of GT1 with F3 and F4

stage disease could replace PR therapy in all of these patients at current WAC prices and remain under 1% threshold for PMPM increase.

D. Benefits of HCV treatment beyond achieving sustained virologic response

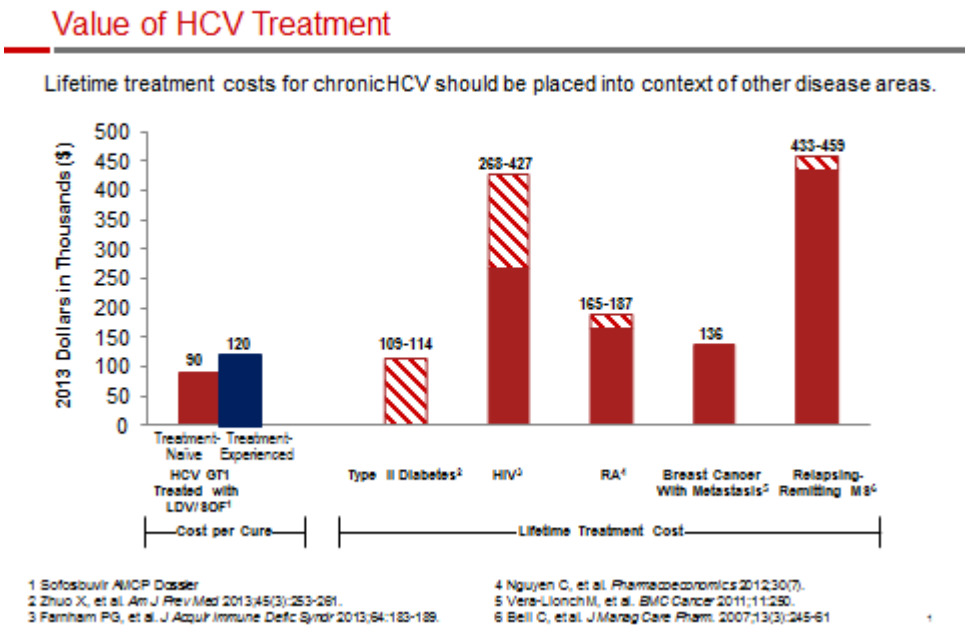
- Patient perspective is not accounted for in the draft CTAF analysis. Therefore, it is important to consider the implications of patient-reported outcomes data on disability and adherence to treatment.[8,27]

- 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. Transmission of Infectious Disease: Some of the analyses in this report compare different treatment strategies, specifically "Treat All" (treat everyone with HCV, regardless of fibrosis stage) vs. "Treat Advanced" (treat only those with HCV who have reached fibrosis scores of F3 and higher). However, the transmission of HCV is not included in the care value model. Since HCV is a serious infectious disease, evaluating the full benefits of different treatment strategies is incomplete if transmission effects are left out. The transmission effect is perhaps the most important element in the rationale for a Treat All strategy; without it, these analyses underestimate the benefits of treatment for *any* strategy. The underestimation is greater for strategies that treat a larger portion of the infected population.

- A meta-analysis has been submitted for presentation at DDW assessed the impact of extra-hepatic manifestations in HCV patients. The prevalence of mixed cryoglobulinemia was 32%, diabetes mellitus was 15%, each of which were higher than in the non-HCV population. The odds ratio of developing Chronic Kidney Disease/End Stage Renal Disease in patients with HCV compared to non-HCV group was 1.29 (95% CI: 1.13-1.45), and the risk of lymphoma was 64% higher (OR= 1.64; 95% CI: 1.18-2.11) in patients with HCV compared to non-HCV population. In addition, the prevalence of lichen planus, Sjogren's syndrome and porphyria cutanea tarda were each significantly elevated compared to the non-HCV population.

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

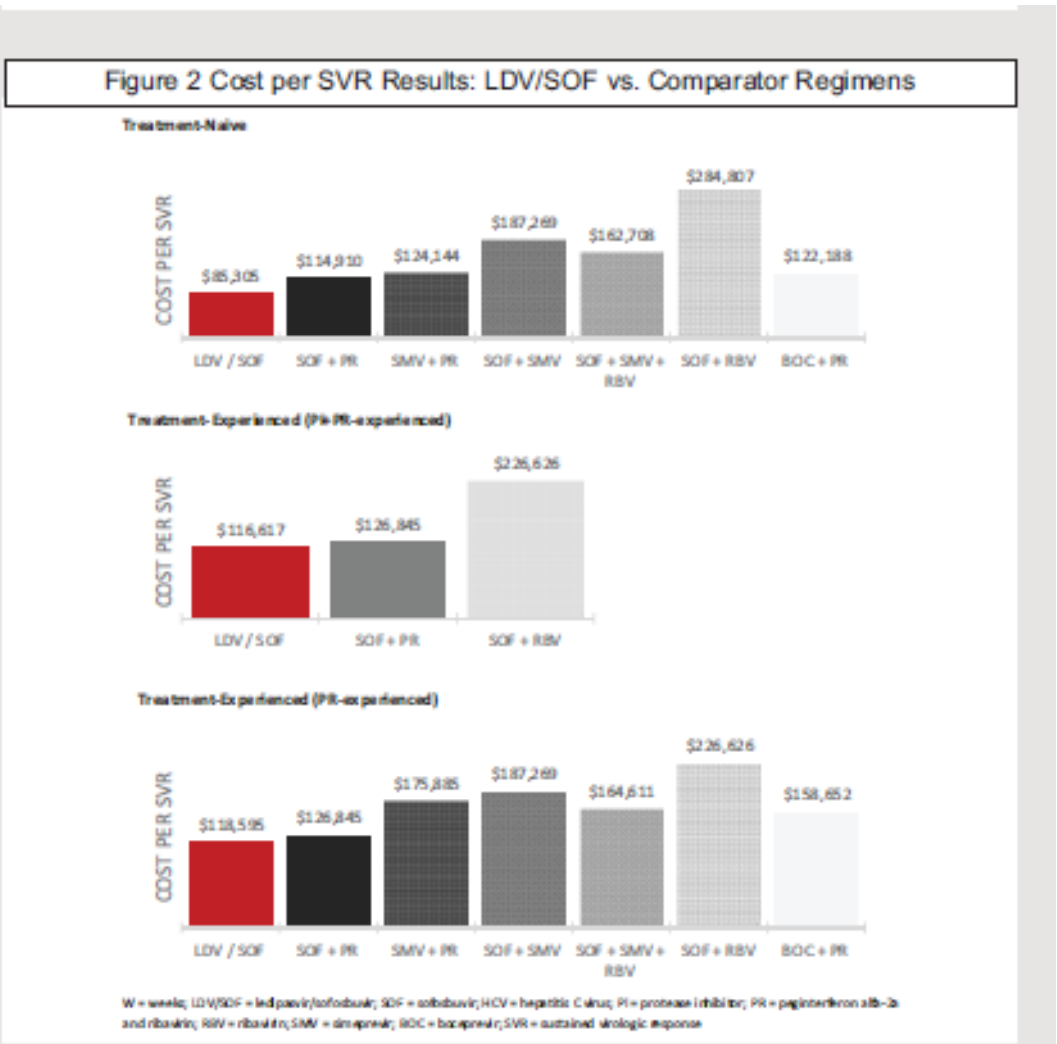
Because HCV treatment is a one-time cost for almost all patients now receiving therapy, it is relevant to compare the lifetime treatment costs with regard to other chronic conditions such as HIV, diabetes, cancer and multiple sclerosis.[28]



