The Comparative Clinical Effectiveness and Value of Novel Combination Therapies for the Treatment of Patients with Genotype 1 Chronic Hepatitis C Infection

Summary of Public Comments And Response on Draft Report

January 30, 2015

Response to Public Comments

The Institute for Clinical and Economic Review (ICER) produces publicly-available evidence reviews for consideration by the California Technology Assessment Forum (CTAF). As part of this process, ICER welcomes public comment from individuals and organizations on its proposed project scope, voting questions, and evidence assessment. For transparency, all those submitting comments during the public comment period are acknowledged in this response document. However, detailed responses are focused on those comments pertaining to the project scope, evidence assessment, and major assessment findings.

This document responds to comments from the following parties:

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

	Comment	Response
Rachel McLean, MPH, Viral Hepatitis Prevention Coordinator / STD Healthcare Policy Analyst, STD Control Branch, California Department of Public Health, Sacramento, CA		
1	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.	*Thank you for your comments. We have added a note in the executive summary regarding the drugs that were included in the cost-effectiveness analysis.*
2	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.	*We understand the capacity and other logistical challenges associated with increasing awareness of infection and treatment options. However, we also noted at the meeting that our analysis included a very conservative estimate for infection prevalence in a Medi-Cal/Dept of Corrections population (1.2%). Using prevalence estimates that have been reported in the literature (~4% for Medicaid, ~30% for corrections) suggests that an appropriate "starting point" would have been approximately 300,000 (vs. 93,000 in our analysis). In any event, 50% of 93,000 and 15% of 300,000 yield essentially the same population size for analysis. We have modified the report to reflect these countervailing effects.*
3	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.	*The focus of the evidence review was on the comparative effectiveness and economic value of the newest agents available for hepatitis C. While we agree that broader health-system interventions to reduce the burden of infection may be warranted, this was beyond the scope of our review. This limitation was already noted in the draft report.*

	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.	
Folashade Naku, PharmD, MS, BCPS		
1	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.	*Thank you for your comments. We are unsure what this comment refers to – the draft report included full documentation of the results of the cost-effectiveness analysis as well as relevant Appendices.*
2	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. 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.	*We disagree that "there should be no 'cost offsets' in a budget impact analysis." In fact, as stated in the ISPOR document the commenter mentions:* *"The introduction of new interventions may result in changes in the symptoms, disease duration, disease outcomes, or disease-progression rates associated with the health condition and, thus, in changes in the use of condition-related health care services…if credible data are available and these changes have an impact on healthcare budgets, condition-related costs should be presented in the BIA."*
3	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.	*The terminology was derived as part of an ongoing multi-stakeholder conversation regarding the tension between cost-effectiveness and health-system affordability.*
4	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). 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. Since these are current treatment recommendations the size and characteristics of the eligible population should be properly accounted for in the economic analysis.	*We used the best available estimates of current disease prevalence in the populations of interest for our evaluation, rather than relying on a separate modeling study that is based on one estimate regarding what effects expanded screening will have.*
5	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	*The budget impact analysis was based on a one-year time horizon. Cost offsets at 5 and 20 years were provided for*

	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.	*informational purposes only. We have clarified this in the final report.*
Laura Bessen, MD, Vice President, Head of US Medical, Bristol-Myers Squibb Co., New York, NY		
1	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.	*We agree that it is difficult to make comparisons between the trial results because of the potential for selection bias. We would welcome randomized trials directly comparing regimens. Throughout the assessment, we attempted to highlight the poor evidence base for comparative effectiveness. For instance on pages 24-25 when discussing the methods, we wrote "any comparison of these summary SVR12 rates between treatments should be made cautiously because differences in the study samples may explain some of the differences in response rates."*
2	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.	*The data for the DCV + SOF + RBV arms are included in the tables. We could not include all study arms in the figures and picked the ones that were either FDA approved or appeared likely to form the basis of FDA approval, and we tried to maintain comparability across study arms. We do not think that there is a compelling reason to change the figures at this time.*
3	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.	*While we recognize that the evidence review focused on genotype 1 alone, we thought that the most responsible assessment of budget impact would include the other common genotypes. Of note, we focused on FDA-approved regimens for the analysis, and so the regimen suggested would not have been applicable. The final report includes clarification on how certain estimates for the budget impact analysis were derived.*
4	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	*Reference #29 reviews the world's literature on mortality both in countries in which a large proportion of the HCV infections are attributable to injection drug use (like the US) as well as other countries with different patterns of infection. The last sentence of the paragraph highlights some of the*

