Gilead Consultation Response – 4 July 2014

Single Technology Appraisal – Appraisal Consultation Document –Sofosbuvir for treating chronic hepatitis C

Thank you for the opportunity to comment on the above Appraisal Consultation Document (ACD). Our response will cover the following points:

1) This is a complex appraisal covering multiple genotypes (GTs) and regimens. However we would like to draw the Appraisal Committee's attention to the fact that the majority of patients in the England who would be treated fall into the most cost-effective groups. This can be demonstrated by conducting a simple weighted ICER for the overall population showing that sofosbuvir is £16,199.07 for the average patient in England

2) The applicability of the 12 and 24 week sofosbuvir treatment regimens

3) The fact that the analysis presented reflects an overall conservative view of the cost effectiveness of sofosbuvir particularly in relation to the following points:

   a) Trial design and population

   b) SVR rates included in the modelling

   c) The impact on onward transmission which is not included in the modelling

4) The use of sofosbuvir in HIV co-infected populations

- **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

No, for the reasons stated above and expanded in the next section below.

- **Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence**

With regard to clinical and cost-effectiveness we would like to highlight the following areas which we consider are important to clarify.

1. Overall cost-effectiveness

We believe that it is important to consider the overall cost-effectiveness of the HCV population in totality.

A global ICER based on all patients mono-infected with HCV has been estimated for genotypes (GTs) 1 to 6 at £16,199.07 (Table 1).

This figure was calculated based on a weighted average from tables 1- 5 presented in appendix 1 which incorporate the following assumptions:

- The incremental cost effectiveness ratios from the base case model.
- The market share of GT1 treatment naïve (TN) and treatment experienced (TE) regimens to create a weighted ICER from the comparators[1]
- The prevalence of HCV patients by genotype[2]
- The prevalence of TN and TE experienced patients by genotype[3]
- The split between those HCV patients who are interferon eligible (IE) and those who are unsuitable for interferon (UI) and have no current treatment option (NT).

Table 1- Weighted Global ICER

Weighted average	**ICER (£/QALY)**
Genotype 1	10,753
Genotype 2	31,361
Genotype 3	18,671
Genotype 4/5/6	26,797
Global ICER	**16,199.07**

2. Applicability of 12 vs. 24 week sofosbuvir regimens

We are concerned that there is confusion on the exact duration of sofosbuvir treatment regimens and in particular concerns over the proportion of interferon eligible patients likely to receive sofosbuvir (SOF) plus ribavirin (RBV) for 24 weeks (ACD sections 3.58, 4.16 and 4.17). Clarification is provided below.

<u>12 weeks of SOF+Peginterferon-alpha +Ribavirin (PR) vs. SOF+RBV for 24 weeks for GT3</u>

The European Medicines Agency (EMA) licence for sofosbuvir allows for the use of either a 12 week interferon (IFN) containing regimen or a 24 week IFN-free regimen for GT3. UK clinical opinion has consistently asserted that where IFN can be tolerated by the patient the 12 week regimen would be preferable for reasons of efficacy, overall treatment duration as well as cost.

Gilead is not requesting, nor do we anticipate, that any patient who is IFN eligible would be given the option of the 24 week IFN-free sofosbuvir regimen.

The Committee requested Gilead conduct analysis of the 24 week IFN-free regimen versus 24 weeks PR and this has been completed and provided separately. However given that this scenario represents treating an IFN eligible population with an IFN-free regimen we do not believe this is an appropriate comparison.

[1] GT1 patient share data from Ipsos UK HCV Monitor Q2-Q4 2013 datasets (138 patients)
[2] Genotype distribution from the PHE genotype surveillance report 2008-2012, Published Jan 2014 p9
[3] Split of treatment naïve and treatment experienced patients of patients under care from Ipsos UK HCV Monitor dataset

There is also a level of uncertainty around the proportion of patients who would be unable to tolerate IFN with estimates from the ERG's clinical specialists ranging between 2% and 20% (ACD section 3.58). Gilead's discussions with leading English clinicians suggest that this group comprises no more than 10% of English patients. It should be noted that this group are unable to tolerate IFN and therefore the only possible comparator is no treatment.