The 1-year cost per SVR is lowest for LDV/SOF in all the patient subpopulations examined in the model (Figure 2). For treatment-naïve patients, LDV/SOF results in costs per SVR ranging from 17.9% to 90.0% lower than those observed for comparator therapies. In PI+PR- and PR-experienced treatment-experienced patients, LDV/SOF results in a cost reduction of 8.1% to 48.5% and 6.5% to 47.7%, respectively per successfully treated patient to currently recommended therapies.[28]

When initiating treatment in F0-F1, F2, or F3-F4 in treatment-naïve patients, LDV/SOF is associated with the lowest cost per SVR of all comparator regimens. The estimated reduction in cost per SVR is 19.13% to 67.35%, 20.84% to 67.50%, and 13.89% to 75.79% with LDV/SOF treatment initiated in F0-F1, F2, and F3-F4 versus comparator regimens, respectively.[28]

Figure 2 Cost per SVR Results: LDV/SOF vs. Comparator Regimens



W = weeks; LDV/SOF = ledipasvir/sofosbuvir; SOF = sofosbuvir; HCV = hepatitis C virus; PI = protease inhibitor; PR = peginterferon alfa-2a and ribavirin; RBV = ribavirin; SMV = simeprevir; BOC = boceprevir; SVR = sustained virologic response

For patients with HCV GT1 infection, HARVONI is a cost-effective treatment option, providing patients with the longest life-expectancy and the most QALYs as compared to other regimens with published Phase 3 data (Table 6 below).[28] In addition, HARVONI is either dominant or well within the willingness-to-pay (WTP) threshold of US payers ($50,000/QALY) in terms of ICERs as compared to other regimens with published Phase 3 data.[29]

Treatment-naïve patients treated with LDV/SOF live 0.31, 0.70, 0.25, 0.07, 1.19, and 1.13 years longer than patients treated with SOF+PR, SMV+PR, SOF+SMV, SOF+SMV+RBV, SOF+RBV, or BOC+PR, respectively. Treatment-experienced patients treated with LDV/SOF who have previously been treated with PR therapy live 0.55, 1.03, 0.12, 0.14, 0.64, and 1.40 years longer than SOF+PR, SMV+PR, SOF+SMV, SOF+SMV+RBV, SOF+RBV, and BOC+PR, respectively. In addition, LDV/SOF is the only all-oral regimen evaluated in PI+PR-experienced treatment-experienced patients; in these patients, LDV/SOF is associated with an additional 0.46 and 0.54 life years compared with SOF+PR and SOF+RBV.

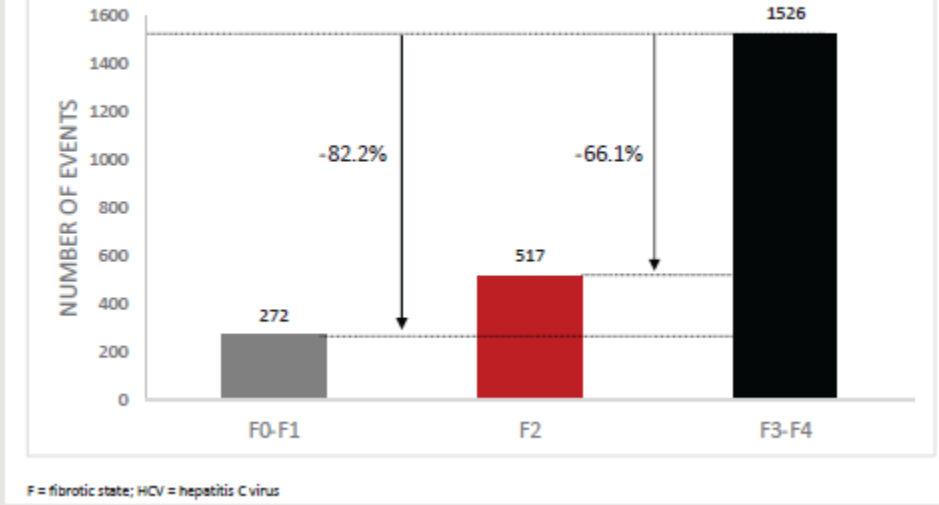
Table 6: Model Long-Term Economic Outcomes