	reality. Of note, more data is pending from the CDC on the evaluation of death certificates. HCV is largely underreported in death certificates.	*uncertainty in the data. We look forward to additional data from more representative cohorts. Physicians should not stigmatize the IDU population or the larger population of HCV-infected patients. Both populations deserve compassionate care and appropriate treatment.*
5	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))	*Table 1 reflects the CDC estimates. The estimates from the model described in Table 2 of the "Aging of HCV population" publication has similar estimates at 20 years to the CDC. The second reference is a cohort in Taiwan that was unable to estimate the length of time since diagnosis, so the data in the suggested reference are not directly applicable.*
6	Page 4 - Please consider adding genotype to the list of factors associated with cirrhosis (Source: AASLD Guidelines)	*We agree that some genotypes are associated with an increased risk for cirrhosis, but we did not include genotype in the list of factors for this assessment because it is focused on genotype 1 only.*
7	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.	*We agree that the CVS/Caremark results have not been peer-reviewed, but the HCV-TARGET and TRIO data presented at the 2014 AASLD meeting have also not yet been through peer review. Furthermore, the HCV-TARGET data were SVR4 results and not SVR12. In the TRIO study, 8% did not complete therapy, which is very similar to the CVS/Caremark results. In addition, the SVR12 for patients with genotype 1 was less than 90%.* *The fact that the pharmaceutical funding for HCV-TARGET was through unrestricted grants has been added.*
8	Page 21, Table – For ALLY-2, recommend adding under column "Comparator" DCV+SOF for 8 weeks vs. DCV+SOF for 12 weeks.	*We have made this change.*
9	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.	*Noted. We elected to use a fixed-effects model because statistical heterogeneity was not present in most cases and to avoid unduly weighting very small studies. If a random-effects model was used, the confidence intervals would have been even wider.*
10	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.	*A detailed methodology document is available from the ICER website and is referenced in the CTAF report (see citation 110).*
11	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	*We have now clearly stated that FDA guidance recommends SVR12 as the primary outcome of studies of DAAs. However, both SVR12 and SVR24 are intermediate outcomes.*

	http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm225333.pdf).	
12	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.	*Thank you for the clarification. We have updated Table 5. However, we decided against adding DCV + SOF + R given that ribavirin is unlikely to be added to the combination therapy given the high SVR without R.*
13	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.	*Thank you for the clarification. We have updated the table.*
14	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.	*Thank you for the clarification. We have updated Table 7. However, we decided against adding DCV + SOF + R given that ribavirin is unlikely to be added to the combination therapy given the high SVR without R.*
15	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.	*Thank you for the clarification. We have updated the table.*
16	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%.	*Thank you – the numbers have been corrected.*
17	Page 50, Table 11 – With regards to the annual cost of CHC-related health care by disease state (McAdam 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 healthcare, it doesn't appear that the costs were adjusted to 2014 dollars. This has an effect, albeit limited, on the reported cost-offsets.	*We chose to use incremental costs, i.e., the added costs for individuals with HCV as compared with similar individuals without HCV. We believe this is the most appropriate approach if the goal is to model HCV costs and potential savings from treatment. Our numbers are derived from Razavi (2013), though focused more narrowly on those with known HCV infection. Razavi relied on McAdam-Marx (2011) for the in-care costs. The cost for year 1 liver transplant is listed in Supplement – Appendix D as $178,130, which we then adjusted to $188,671 to reflect 2014 dollars.*
18	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.	*The calculations for the cost to avert one HCV-related death have been added to the report.*
19	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.	*The PMPM was taken directly from a published document provided by the California Department of Health Care Services, as noted in the report (reference #179). The baseline used for our calculation was PR therapy, as mentioned in the report.*
20	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	*Supplemental rebates are not published, so we could not reflect those in our analyses. We have added a sensitivity*