12 weeks of SOF+PR vs. SOF+RBV for 24 weeks for GT1

For patients with genotypes 1, 4, 5 and 6 HCV, section 4.4 of the Summary of Product Characteristics for sofosbuvir states that IFN-free regimens *"should only be used for patients that are intolerant to or ineligible for interferon, therapy, and are in urgent need of treatment.'*

Whilst it is necessary to have options for this patient group which are associated with high unmet need it is anticipated that the number of patients receiving 24 weeks SOF+RBV in GT1 will be extremely low. In addition, since the Gilead submission to NICE an IFN-free option for these patients has been licensed (SOF/simeprevir [SMV] for 12 weeks) and another regimen has received positive CHMP opinion (SOF/daclatasvir [DCV]). Both of these options offer a highly efficacious treatment option.

Extending sofosbuvir treatment duration beyond 12 weeks for patients with factors predictive of poorer response

Within the sofosbuvir licence there is an option to extend IFN-containing treatment duration up to 24 weeks in more challenging patient types at the clinician's discretion. This option was added to the licence by the regulators based on the safety data for sofosbuvir. In the Phase 2 trial (ATOMIC), no difference was observed in the proportion of GT1 patients achieving SVR12 with 12 weeks (89%) compared with 24 weeks (89%) SOF+PR (see Gilead submission section 6.5.3.2). Based upon this finding, the GT1 Phase 3 programme investigated 12 weeks SOF+PR only and there are no data to support that extending treatment duration beyond 12 weeks increases efficacy. It is anticipated that in clinical practice the number of patients receiving IFN-containing sofosbuvir regimens for >12 weeks will be extremely low.

3. Trial design and comparators

3.1 Trial design

While we recognise the issues with the clinical evidence base for sofosbuvir with regards to the single-arm and open-label design and the use of historical controls we would reinforce the views of the clinical specialists that the designs and the use of historical controls are both appropriate and relevant. We disagree with the Committee's conclusion that due to the design of the trials there is uncertainty relating to the true magnitude of benefit of sofosbuvir.

Single arm trials

Active comparator trials in the area of HCV where products are IFN-sparing or IFN-free are problematic. Single arm trials have become a standard approach accepted by regulatory authorities, and there are no head to head data anticipated for sofosbuvir.

- For regimens that are IFN sparing, e.g. the NEUTRINO study in GT1 patients, the use of a comparator arm would not have provided a robust or credible approach. The same

> factors responsible for limiting the number of patients choosing treatment in clinical practice also impact on patients' involvement in trials. Taking the NEUTRINO study as an example, if a comparator arm had been added (using either dual or triple therapy) that comparator arm would effectively have become un-blinded at week 13 of the trial, when sofosbuvir based treatment ended. Even if a sham injection were used, patients continuing to take IFN would have known that they were in the comparator arm due to the very distinctive and near universal side-effects of IFN. The continuation of patients in the comparator arm would then have been dependent on the willingness of the patient to continue for another 12 to 36 weeks on therapy, knowing the (relatively lower) likelihood of successful treatment with this standard of care. It would be reasonable to assume that a very high proportion would drop out at the point that they became aware that they were not in the sofosbuvir arm. This would then have over-estimated the benefit of sofosbuvir, and would also have severely compromised the integrity of the trial. This issue is the same for all regimens that reduce or eliminate IFN therapy[4]

The use of historical controls in HCV trials is valid and well accepted by both the regulatory authorities and clinical experts. The clinical specialists at the Appraisal Committee meeting highlighted as documented in section 4.4 of the ACD, *'...it was not unreasonable to use historical controls'.*

3.2 Trial population

The sofosbuvir clinical trial programme represents a relatively hard to treat patient population, more representative of the real world, as compared with the comparator studies selected. Therefore the improvement in efficacy from sofosbuvir used in the modelling is likely to be underestimated. Detailed comparisons are included in appendix 2 to this response.

3.3 SVR rates

In response to the request from the Appraisal Committee (ACD sections 4.14 and 4.23) we have provided alternative SVR response rates for PR in GT1 treatment-naïve (TN) patients including those from Hadziyannis et al. (2004)[5]. We have concerns regarding this approach because of the level of difference between the Hadziyannis population and those enrolled in NEUTRINO.