	LIFE YEARS	QALYs	INCREMENTAL LIFE YEARS	INCREMENTAL QALYs	TOTAL COSTS	INCREMENTAL COSTS	INCREMENTAL COST PER QALY GAINED
TREATMENT-NAÏVE							
LDV/SOF	19.23	16.02	-	-	$90,656	-	-
SOF + PR 12W	18.92	15.53	-0.31	-0.49	$121,896	$31,240	LDV/SOF dominates
SMV 12W + PR 24W	18.53	15.07	-0.70	-0.95	$132,408	$41,752	LDV/SOF dominates
SOF + SMV ***	19.26	16.03	+0.03	+0.01	$186,882	$96,226	SOF+SMV more effective but more costly
SOF + SMV + RBV 12W	19.15	15.86	-0.08	-0.16	$165,911	$75,255	LDV/SOF dominates
SOF + RBV 24W	18.07	14.60	-1.16	-1.42	$233,571	$142,915	LDV/SOF dominates
BOC + PR (RGT)	18.12	14.55	-1.11	-1.47	$133,127	$42,471	LDV/SOF dominates
No treatment	16.48	12.66	-2.75	-3.36	$146,828	$56,172	LDV/SOF dominates
TREATMENT-EXPERIENCED, PI+PR EXPERIENCED							
LDV/SOF	19.26	16.05	-	-	$120,481	-	—
SOF + PR 12W	18.69	15.23	-0.57	-0.82	$133,244	$12,763	LDV/SOF dominates
SOF + RBV 24W	18.60	15.21	-0.66	-0.84	$209,762	$89,281	LDV/SOF dominates
No treatment	16.48	12.66	-2.78	-3.39	$146,828	$26,347	LDV/SOF dominates
TREATMENT-EXPERIENCED, PR EXPERIENCED							
LDV/SOF	19.23	16.00	-	-	$122,620	-	-
SOF + PR 12W	18.69	15.24	-0.54	-0.76	$133,244	$10,624	LDV/SOF dominates
SMV 12W + PR*	18.22	14.68	-1.01	-1.32	$166,305	$43,685	LDV/SOF dominates
SOF + SMV **	19.26	16.03	+0.03	+0.03	$185,881	$63,261	SOF + SMV is more effective but more costly
SOF + SMV + RBV 12W	19.08	15.78	-0.15	-0.22	$167,373	$44,753	LDV/SOF dominates
SOF + RBV 24W	18.60	15.21	-0.63	-0.79	$209,762	$87,142	LDV/SOF dominates
BOC + PR (RGT)	17.86	14.25	-1.37	-1.75	$149,948	$27,328	LDV/SOF dominates
No treatment	16.48	12.66	-2.75	-3.34	$146,828	$24,208	LDV/SOF dominates

W = weeks; LDV/SOF = ledipasvir/sofosbuvir; SOF = sofosbuvir; PI = protease inhibitor; PR = peginterferon alfa-2a and ribavirin; RBV = ribavirin; SMV = simeprevir; BOC = boceprevir; RGT = response-guided therapy; * Duration of PR therapy dependent on previous treatment experience; ** SOF + SMV 12W in NC patients, SOF + SMV 24W in CC patients; QALYs = Quality-Adjusted Life Years

When initiating LDV / SOF treatment in F0-F1 or F2 as opposed to F3-F4, the model projected lower incidence of liver disease progression, including new cases of decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), liver transplants (LT), and HCV-related deaths. The estimated absolute reduction of these sequelae is 82.2% and 66.1% when initiating treatment with LDV / SOF in F0-F1 or F2 as opposed to F3-F4, respectively, over the life time (Figure 2).[4]

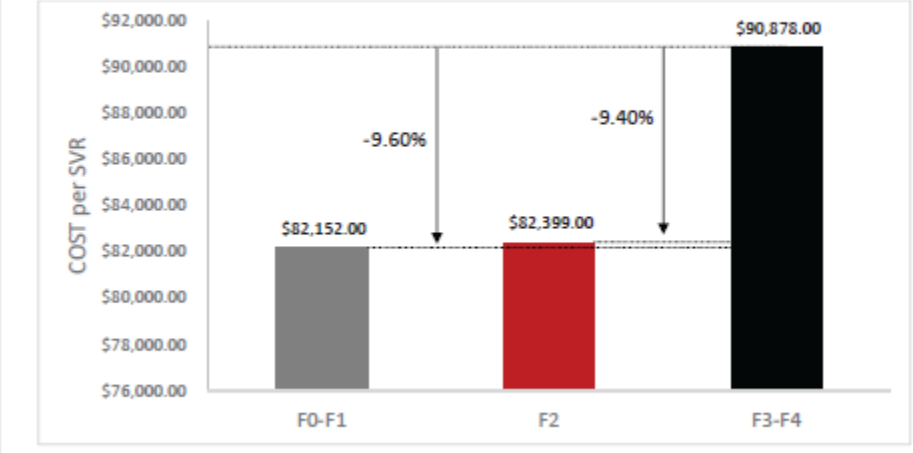
Figure 2 Aggregated Occurrence of Liver-Disease Sequelae with Different Treatment Strategies for Genotype 1 HCV Patients treated with LDV/SOF Regimens



F = fibrotic state; HCV = hepatitis C virus

In addition, the cost per SVR is reduced by approximately 10% for treatment initiation in F0-F1 or F2 compared to F3-F4, highlighting the cost savings accrued from LDV / SOF treatment during early disease.[4]

Figure 3 Cost per SVR at Different Fibrosis Initiation Points for Genotype 1 HCV Patients treated with LDV/SOF Regimens



F = fibrotic state; HCV = hepatitis C virus; SVR = sustained virologic response

Conclusion

The treatment of HCV infection is rapidly evolving, with the LDV/SOF single tablet regimen achieving 94-100% SVR rates in a broad range of treatment-naïve and treatment-experienced patients in 8-12 weeks in most cases, including those with cirrhosis.

Data recently presented at AASLD 2014 demonstrated that real world outcomes of sofosbuvir-based regimens achieved similar efficacy and tolerability as in phase 2 and 3 clinical trials, despite differences in patient composition (more advanced fibrosis and cirrhosis, and inclusion of patients with decompensated cirrhosis, liver transplant and HCC).