	pharmaceutical manufacturer pays to the State Medicaid programs (http://www.medicaid.gov/medicaid-chip-program-information/by-topics/benefits/prescriptiondrugs/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.	*analysis using the 23.1% rebate to the final report.*
21	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.	*Thank you for the clarification. The sentence about likely recommended dosing has been removed to avoid the erroneous implication.*
22	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).	*Appendix D, Table D2 lists the post-SVR progression probabilities and regression rates. Martin et al do not use post-SVR progression or regression of fibrosis in their model. Page 49, Table 11 of the report lists the natural history progression probabilities. Our model set up for natural history is different compared to Martin et al. The model we employ attempts to distinguish between each natural history source and target states, whereas the Martin model limits the distinctions. For example, Martin et al do not break down the F0-F4 transition probabilities, so these would not be useable in our model. The observations are similar for other transition probabilities. However, it should be noted that many of the base case transition probabilities used by Martin et al are covered in our sensitivity analysis ranges.*
23	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	*This was not a recommendation but a statement of the pricing range that would meet the 0.5-1.0% PMPM benchmark for an increase over baseline costs given the prevalence of the condition under study. Cost offsets were included in the economic*

	associated offset of other treatment costs, while also encouraging future innovative development.	*modeling, and policies to encourage innovation were discussed during the second policy roundtable at the CTAF public meeting on December 18, 2014.*
Emalie Huriaux, MPH, Director of Federal and State Affairs, Project Inform, San Francisco, CA		
1	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.	*Thank you for your comments. Please see our response to comment 3 on page 3.*
2	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.	*Thank you for the input. We made the decision to address the quality of life issues in the model. Please see the utilities described in the modeling section for the references on which our quality of life assumptions were based.*
3	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.	*This report is final based on the regimens approved by the FDA when the analyses were conducted. This does not preclude the conduct of an updated review at a future point in time, however.*
4	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.	*We did not intend to imply that the AASLD/IDSA/IAS-USA guidelines are intended for payers. We have left our summary as is. Interested readers can review the guidelines since they are available online.*
5	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.	*Any report will always quickly be out of date because the field of hepatitis C treatment is moving quickly. An exhaustive review of abstracts presented at AASLD is beyond the scope of our assessment. The most important results were discussed during the public meeting and were part of the panel's consideration when they voted.* *The HCV TARGET data presented at AASLD were still preliminary: SVR4, not SVR12, results were presented, and 18% of patients were still on treatment. The TRIO data presented at AASLD were complete for SVR12 and are more likely to be representative of real world data.*
6	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	*Please see our response to comment 2 on page 3.*