In our initial model, SVR rates from McHutchison et al. (2009)[6] were used. Clinical expert opinion deemed McHutchison et al. (2009) as the most appropriate source since it is the largest (1035 vs. 271 patients in Hadziyannis et al) and most recent publication and is also commonly cited as being the most representative of current treatment practice and outcomes. It should also be noted that compared with the Hadziyannis study the patients in the McHutchison study were older (48 years vs. 43 years), heavier (82.8kg. vs. 77.3kg) and with a higher proportion of

[4] This is not relevant for the new protease inhibitor regimens which have the potential for 48 weeks of IFN therapy

[5] Hadziyannis SJ, Sette J, Morgan TR, Balan V, Diago M, Marcellin P et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004; 140(5):346-355.

[6] McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffmann R et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med 2009; 360:1827-1838

patients with black ethnicity (19% vs. 3%), thus being more representative of the population seen within the NEUTRINO trial for GT1.

In addition the SVR rates for both McHutchison et al and Hadziyannis et al. (2004) are reported for F0-F2 and F3-F4 METAVIR scores. This offers significant bias against sofosbuvir since in the NEUTRINO trial, non-cirrhotic and cirrhotic patients were defined as F0-F3 and F4, respectively. Thus, our initial approach is already conservative.

We would also like to highlight that whilst we could also have included data from Roberts et al. (2009)[7] where an SVR of 6% for patients with a F4 METAVIR score was reported the decision was made to use McHutchison for the reasons above and the fact that the SVRs were more conservative. In the event the Roberts data had been used the overall ICER would have been reduced, again demonstrating the conservative approach.

3.4 Impact of onward transmission

As noted by the Committee (ACD section 4.22) no benefit is taken into account in the ICERs for the expected reduction of onward transmission for those reaching SVR and thus all ICERs presented are conservative, particularly in the non-cirrhotic cohort.

4. Cost-effectiveness of sofosbuvir in HCV/HIV co-infected people

The preferred regimen for HCV/HIV co-infected patients is SOF+PR (12 weeks) as stated in the sofosbuvir licence. This is as per HCV mono-infected patients unless patients are unsuitable for interferon. Table 2 details the SVR rates for HCV/HIV co-infected patients and HCV mono-infected patients treated with 12 or 24 weeks of SOF+RBV within each genotype. SVR rates for HCV mono-infected patients versus HCV/HIV co-infected patients were similar:

- 68% versus 76% (GT1 treated with SOF+RBV for 24 weeks)
- 56% versus 67% (GT3 treatment naïve, treated with SOF+RBV for 12 weeks - unlicensed regimen)
- 85% versus 92% (GT3 treatment-experienced, treated with SOF+RBV for 24 weeks)

Table 2 was presented in our response to the ERG report.

It should also be noted that current treatment guidelines recommend that HCV/HIV co-infected patients should be treated the same as mono-infected patients and the recently published '2014 EASL (European Association of the Study of the Liver) Recommendations on the Treatment of Hepatitis C' highlights the following:

- Indications for HCV treatment in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection (Recommendation A1)
- The same treatment regimens can be used in HIV co-infected patients as in patients without HIV infection, as the virological results of therapy are identical (Recommendation A1)

[7] Roberts SK, Weltman MD, Crawford DH, McCaughan GW, Sievert W, Cheng WS et al. Impact of high-dose peginterferon alfa-2A on virological response rates in patients with hepatitis C genotype 1: a randomized controlled trial. Hepatology 2009; 50:1045-1055.

- No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs (Recommendation A2)

Please note that the British HIV Association Guidelines for HCV/HIV co-infection are currently being updated to reflect a similar position to the European guidelines.

Table 2 – Comparison of SVR rates for sofosbuvir between mono- and co-infected patients

Trial	Genotype	TN/TE	Regimen	Duration (weeks)	Number of patients achieving SVR12	SVR12 Response (%)
PHOTON-1**	GT1	TN	SOF+RBV	24	87/114	76
SPARE	GT1	TN	SOF+RBV	24	17/25	68
PHOTON-1**	GT2	TN	SOF+RBV	12	23/26	88
VALENCE	GT2	TN	SOF+RBV	12	68/73	93
PHOTON-1**	GT3	TN	SOF+RBV*	12	28/42	67
FISSION	GT3	TN	SOF+RBV*	12	102/183	56
PHOTON-1**	GT3	TE	SOF+RBV	24	12/13	92
VALENCE	GT3	TE	SOF+RBV	24	212/250	85
STUDY 1910**	GT1	TN	SOF+PR	12	17/19	90
NEUTRINO	GT1	TN	SOF+PR	12	262/292	90

**Unlicensed regimens, **co-infected patients*
GT:Genotype; RBV: Ribavirin; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve;

Since the initial Gilead submission, additional data from study 1910[8] has become available and we have provided this information. This information was also previously provided, with the agreement of NICE, in response to the ERG clarification queries. In this study SVR rates for HCV mono-infected patients versus HCV/HIV co-infected patients were 90%, reinforcing that similar response rates were seen in HCV/HIV co-infected patients as HCV mono-infected patients treated with SOF+PR in GT1 patients.