Several assumptions in the cost-effectiveness and budget impact models could benefit from amended inputs to reflect the Medicaid and Corrections populations in California, and we look forward to discussions with CTAF and ICER regarding a few areas of focus for your consideration - unmet medical needs of HCV patients, specific data points within the report, benefits of HCV treatment beyond achieving sustained virologic response, such as patient reported outcomes, decreased viral transmission and its impact on public health, and extrahepatic manifestations of infection. It is important to understand the value of HCV treatment in the context of other disease areas.

Gilead commends the California Technology Assessment Forum and the Institute for Clinical and Economic Review for conducting a thorough, timely and comprehensive review of the available literature regarding treatments for chronic HCV infection, and we appreciate the opportunity to respond to the draft CTAF/ICER report and to provide the enclosed information for the Committee's consideration.

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Page # per PDF	Paragraph	Comment
8/140	1	where does 67% come from (this is also cited in the Summary on page 41 of the document)? It is not reflected in the figure on page 9/140. Also on page 55/140
8/140	2	CI are wide for all 4 DAA…. What is defined as a wide CI? This is a subjective statement and does not apply to 3D. Also on page 56/140
8/140	3	When pt characteristics require longer..... Refer to Poordad publication in NEJM (Turquoise II) the rate of grade 1, 2, 3, and 4 hemoglobin was not significantly different between the 12 and 24 week arms AND the # of total serious AE's did not statistically differ between the arms. Also on page 56/140
9/140	Figures and Tables	Add N's and References to all figures and tables in the document
14/140	1	PMPM increases of 0.5-1%....What is the reference for this threshold? Is this consistent with average PMPM increases seen in 2013 or is this an arbitrary threshold?
14/140	2	We also conducted a hypothetical analysis….What is the time horizon of treating patients? Should that be across several years vs. 1 year?
19/140	1	Definition of null response and partial response should be a 2 log drop.
20/140	1	the primary goal of hcv treatment.... Isn't the goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by an SVR.
22/140	4	for those patients who are HIV co-infected… Simeprevir is not indicated for co-infected.
24/140	Table 2	Add Moderiba and Ribapack under nucleoside analog
26/140	3	On August 11, 2014…. Update this paragraph since guidelines were updated on 11/20.
27/140	2	EASL has also not yet… DAC is not approved in US.
34/140	NCT02114151	These were COMPENSATED CIRRHOTICS
34/140	NCT02206932	Please confirm as CT.Gov states this study is withdrawn
36/140	nct02219477	Change RCT to Cohort with multiple arms and October 2016
36/140-	nct01939197	This is a phase II/III study
37/140	Topaz I and Topaz II	Change VS to OR.
37/140	Topaz I and Topaz II	Add primary outcomes: Incidence of pre-defined clinical outcomes observed during the study [Time Frame: Up to Post-Treatment week 260 after the subject has taken his/her last dose of study drug. Measured by all-cause death, liver-related death, liver decompensation, liver transplantation, and hepatocellular carcinoma
37/140	Topaz II	Change multiple arms to single arm
38/140	1	Instead, we summarized the proportion of patients achieving SVR 12…. Add desc or ref for the meta analysis of proportions methodology

Page # per PDF	Paragraph	Comment
43/140	2	The quality of the data for simeprevir + PR is higher….. Add qualifier to "any of the therapies". The 3D program had greater pts enrolled with PBO comparators in some of the studies.
44/140	1	Consider adding Target and Trio data from AASLD
44/140	4	The evidence base is larger for the combination….. This is a generalized statement. Delete larger as 3D studied over 2300 patients
45/140	2	Delete ABT 450. Also change MOST OFTEN to WITH OR WITHOUT in the 2nd sentence
45/140	2	PR or single DAA...Please update with the following studies as they had active comparator NCT01854697; NCT01854528
45/140	3	Add Turquoise I Coinfected Study for 3D. Wyles AASLD 2014
45/140	3	There do not appear to be an unexpected interactions…. May want to consider deleting based on Tenofovir with Led/Sof interaction
45/140	4	Add 3D Coral data on post transplant. Kwo, P NEJM 2014
45/140	4	Data from the pre-transplant population suggest that the earlier…. Please clarify as this is not clear
47/140	Table 5	DAC is not approved in US
47/140	Table 5	3D+R cannot confirm DR numbers. Need reference
47/140	2	Third, the discontinuation rates… CIs overlap, consider deleting as this is a generalized statement
51/140	1	The study sizes are generally small…. Define small as the Turquoise II study had 220 pts
52/140	Table 8	3D+ R 12wks change SVR rate CI to .902 (.849-.954), 3D + R 24 wks change to .969 (.935-1.00)
53/140	Table 9	Suggestion to split table by CIRR and NON CIRR
62/140	2	Recently, the WHO has promulgated suggested…. Should this be GPD per capita?
68/140	Table 14	Confusing table. Suggest rank in ascending order of efficacy vs. costs
69/140	table 15	Clarify what is defined by net costs? Also these costs do not reflect current WAC. Also clarify the methodology for the calculations. Lastly, the table should clarify if the comparisons are relative to the next less exp undominated or ext dominated therapy. also define dominated and absolutely dominated as it seems to be used interchangeably.
70/140	1	Should PR be used as a benchmark since it is no longer SOC
71/140	table 18	Is this incremental net cost or net cost
72/140	table 19	Are ICERs calculated relative to 'no treatment'? please clarify this in table 19. Also, why is 'no treatment' used as the baseline comparator here but not in the other tables?
74/140	4	clarify what these ICERs are relative to?
74/140	5	Clarify what regimens are used as comparators for these ICERs
75/140	1	In the tornado diagrams…. What was the criteria to determine if a results was sig affected?
75/140	3	Consider NO Treatment as a comparator vs PR
76/140	Figure 6	Please reference the costs?