	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.	
7	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 have clarified the report to note this limitation. In addition, we have added a sensitivity analysis to incorporate the mandated discount received by Medicaid, which is publicly-available.*
Connie Chiang, PharmD, Associate Director, Medical Information, Janssen Scientific Affairs, LLC, Titusville, NJ		
1	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.	*The model results suggest that the clinical effects of SMV + SOF and LDV/SOF, when applied to a prevalent population that includes both treatment-naïve and treatment-experienced patients with and without cirrhosis, are very similar. As with any model, clinical benefits are calculated based on a number of estimates. In this case, SVR and adverse events are the primary drivers of effectiveness.*
2	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.	*We agree. We have amplified our discussion of this issue by adding the following sentences to the section on SMV + PR on page 29 of the assessment: "For this assessment, we elected to present the SVR results for simeprevir + PR in all patients with genotype 1 infections to allow direct comparisons with the new DAA combinations being evaluated. This underestimates the efficacy of simeprevir + PR in patients without the Q80K polymorphism. Please see our prior assessment for the efficacy estimates in patients without the Q80K polymorphism."*
3	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.	*We agree. On page 41 of the report, the summary of clinical efficacy states "Due to the lack of head-to-head trials and the lack of trials with common comparators, it is difficult to know if one of the DAA combination therapies is clearly superior to another." The votes at the meeting also reflected equipoise based on current data.*

Hans Reiser, MD, Senior Vice President, Medical Affairs, Gilead Sciences, Inc., Foster City, CA		
1	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 < $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.	*Thank you for your comments. No changes to final report.*
2	*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 4 therapy as HCV mono-infected patients. Gilead requests that the report be updated to reflect these updated data.	*The sentence about preliminary results has been removed, and Appendix Table C18 has been updated with the results from the AASLD meeting.*
3	*Page 35, Table 6 and Figure ES1:* 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. 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.	*Thank you for pointing out this important distinction. We have added a footnote to Appendix Table C10 highlighting the unique population in the ELECTRON-2 study and updated the SVR in Table 6 and Figure 3 as well as Figure ES1.*
4	*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. 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. 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	*We agree that the new data from AASLD are intriguing, but they do not reflect the current FDA indication for LDV/SOF. We have elected not to change the final assessment based on these new abstracts.*

	weeks achieved 96% SVR, compared with 100% SVR in subjects treated with 24 weeks of LDV/SOF.	
5	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. 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.	*We agree that the elimination of ribavirin is also desirable. We note in this section "The combinations that include ribavirin have an increased incidence of anemia, particularly when taken for 24 weeks or when combined with interferon." However, we think that the major benefit of the new DAA combination therapy is the elimination of interferon and chose to emphasize that fact.*
6	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. 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.	*We do not think that the results from abstracts at AASLD materially change the conclusions or implications of data in the assessment as it stands. The HCV-TARGET study reports SVR4 results, and 18% of patients had not completed therapy. The TRIO results were similar to those of the CVS/Caremark data. None of the 3 study results have been published in a peer-reviewed journal.*
7	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. Suggestion: 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	*The base case cohort age of 60 years was used based on clinical expert advice and to reflect the aging of a typical HCV cohort since the most recent epidemiological data have been published. It is also important to note that, while overall cost-effectiveness improved in sensitivity analyses that focused on a 50 year-old cohort, relative differences between treatment regimens were similar to those in the base case.* *We have acknowledged the limitation of not including co-infection with HIV in the evidence review or model.*
8	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%.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.	*LDV/SOF + RBV was not modeled for economic analysis as the addition of RBV is not FDA-approved. Table 10 lists the modeled therapies.*
9	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	*We cite Razavi 2013 who derived the $47,525 figure from McAdam-Marx 2011. This figure both excludes liver transplant*

	transplanted patient compared to a mean cost of $100,299 for a patient who does not receive a transplant).	*costs and is incremental to other care costs. In contrast, the AASLD abstract (Catana et al) evaluates all direct medical costs, without adjusting for a non-HCV comparison group, which may account for a large portion of the difference between $100,299 and $47,525. Finally, while the difference in costs would have an effect on cost-effectiveness findings compared with no intervention, it would only have a small effect on the comparative cost-effectiveness ratios among regimens that were the focus of this report.*
10	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.	*Disutility due to treatment was weighted for the frequency and duration of common and serious adverse events across all treatments. We attempted to employ a consistent approach for all therapy options. We do acknowledge that our approach for calculating disutility may be conservative. However, two important notes must be considered: 1) The utility loss due to LDV/SOF treatments using our approach is very small – a total loss of 0.0116 or 0.0174 QALYs for 8 or 12 week durations, respectively--reflecting the favorable side-effect profile of LDV/SOF; and 2) Our one-way and probabilistic sensitivity analyses included a utility loss of 0 with all treatments. Model results were not significantly affected in sensitivity analyses.*
11	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.	*Please see our response to comment 20 on page 7.*[KS1]
12	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.	*Please see our response to comment 2 on page 3.*
13	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	*Please see our response to comment 2 on page 3.*