[8] Rodriguez-Torres M, Rodriguez-Orengo JF, Gaggar A, et al. Sofosbuvir and Peginterferon Alfa-2a/Ribavirin for Treatment-Naïve Genotype 1-4 HCV-Infected Patients Who Are Coinfected With HIV. 53rd ICAAC 2013. Sept 10-13, 2013, 2013; Denver, CO

Table 3 shows the ICERs/QALY gained for SOF+PR against PR using the data from 1910 for a non-cirrhotic cohort. SOF+PR given for 12 weeks remains a cost-effective treatment option for GT1 HCV/HIV co-infected patients.

Table 3 – ICERs/QALY for GT1 HCV/HIV co-infected with data from 1910

		ICERS (£/QALY)	
Indication	**Treatment strategies**	**Base case model**	**Scenario analysis model**
GT1 TN	SOF+PR (12 wks) vs. PR	14,745	15,866

ICER: Incremental cost-effectiveness ratio; IE: Interferon eligible; GT: Genotype; PR: PEGIFN2a + RBV; QALY: Quality-adjusted life years; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; wks: Weeks

We would also like to stress again that the ICERs originally submitted in the appendices for GT3 HCV/HIV co-infected patients used data from the PERICO trial[9]. These data presented a few limitations:

- First, the SVR rate (86%) was reported for all patients but not for non-cirrhotic and cirrhotic patients separately. Therefore an assumption had to be made that the SVR rate of 86% applied to the non-cirrhotic cohort. An adjustment based on Laguno et al. (2009)[10] was then applied to obtain the SVR rate for cirrhotic patients of 61%. Given that co-infected patients are expected to have response rates similar to mono-infected patients, the SVR rate of 61% for the cirrhotic population is likely to be inflated. For instance, we estimated a SVR rate of 35% for mono-infected cirrhotic patients based on the publications by Lagging et al (2013)[11] and Shoeb et al (2011)[12]
- Second, the SVR rates for TE patients were assumed to be the same as those for TN patients (as mentioned previously, 86% and 61% for non-cirrhotic and cirrhotic patients, respectively) as no data was available for this population in the TE indication. This is considered to be a big limitation since a significant difference has been observed in the SVR rates between TN and TE in mono-infected patients. In the event we had used a more conservative estimate such as Lagging et al (2013) this would have resulted in similar ICERs to those seen in the mono-infected population. However, at the time of the analysis no publication was found that provided efficacy data on TE HCV/HIV co-infected patients. Consequently, we have conducted a further scenario analysis assuming a more likely scenario for the TE population using the SVR rate from Lagging et al. (2013) and the distribution between relapsers and non-responders from Shoeb et al (2011). These are presented in Table 4.

[9] Labarga P, Barreiro P, da SA, Guardiola JM, Rubio R, Aguirrebengoa K, et al. Comparison of high ribavirin induction versus standard ribavirin dosing, plus peginterferon-alpha for the treatment of chronic hepatitis C in HIV-infected patients: the PERICO trial. J Infect Dis 2012 Sep 15;206(6):961-8.

[10] Laguno M, Cifuentes C, Murillas J, Veloso S, Larrousse M, Payeras A et al. Randomized trial comparing pegylated interferon -2b versus pegylated interferon -2a, both plus ribavirin, to treat chronic hepatitis C in human immunodeficiency virus patients. Hepatology 2004; 49:22-31.

[11] Lagging M, Rembeck K, Buhl MR et al. Retreatment with peg-interferon and ribavirin in patients with chronic hepatitis C virus genotype 2 or 3 infection with prior relapse. Scandinavian journal of gastroenterology 2013;48:839-847.

[12] Shoeb D, Rowe IA, Freshwater D et al. Response to antiviral therapy in patients with genotype 3 chronic hepatitis C: fibrosis but not race encourages relapse. *Eur J Gastroenterol Hepatol* 2011;23:747-753

In summary, as highlighted in the 2014 EASL guidelines (recommendation A1) and supported by the results from our trials (see Table 2) we believe the HCV/HIV co-infected population responds in a similar manner to the mono-infected population.