Page # per PDF	Paragraph	Comment
82/140	2	Clarify how cost per death averted was calculated and defined
115/140	appendix table c2	is this svr 12 ?
119/140	appendix table c9	change heading to treatment naïve or exp
119/140	appendix table c9	ion3 was naïve pts
122/140	appendix c15	PEARL 2 and 3 did have RBV as PBO controlled
122/140	appendix c16	consider showing outcomes on patients that did not take RBV with 3D
122/140	appendix c16	Sapphire I DR was 1.7% and Sapphire II DR was 1.3%
123/140	appendix table c17	Add Turquoise I Coinfected Study for 3D. Wyles AASLD 2014
124/140	appendix table c19	Add Coral study for 3D. KWO, P NEJM NOV '14

Public Comments for California Technology Assessment Forum on Newest Treatments for Hepatitis C, Genotype 1

1111 Broadway, 7th floor
Oakland, CA 94607

Thursday, December 18, 2014 from 9:30 AM to 4:30 PM (PST)

A) Clinical Considerations B) Specialty Drug Payment and Pricing

Oral statement:

My name is Bill Remak, 61 years of age, Medical Technologists and BSN in Public Health, I was previously on the staffs of pathology labs at UC San Francisco and San Francisco General Hospital. For over twenty years I have been a patient and health policy advocate for chronic and liver diseases also organ donation. Thank you for the opportunity to speak with you today.

I have served on the Board of Directors of the American Liver Foundation of Northern California/Nevada, founded the California Hepatitis C Task Force and the National Association of Hepatitis Task Forces, am a founding executive board member of the California Chronic Care Coalition, Executive Director of the National Working Group on Evidence Based Healthcare, Community Advisory Board member of the VA Hepatitis C Program and also on the Community Advisory Board of the Partnership Health Plan of California. Member of Society of Gastroenterology Nurses and Associates, Association of Health Care Journalists, National Viral Hepatitis Roundtable, World Hepatitis Alliance. I am the Board Secretary of the FAIR Foundation and the National Advocacy Director. I am a core member of the group that were drivers of proposition 71 that saw the passage and creation of the California Institute of Regenerative Medicine and provided perspective on the initial governance.

I am here primarily to bring you a patient perspective and perhaps you will consider my story in the context that we now have a tremendous opportunity with the development of these Direct Acting Anti-Virals (DAA's), to change the future with a vision of eliminating hepatitis C. My story paints the picture of the past. The past is something we learn from and for nearly half a century since I was admitted with acute liver failure to the Kaiser Hospital ICU in San Rafael, CA in 1967 then called chronic persistent hepatitis and non-A and Non-B hepatitis which was later to be called in the mid 80's hepatitis C while through those years with routine medical exams and test this illness slowly eroded my health despite a very active and relative healthy quality of life in which I got an education, embarked on a career , married, raised four children and now have three grandchildren. Life has thrown some curves but I am here today because of the science, the skillful application of medicine by a team of thoughtful and motivated doctors, navigate the system and knowing that giving up was not an option and last but not least, my determination to survive! The last 25 years has been a contest of endurance and my medical background and knowledge has played an important role in helping me succeed along with the support of my family and friends.

In 1990 bacterial spinal meningitis nearly took me, 95' gall baller removed, 98' Hepatocellular Carcinoma and Liver transplant, 1999 to 2006 3x combination Rib. Interferon therapy with Neupogen and Procrit then 3x pegylated treatment each time 48 weeks= six full 48 week treatments. Spring of 2007 2nd liver transplant severe complications. Since 1996 I have been insulin dependent with type 2 diabetes, have bone degeneration with osteoarthritis of the spine and stage 3 chronic kidney disease, And I still have hepatitis C genotype 1! After 48 years, now is my chance to be cured. The difference is that these treatments really work.

My personal healthcare costs covered by my health plans exceeded 3.5 million dollars over the last 24 years. The reality that what I have endured over 48 years can now be resolved with 8 weeks of a medical regimen and obtain a lasting cure is miraculous and I am ecstatic. From my perspective it opens the door to a new life without this chronic disease. For me it means the end of a long crusade and a new beginning that is priceless. The fact is that whatever the costs of these DAA's, the suffering, costs and resources that I have depended on which kept me alive before these new treatments but not cured the disease, have exceeded 50 times the health costs burden. End the suffering, the cost savings speak for themselves. The manufacturers and the health plans need to come to a real collaboration to resolve the problems, focus on common ground issues, to have the goal for affordable health access to get cures for their patients. All stakeholders will come out ahead on this and it is the right thing to do. The California Chronic Care Coalition (CCCC) is leading a national forum of stakeholders to help facilitate the dialog to reach resolutions on the specialty medications and disparities that hamper affordability and access for patients.

This research has yielded a pathway of hope for many and as we sit here today I am involved in efforts that will help build and educate the workforce capacity to deliver the necessary hepatitis C specialty care that people need to compensate for the provider and specialty care shortage. I would like to share my knowledge to continue to work to address this important public health issue as long as I am able. New science must be allowed to progress. Transplantation, Regenerative medicine, personalized medicine, stem cell therapies and precision medicine are with us. Technology is helping change the world for people and when it is about people, then it is about better health. Thank you for listening.

Bill Remak

Petaluma, CA

12-15-2014

To Whom It May Concern:

Dr. Steven Pearson suggested that it might not be too late to submit our comments on your hepatitis C document. We are the organizers of the action outside your event. The comments we distributed to the public are below and we submit these for your consideration:

The O.A.S.I.S. Clinic organized this action because the Institute for Clinical and Economic Review (ICER) has failed to incorporate language about drug users in its hepatitis C report. This report will be discussed today when the California Technology Assessment Forum meets to assess the comparative effectiveness and value of multiple new treatments for hepatitis C (HCV). Because injection drug users represent the majority of new and existing cases of HCV, we believe that any HCV report that fails to include recommendations about treating drug users is of limited relevance. We respectfully request that the following be considered, and that appropriate recommendations be included in the ICER report:

1. Injection drug use is responsible for over 70% of cases of HCV in the U.S. and is the means by which the majority of new cases of HCV are transmitted.[1] Data have shown that each active drug injector is likely to infect about 20 other people, and half of those transmissions occur in the first two years after the initial infection.[2] Cost effectiveness analyses should incorporate the magnified impact of treating a single active injector on the overall cost benefit of treating this population.