	to a rare disease. 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.	
14	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 Medi-Cal 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. Cost per SVR should include all drug and medical costs for those who achieve SVR.	*Given that the PMPM estimate ($611) was a 2014 figure, we expect that 2014 expenditures for commonly-used hepatitis C therapies were included in this figure.* *While real-world data provide an important source of alternate estimates, they are challenged by the biases attendant to observational data. We nevertheless used real-world estimates for sensitivity analyses in the care value analysis.*
15	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. 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.	*This comment appears to confuse the two analyses. The care value analysis was based on a 60 year-old "base case" but also included a sensitivity analysis for 50 year-olds. The budget impact analysis was based on all individuals with prevalent and chronic infection, without regard to age.*
16	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.	*The Gordon 2012 study referenced by the commenter evaluates costs for patients identified as in care for chronic HCV infection. Our estimates, by contrast, include people who are not currently undergoing treatment for their HCV. In addition, we varied F0-F4 costs widely in sensitivity analyses (both one-way and multi-way) – the cost variations were 50% to 300%. These variations did not significantly impact our findings.*
17	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.	*As noted in the report and at the meeting, this is based on conversations with multiple stakeholders, not a published standard.*
18	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.	*This was already varied from 30-90% in sensitivity analyses.*
19	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.	*Our attempt to estimate health-state utilities was derived from studies that featured primary collection of patient-reported outcomes data.*

20	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.	*Please see our response to comment 3 on page 3.*
21	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.	*We thought it more important to compare the economic impact of alternative treatments for the condition of interest.*
Nikil Patel, PharmD, Director, Healthcare Solutions, Global Medical Affairs, AbbVie, Inc., Mettawa, IL		
1	Page 8/140, paragraph 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	*The SVR for SMV + SOF for 12 weeks in treatment-naïve patients with cirrhosis is 67% (see Table 6).*
2	Page 8/140, paragraph 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	*We agree that "wide" is subjective and that the confidence intervals are narrower for 3D in general. The confidence intervals are all presented visually and numerically, so that each reader can judge for himself or herself.*
3	Page 8/140, paragraph 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	*Noted, thank you.*
4	Page 9/140 and rest of report: Add N's and References to all figures and tables in the document	*We think that the tables are adequately annotated.*
5	Page 14/140, paragraph 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?	*Please see our response to comment 17 on page 14.*
6	Page 14/140, paragraph 2: We also conducted a hypothetical analysis….What is the time horizon of treating patients? Should that be across several years vs. 1 year?	*As stated in the report, per the typical reporting standard, the timeframe for the budget impact analysis was 1 year.*
7	Page 19/140, paragraph 1: Definition of null response and partial response should be a 2 log drop.	*Thank you, this has been corrected.*
8	Page 20/140, paragraph 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.	*We think our description of the primary goal of treatment is not discordant with yours, although we disagree that SVR is a perfect surrogate for the outcomes that matter to patients.*
9	Page 22/140, paragraph 4: for those patients who are HIV co-infected… Simeprevir is not indicated for co-infected.	*Paragraph 3 is about simeprevir; paragraph 4 is about sofosbuvir.*
10	Page 24/140, table 2: Add Moderiba and Ribapack under nucleoside analog	*They have been added.*
11	Page 26/140, paragraph 3: On August 11, 2014…. Update this paragraph since guidelines were updated on 11/20.	*We have made the change.*