2. Mathematical modeling has shown that increasing HCV treatment coverage of injection drug users will lead to rapid and substantial reductions in seroprevalence and seroincidence.[3,4] This will significantly reduce the per-person cost of treating active drug users and therefore ICER should incorporate this data into cost effectiveness models and subsequent treatment recommendations.

3. Eliminating HCV in active drug users is the key to eradicating the HCV epidemic and will substantially eliminate its forward costs. This consideration should be reflected in the report's recommendations.

4. The added effectiveness of treating HCV when the infection is acute[5] should further improve the cost benefit of treating active drug injectors and should be incorporated into the ICER economic analyses.

5. A failure to adhere to medication regimens is frequently cited in decisions to withhold HCV treatment from drug users. However, studies have shown that drug users adhere to medical treatments at rates similar to those of non-drug users[6] and that HCV treatment outcomes are similar in drug-using and non-drug using populations.[7,8,9] Therefore, the potential benefits of treating drug users as the majority HCV population should be specifically examined in the ICER report.

6. HCV reinfection is frequently cited in decisions to withhold HCV treatment from drug users. However, studies have shown that reinfection is an uncommon outcome in persons

who continue to share needles or other injection equipment.[10,11] The economic costs of reinfection should be factored into the ICER's analyses in an evidence-based fashion.

7. We recognize that there are no outcomes data for treating active drug users with ledipasvir/sofosbuvir or simeprevir/sofosbuvir. However, ICER's failure to acknowledge the potential cost benefits of treating drug users helps promulgate discriminatory policies that exclude drug users from receiving HCV treatment. Indeed, the preliminary ICER report mentions that Anthem, Wellpoint, Express Scripts, and United Healthcare limit access to lifesaving treatment when a person is using drugs. There are no data in support of these policies and this should be reflected in the ICER report.

8. Because ICER is supported by health insurers that may financially benefit when drug users are excluded from treatment, extra care should be taken that this conflict of interest does not influence decisions about treatment candidacy. This issue is especially pressing because the CTAF panel does not include members with expertise in Addiction Medicine.

O.A.S.I.S. Clinic
Oakland, CA
December 17, 2014

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Thank you for the opportunity to provide additional public comment after the December 18, 2014 meeting at which the CTAF report "The Comparative Clinical Effectiveness and Value of Novel Combination Therapies for the Treatment of Patients with Genotype 1 Chronic Hepatitis C Infection" was reviewed. Project Inform previously submitted written comment prior to the meeting. This additional post-meeting commentary is in conjunction with the National Viral Hepatitis Roundtable (NVHR).

1. Hepatitis C among People Who Inject Drugs

Our first and most important comment in light of the meeting proceedings is profound concern about the lack of expertise about treating hepatitis C in people actively engaged in drug use on both the voting panel and on the roundtable panels. There was a clear lack of cultural competence, a lack of knowledge of behavioral health, and a demonstrated poor understanding of the care and treatment of people who inject drugs (PWIDs). There was no discussion of the data on treatment outcomes for PWIDs. Assumptions were made regarding the ability of PWIDs to adhere to HCV treatments, as well as the reinfection risk in this patient group. Indeed, when one of the invited panelists—one with HCV treatment expertise—explicitly stated that she knew the question of reinfection would come up and that she specifically reviewed it for the occasion, her citation of statistics on the relatively low rate of reinfection among PWIDs seemingly fell upon deaf ears. Additionally, one voting member of CTAF questioned if hepatitis C is really an infectious disease, while another questioned if people who inject drugs are a waste of money because if they continue injecting they will get hepatitis C again. In general members and panelists referred to people who use drugs as "addicts," which is stigmatizing and non-person/patient-centered language. The stigma that most PWID experience in society and often experience in healthcare settings was clearly reflected by the attitudes and language used by the panel as a whole.

In 2001, Brian Edlin and colleagues penned a very influential article, "Is it Justifiable to Withhold Treatment for Hepatitis C from Illicit-Drug Users," in the *New England Journal of Medicine*. It highlighted four potential reasons for denying treatment: poor adherence, side effects of treatment, risk of reinfection, and a lack of urgency to initiate treatment.[1] At the time, pegylated interferon (PEG-INF) and ribavirin (RBV) were the standard of care, and people who used drugs were explicitly denied treatment unless they were abstinent from all drug use for at least six months. This article deconstructed the arguments used to justify this recommendation, and helped change these guidelines, so that in 2002, the National Institutes of Health recommended that all

[1] BR Edlin, KH Seal, J Lorvick, AH Kral, DH Ciccarone, LD Moore, B Lo. *Is it justifiable to withhold treatment for hepatitis C from illicit-drug users?* NEJM 345 (3), 211

people with HCV who were actively using drugs should be considered for treatment on a case-by-case basis.[2]

Fast-forward to 2014, in an era of DAAs for HCV that are far simpler to take and have fewer side effects. Sadly, many of the same fallacious arguments Edlin and colleagues dispelled were made at the CTAF meeting.

In a review of people who were actively injecting drugs while undergoing dual therapy of PEG-INF and RBV, Aspinall and colleagues found that HCV treatment outcomes for this very challenging regimen in PWID were comparable to those among people who were not using drugs. In reviewing 6 studies of PWIDs who took HCV treatment, the authors found a pooled estimate of SVR to be 55.9% for people with HCV genotype 1-4.[3] These SVR rates were comparable to large clinical trials for PEG-INF and RBV.[4] In a meta-analysis of 32 studies on HCV treatment in PWIDs, Dimova and colleagues found a treatment completion rate of 83.4%.[5] Similarly, treatment discontinuation was similar among PWIDs as it was among their non-injecting counterparts: 22% in PWIDs compared to 15%-25% in non-PWIDs.[6] People who use drugs adhere to and have similar treatment outcomes as do people who do not use drugs.

The assumption that PWIDs automatically have poor adherence to treatment is one based more on stigma than on facts. The pooled analysis by Aspinall and colleagues found adherence rates among PWIDs to be 82% (which, by standards for PEG-INF and RBV is considered high). Similarly, in a study assessing the adherence to PEG-INF and RBV in recently infected patients, the majority of whom were PWIDs, Grebely and colleagues found no difference between the adherence rates of PWIDs and people who did not use drugs. Indeed, the authors concluded:

> *This study demonstrates that PEG-INF adherence is high among participants with recent HCV infection acquired primarily through [injection drug use]. Further [injection drug use], prior to, and during PEG-INF treatment was not associated with reduced adherence or treatment completion. These data suggest that adherence is not compromised among [injection drug users], supporting guidelines that active [injection drug users] should not be excluded from HCV*

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[2] NIH Consensus Statement on the Management of Hepatitis C. Accessed on December 24, 2014 at http://consensus.nih.gov/2002/2002hepatitisc2002116html.htm

[3] Aspinall EJ, Corson S, Doyle JS, Grebely J, Hutchinson SJ, Dore GJ et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: A systematic review and meta-analysis. Clinical Infectious Diseases 2013;57 (Suppl 2):S80-S89

[4] Manns MP[1], Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. Gut. 2006 Sep;55(9):1350-9.

[5] Dimova RB[1], Zeremski M, Jacobson IM, Hagan H, Des Jarlais DC, Talal AH. Determinants of hepatitis C virus treatment completion and efficacy in drug users assessed by meta-analysis. Clin Infect Dis. 2013 Mar;56(6):806-16. doi: 10.1093/cid/cis1007. Epub 2012 Dec 7.

[6] Aspinall EJ, Corson S, Doyle JS, Grebely J, Hutchinson SJ, Dore GJ et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: A systematic review and meta-analysis. Clinical Infectious Diseases 2013;57 (Suppl 2):S80-S89

therapy and the decision to initiate HCV treatment in active [injection drug users] should be made on a case-by-case basis.[7]

Again, this supports the inclusion of PWIDs for HCV treatment as their adherence rates are similar to those who do not use drugs.

There are generally low rates of reinfection among people who inject drugs, estimated at 2.4 (95% CI 0.9 –6.1) per 100 person-years[8]. In a review of 7 studies that looked at reinfection of PWIDs following HCV treatment, Grady and colleagues estimate the risk to be between 1-5% per year. [9]

Its also worth noting that the authors state "in communities with a higher local background HCV epidemic, treated PWIDs are like to have a higher risk of reinfection," thus supporting the notion of "cure as prevention" for PWIDs: The more people cured who are at risk of transmitting HCV, the fewer transmissions will occur. Models have shown that treating PWIDs can significantly reduce HCV prevalence: Estimated HCV prevalence is cut in half when treatment is increased to 15, 40, or 76 per 1000 PWID annually in Edinburgh, Melbourne and Vancouver, respectively.[10]

A useful summary of the literature on HCV reinfection can be found can be found at http://www.ohtn.on.ca/wp-content/uploads/2014/11/RR89-HCV-reinfection.pdf

Ultimately, the onus is on systems to say that HCV treatment doesn't work in PWID – not the other way around. Are there any other medical conditions for which we would deny people who use drugs access to effective treatment? The answer is emphatically no. Restricting access to people based on substance use is discriminatory, unethical, and not based in ANY evidence. We suggest a careful review of the Scottish experience to help inform the panelists understanding of how treating people who inject drugs is possible and necessary to comprehensively address hepatitis C.[11] Further, the "Recommendations for the Management of Hepatitis C Virus Infection Among People

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[7] Grebely J, Bryant J, Hull P, Hopwood M, Lavis Y, Dore GJ, Treloar C. Factors associated with specialist assessment and treatment for hepatitis C virus infection in New South Wales, Australia. J Viral Hepat. 2011 Apr;18(4):e104-16. doi: 10.1111/j.1365-2893.2010.01370.x. Epub 2010 Sep 14.

[8] Aspinall EJ, Corson S, Doyle JS, Grebely J, Hutchinson SJ, Dore GJ et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: A systematic review and meta-analysis. Clinical Infectious Diseases 2013;57 (Suppl 2):S80-S89

[9] Grady BP[1], Vanhommerig JW, Schinkel J, Weegink CJ, Bruisten SM, Lindenburg CE, Prins M. Low incidence of reinfection with the hepatitis C virus following treatment in active drug users in Amsterdam. Eur J Gastroenterol Hepatol. 2012 Nov;24(11):1302-7.

[10] Martin NK[1], Vickerman P, Grebely J, Hellard M, Hutchinson SJ, Lima VD, Foster GR, Dillon JF, Goldberg DJ, Dore GJ, Hickman M. Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. Hepatology. 2013 Nov;58(5):1598-609. doi: 10.1002/hep.26431. Epub 2013 Aug 26.

[11] Scottish National Hepatitis C Action Plan. Accessed December 22, 2014 at http://www.inhsu.com/symposium2013/pdf/sharon-hutchinson-translating-research-into-public-health-policy-the-scottish-national-hepatitis-c-action-plan.pdf

Who Inject Drugs"[12] provides both guidance for HCV treatment in PWIDs as well as a comprehensive literature review of 130 peer-reviewed articles and other references.

Competence and understanding about the relationship of injection drug use and hepatitis C are vital to appropriately assessing the hepatitis C care and treatment landscape, as the majority (more than 50%) of prevalent infections are among people with a history of injection drug use and a recent study identified injection drug use as the risk factor for 84% of individuals diagnosed with acute HCV. Approximately 20 to 30% of persons who inject drugs are infected with HCV within the first 2 years of starting to inject drugs and 75 to 90% of PWID are HCV-antibody reactive. Incidence of HCV in PWID has markedly declined in the past 20 years, likely secondary to use of sterile syringe programs that arose in response to the HIV epidemic and saturation of HCV infection among PWID. Recent reports have identified a new cohort of HCV-infected PWID with the following characteristics: age 24 or younger, white race, residence in non-urban areas, and use of oral prescription opiates prior to using heroin. The prototypical new heroin user initiates some type of substance use at about age 13, transitions to using oral opiates, most often oxycodone, around age 17, then eventually starts using cheaper and widely available heroin by about age 18.[13] This is critical context for understanding incident infections in the United States that nobody on the panel or on the roundtables mentioned throughout the entire day.