12	Page 27/140, paragraph 2: EASL has also not yet… DAC is not approved in US.	*That is correct.*
13	Page 34/140, NCT02114151: These were COMPENSATED CIRRHOTICS	*Clarified.*
14	Page 34/140, NCT02206932: Please confirm as CT.Gov states this study is withdrawn	*Deleted as the study is withdrawn.*
15	Page 36/140, nct02219477: Change RCT to Cohort with multiple arms and October 2016	*Updated.*
16	Page 36/140, nct01939197: This is a phase II/III study	*Added the study phase.*
17	Page 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"	*Done.*
18	Page 37/140, Topaz II: Change multiple arms to single arm	*Done.*
19	Page 38/140, paragraph 1: Instead, we summarized the proportion of patients achieving SVR 12…. Add description or reference for the meta analysis of proportions methodology.	*Reference (Newcombe 1998) has been added.*
20	Page 43/140, paragraph 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.	*Changed "any" to "most" as a qualifier.*
21	Page 44/140, paragraph 1: Consider adding Target and Trio data from AASLD	*As noted above, the TARGET data are still preliminary (SVR4, 18% still on therapy), and the TRIO results are similar to the CVS/Caremark results. All 3 studies are not published in peer-reviewed journals. There is little value in adding more detail from abstracts.*
22	Page 45/140, paragraph 2: PR or single DAA...Please update with the following studies as they had active comparator NCT01854697; NCT01854528	*These are ongoing studies listed in Section 5, not yet published. They do not belong here.*
23	Page 45/140, paragraph 3: Add Turquoise I Coinfected Study for 3D. Wyles AASLD 2014	*We are not including studies from the AASLD 2014 unless they significantly impacted the voting questions.*
24	Page 45/140, paragraph 3: There do not appear to be an unexpected interactions…. May want to consider deleting based on Tenofovir with LDV/SOF interaction	*Noted. We intended this sentence to apply to the new DAA combinations considered in this review. The text has been edited to make that clear.*
25	Page 45/140, paragraph 4: Add 3D Coral data on post-transplant. Kwo, P NEJM 2014	*Added to text and to appendix tables C19 and 20.*
26	Page 45/140, paragraph 4: Data from the pre-transplant population suggest that the earlier…. Please clarify as this is not clear	*See Curry 2014: the longer the time from SVR to transplant, the more likely the patient was HCV-free post-transplant.*
27	Page 47/140, Table 5: 3D+R cannot confirm DR numbers. Need reference	*See Appendix Table C16.*
28	Page 47/140, paragraph 2: Third, the discontinuation rates… CIs overlap, consider deleting as this is a generalized statement	*Considered but decided to retain the statement.*
29	Page 51/140, paragraph 1: The study sizes are generally small…. Define small as the Turquoise II study had 220 pts	*The numbers are in the tables and text, and it is clear from the text that the 3D + R therapy has the largest number.*
30	Page 52/140, Table 8: 3D + R 12 wks change SVR rate CI to .902 (.849-.954), 3D + R 24 wks change to .969 (.935-1.00)	*The CI for 12 weeks is correct using the exact binomial distribution. Thank you for pointing out the error in the point estimate for 24 weeks. Again, we used the*