We find it troubling that the CTAF membership will be reviewing integration of behavioral health in primary care at the next CTAF meeting, when they exhibited obvious biases and misunderstanding of people who use drugs. Without a full understanding of the complexity of the syndemics of mental health and substance use, we fear any recommendations made will be as damaging to the care and treatment of patients in need of behavioral health services as CTAF's prior hepatitis C report had on access to curative treatment for people living with HCV.

2. Patient-related outcomes and quality of life

Second, we were surprised by how little the panelists seemed to understand the impact that curing HCV has on patient-related outcomes and quality of life issues for people living with hepatitis C who have no or mild liver disease. One panelist stated that if people are asymptomatic perhaps they don't need treatment. Anyone with a basic understanding of hepatitis C knows that being asymptomatic is common and that it does not mean there are no underlying disease or quality of life issues.

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[12] Robaeys et al. *Recommendations for the Management of Hepatitis C Virus Infection Among People Who Inject Drugs,* Clinical Infectious Diseases 2013;57(S2):S129–37

[13] University of Washington. HCV Epidemiology in the United States. Hepatitis C Online: Accessed December 23, 2014 at http://www.hepatitisc.uw.edu/pdf/screening-diagnosis/epidemiology-us/core-concept/all

These issues are well documented. Younossi and colleagues note that the associations of HCV with cirrhosis, HCC, liver-related mortality, type 2 diabetes mellitus, rheumatological diseases, and quality of life impairments are supported by strong evidence. Also, there is strong evidence that sustained viral eradication of HCV can improve important outcomes, such as mortality and quality of life. The current evidence suggests that HCV has been associated with tremendous clinical and quality of life deficits.[14] This type of information should be considered, as it is critical to providing the full picture of the value of curative treatments.

Similarly, to not consider this within an analysis of the value and cost-effectiveness of curing people of HCV severely limits the analysis and underestimates the true impact of eradicating this disease. As Younossi, a leading expert on HCV patient-related outcomes and health economics states:

> *There is increasing evidence that HCV-related liver disease has a significant negative impact on patient reported outcomes [PROs]. This impairment worsens with liver disease severity and improves after achieving SVR. These PROs also impact worker productivity, which leads to a negative impact on society. Additionally, HCV-related liver disease places a substantial economic burden on patients, their families and society. Furthermore, there is an increasing appreciation of HCV as a systemic disease with both hepatic and extrahepatic consequences. If the PRO and the economic impact of the extrahepatic manifestation of CV (cardiovascular disease) are added to its hepatic manifestation, its true clinical, PRO and economic impact can be enormous.*[15]

There is ample evidence of the cost-effectiveness of HCV treatment: A cursory Pub Med review resulted on over 300 articles on the subject. A similar search looking at "quality of life HCV treatment" resulted in 471 articles. We strongly encourage CTAF to due a literature review on patient-related outcomes and include it in the final analysis of the value and cost-effectiveness of HCV curative treatments.

3. Patients not treated now will be more expensive later

Third, in none of the roundtable conversations did anyone mention an essential piece of the treatment access and price puzzle. Since payers are commonly restricting treatment to people with F3-F4 or equivalent, most of the people living with hepatitis C will age into Medicare older, sicker, and with more advanced liver disease, requiring more

[14] Younossi ZM[1], Kanwal F, Saab S, Brown KA, El-Serag HB, Kim WR, Ahmed A, Kugelmas M, Gordon SC. The impact of hepatitis C burden: an evidence-based approach. Aliment Pharmacol Ther. 2014 Mar;39(5):518-31. doi: 10.1111/apt.12625. Epub 2014 Jan 26.

[15] Younossi ZM[1], Kanwal F, Saab S, Brown KA, El-Serag HB, Kim WR, Ahmed A, Kugelmas M, Gordon SC. The impact of hepatitis C burden: an evidence-based approach. Aliment Pharmacol Ther. 2014 Mar;39(5):518-31. doi: 10.1111/apt.12625. Epub 2014 Jan 26.

expensive care and longer treatment durations. This care and treatment will be fully supported through our federal tax dollars. Given the roundtable "Specialty drug payment and pricing" it is shocking that this issue was not raised.

4. Budget Impact Modeling is beyond CTAF's mission and missed critical information

Fourth, the integration of a Budget Impact Model seems to be a significant departure from ICER's (and CTAF's) mission. It is an important issue to raise, but we are concerned that this was not the appropriate venue or the proper level of information to have a useful conversation on the topic.

The benchmark used for the per member per month (PMPM) increase threshold of 0.5-1.0% has no documentation associated with it and does not appear to be evidence based. If CTAF is expanding its mission to look at budget impact than it needs to used an evidence-based approach that is commonly accepted and documented in the literature.

In addition, CTAF needs to review all medical expenditures in the health care system and not just one piece (pharmaceutical pricing) of the system in a vacuum. One roundtable panelist, a payer, mentioned that he wants the insured to "feel" some of the costs associated with high-priced medications, like the new anti-HCV DAAs. This is a fallacious statement – if payers really wanted the insured to "feel" the costs associated with their care they would not levy high-cost sharing only on pharmaceuticals (e.g., up to 30% co-pays or co-insurance on the highest tiered medications), they would levy high cost sharing on brain surgery, emergency room visits, and other expensive procedures. Brenda Gleason, a health policy consultant, noted at the May 29th National Stakeholders Specialty Medication Collaboratory (hosted by the California Chronic Care Coalition in Sacramento) that patients' average co-pay/co-insurance for hospitalizations is 4%, physician services is 17%, outpatient services is 7%, and drug costs is 22%, which points to the fact that payers are not looking systemically and strategically at cost-sharing in all parts of the health care system. In addition, budget impact cannot be accurately reviewed without considering infections averted through a "cure as prevention" strategy, without reviewing reinfection issues, and without reviewing adherence issues. Failure to examine these issues through the lens of budget impact makes absolutely no sense in the context of reality.

Thank for your accepting this addition commentary. We look forward to seeing the final report in late January.