		exact binomial distribution for the confidence interval.
31	Page 53/140, Table 9: Suggestion to split table by cirrhotic and non-cirrhotic	*Thank you for the suggestion. We have elected to leave the table as it is.*
32	Page 62/140, paragraph 2: Recently, the WHO has promulgated suggested…. Should this be GDP per capita?	*Yes, this statement is meant to indicate the use of annual GDP/capita for a cost-effectiveness threshold and has been clarified in the report.*
33	Page 68/140, Table 14: Confusing table. Suggest rank in ascending order of efficacy vs. costs	*The table, as ordered, is necessary for calculation of Incremental Cost-Effectiveness Ratios (ICERs). This is a standard format for presenting cost-effectiveness results.*
34	Page 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.	*Net costs in this context refer to incremental treatment costs less downstream cost offsets. We have clarified this on page 68 of the final report. The structure of the care value model and the use of terms related to "dominance" are clearly explained on report pages 52, 54-55.*
35	Page 70/140, paragraph 1: Should PR be used as a benchmark since it is no longer SOC.	*We agree that PR is not the standard of care (SOC). The reasoning behind use of either PR or No Treatment to compare the new regimens is to provide a common baseline to compare and contrast the cost-effectiveness results of the new regimens and not to use a "benchmark".*
36	Page 71/140, Table 18: Is this incremental net cost or net cost.	*The costs shown in table 18 are incremental costs compared to PR.*
37	Page 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?	*The ICERs are based on "treat all" vs. "treat at F3, F4". For example, treatment-naïve patients being treated with LDV/SOF shows the ICER for treating patients with LDV/SOF at F0, F1, F2, F3, and F4 vs. treating only when they reach F3 and F4.*
38	Page 74/140, paragraph 4: Clarify what these ICERs are relative to?	*The ICERs are based on the incremental changes in costs and benefits of the three therapies listed: No-Treatment, PR, LDV/SOF (8/12 weeks), LDV/SOF (12 weeks).*
39	Page 74/140, paragraph 5: Clarify what regimens are used as comparators for these ICERs.	*See response to comment #38 above.*
40	Page 75/140, paragraph 1: In the tornado diagrams…. What was the criteria to determine if a results was sig affected?	*We ran one-way sensitivity analyses using multiple tornado diagrams on all input variables according to the upper and lower bounds listed in the report. Variables that showed the greatest effect (indicated by the bar length and corresponding ICER values), were selected and further one-way sensitivity analyses conducted. The results of the multiple sensitivity analyses showed, variable-by-variable, which input values had the largest effect on ICER values. The results for the most significant*

		input values were combined into the presented tornado diagrams.
41	Page 75/140, paragraph 3: Consider no Treatment as a comparator vs PR.	*To keep consistent with other portions of the report in which the majority of the data are presented in comparison to PR, it was appropriate to conduct one-way sensitivity analyses also in relation to PR.*
42	Page 76/140, Figure 6: Please reference the costs.	*All costs used in the model are referenced in Table 11, Page 49 of the report. Figure 6 shows the one-way sensitivity analyses on the base case costs listed in Table 11.*
43	Page 82/140, paragraph 2: Clarify how cost per death averted was calculated and defined.	*This has been clarified in the final report on page 68.*
44	Page 115/140, appendix table C2: is this svr 12?	*SVR varies by study. For most it is SVR12, though for some it is SVR24.*
45	Page 122/140, appendix table c15: PEARL 2 and 3 did have RBV as PBO controlled	*The therapies compared were 3D with or without R. There was no placebo arm of the trial even though a placebo was used for R in the 3D-only arm. All patients received 3D.*
46	Page 122/140, appendix table c16: consider showing outcomes on patients that did not take RBV with 3D	*We did not know that the FDA would approve 3D without R for patients with genotype 1b without cirrhosis at the time of the assessment. Since the vast majority of patients studied with 3D also received R, we elected to present the data this way.*
47	Page 123/140, appendix table c17: Add Turquoise I Coinfected Study for 3D. Wyles AASLD 2014	*Given that the information is available only in an abstract made available after the deadline for this assessment, we decided not to add it to this assessment.*
48	Page 124/140, appendix table c19: Add Coral study for 3D. KWO, P NEJM NOV '14	*Thank you, we included the study now that it is published.*
Bill Remak, BSN, President and CEO, and Chairman of the Board, California Hepatitis C Task Force, Petaluma, CA, Petaluma, CA		
1	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.	*Thank you for your comments.*
2	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	*Thank you for your comments.*

	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.	
3	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.	*Thank you for your comments.*
O.A.S.I.S. Clinic, Oakland, CA		
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. 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. Cost effectiveness analyses should incorporate the magnified impact of treating a single active injector on the overall cost benefit of treating this population.	*Thank you for your comments. Please see our response to comment 3 on page 3 regarding the focus of our analysis. In addition, we did not assess the effects of treatment on injection drug users because of a lack of available clinical data.*
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. 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.	*Please see our response to comment 3 on page 3.*
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.	*Please see our response to comment 3 on page 3.*
4	The added effectiveness of treating HCV when the infection is acute should further improve the cost benefit of treating active drug injectors and should be incorporated into the ICER economic analyses.	*Per the AASLD-IDSA guidelines, treatment is only recommended for chronic infection.*
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 and that HCV treatment outcomes are similar in drug-using and non-drug using populations. Therefore, the potential benefits of treating drug users as the majority HCV population should be specifically examined in the ICER report.	*Thank you for your comments. We agree that the IDU population is an important one to treat. It was beyond the scope of the review and modeling to focus specifically on the IDU subgroup.*
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. The economic costs of reinfection should be factored into the ICER's analyses in an evidence-based fashion.	*As has been well-documented in many economic studies, adherence as well as reinfection and subsequent-line treatment are problematic to model because of the lack of comparative data on how alternative treatments perform along these dimensions. These exclusions have been noted as one of the limitations of our modeling approach.*
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	*Our intent was not to promulgate any discriminatory practice, but our model was based on published evidence only. Therefore, we could not include conclusive information on the cost benefits of treating active drug users.*

	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.	*ICER is supported by a diverse set of contributors, including health insurers, manufacturers, philanthropic organizations, and both state and federal agencies. ICER staff are free of financial conflicts of interest, and CTAF panel members are appointed as individuals and not representatives of their employers. For more information please visit www.icer-review.org*
Project Inform and the National Viral Hepatitis Roundtable, San Francisco, CA		
1	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.	*Because of the diversity of topics that CTAF considers, and because of its status as a "standing" panel, it Is not feasible to have detailed expertise on the voting panel itself. With regard to the roundtable, we believe that the clinical expertise present was appropriate to the focus of the report – the comparative effectiveness of newer agents for the populations in which these agents have been studied.*
2	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.	*Thank you for your comments.*
3	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. 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. This type of information should be considered, as it is critical to providing the full picture of the value of curative treatments. 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 do a literature review on patient-	*Thank you for your comment. As noted above, we made the decision to address the quality of life issues in the modeling portion of the assessment. Please see the utilities described in the modeling section for the references on which our quality of life assumptions were based.*

	related outcomes and include it in the final analysis of the value and cost-effectiveness of HCV curative treatments.	
4	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 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.	*Thank you for emphasizing this point. Our modeling updated a prior estimate of the mean age of the infected population from 50 to 60. Thus, in another few years, we can indeed expect Medicare to see the costs of HCV-related illness. Costs, however, were modeled over a sufficiently long period that they reflect what Medicare would be expected to pay, and the results of both the cost-effectiveness and treatment scenario models should be directly applicable and helpful to the Centers for Medicare & Medicaid Services (CMS).*
5	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.	*We disagree; budget impact modeling has been a core component of CTAF activity as well as that of its sister program, the New England Comparative Effectiveness Public Advisory Council (CEPAC) for as long as ICER has been facilitating these efforts.*
6	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 use an evidence-based approach that is commonly accepted and documented in the literature.	*Please see our response to comment 17 on page 14.*
7	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.	*CTAF reviews a variety of topics, including drugs, devices, procedures, and health-system interventions. Wherever feasible, the economic impact of each intervention is considered both in terms of the dollars required to pay for it as well as its effects on other costs in the system.*
8	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.	*Please see our response to comment 6 on page 19.*