Table 4 lists the ICERs from all sofosbuvir trial data available for HCV/HIV co-infection aligned to the final licensed regimens for GT1 and GT3 from the summary of product characteristics (SmPC). That is 12 weeks SOF+PR [Study 1910] or 24 weeks SOF+RBV for the TE population [PHOTON 1].

Table 4 – ICERs/QALY for HCV/HIV co-infected

Indication	Treatment strategies	ICERS (£/QALY) Scenario analysis model
GT1 TN	SOF+PR (12 wks) vs. PR (data for SOF from trial 1910)	15,866
	SOF+RBV (24 wks) vs. NT	27,059
GT3 TE	SOF+RBV (24 wks) vs. PR (SVR for PR from Lagging)	17,167
	SOF+RBV (24 wks) vs. NT	10,376

ICER: Incremental cost-effectiveness ratio; IE: Interferon eligible; GT: Genotype; NT: No treatment; PR: PEGIFN2a + RBV; RBV: ribavirin; QALY: Quality-adjusted life years; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; wks: Weeks

- **Has all of the relevant evidence been taken into account?**

Whilst we can confirm that all relevant clinical trial evidence has been taken into account we are disappointed that consideration does not appear to have been given to the:

- Additional sources of clinical information for HCV GT1 TE patients details of which were provided within the Gilead submission document (section 6.10.1) and in response to the ERG clarification requests
- Modelling performed in response to the ERG clarification requests.

<u>HCV GT1 TE patients</u>

Sofosbuvir in combination with PR was not studied in a Phase 3 study in HCV GT1 TE patients in the first wave of the sofosbuvir development programme.

However during the FDA's Advisory Committee meeting on the 25th October 2013, the FDA asked whether the high SVR rate in GT1 TN population (approximately 90%) provided enough evidence to support use of SOF+PR for treatment of HCV GT1 patients who previously failed to respond to a course of peginterferon and ribavirin.

Clinical efficacy

Historically, approximately 50% of treatment-naïve GT1 patients have responded to PR treatment with 50% failing to respond. In NEUTRINO, 91% of treatment-naïve GT1 patients responded to the combination of SOF+PR. The higher rate of overall SVR observed in NEUTRINO is likely driven by successful treatment of a proportion of patients who would likely be PR failures (with the assumption that all patients that would have achieved SVR with PR

achieved an SVR with SOF+PR). The increase in SVR (from 50 to 91%) is representative of the efficacy of SOF+PR in the 50% non-responders that historically would be expected to be in the study. The FDA therefore concluded that given the high SVR rates in NEUTRINO, 39/50 (78%) of PR non-responders are likely to respond to SOF+PR treatment, yielding the approximate SVR rate of 78% in the GT1 SOF+PR TN population.

Further evidence of the efficacy of sofosbuvir in GT1 treatment-experienced patients was presented by Pol *et al* at the recent EASL conference (a copy of the presentation was provided, with the agreement of NICE, in response to the ERG clarification requests). In summary in GT1 treatment-experienced patients SVR rates were 74% following treatment with SOF+PR for 12 weeks.

Cost-effectiveness

In response to the ERG clarification requests the initial economic model was re-run to provide ICERs/QALY for SOF+PR (12 weeks) in GT1 treatment-experienced patients against telaprevir, boceprevir and PR.

Results show that SOF+PR is cost-effective in GT1 treatment-experienced patients against telaprevir (£8,203/QALY), boceprevir (£683/QALY) and PR (£12,641/QALY) (see Gilead response to the ERG clarification questions).

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

No. We would however support the statement in the ACD (section 4.21) that any recommendations of the use of sofosbuvir do not exclude patients with present or previous drug use or HIV/HCV co-infected patients and that this is clearly communicated to patients and clinicians (ACD section 4.21).

Points of clarification and factual inaccuracies relating to specific sections of the ACD are provided in the following table.

We look forward to the further development of the provisional recommendations and respectfully request that the Committee considers recommending the use of sofosbuvir which remains both clinically- and cost-effective within the majority of populations.

Clarification comments and factual inaccuracies

Page	Section	Comment
5	2.1	Factual inaccuracy 'CC genotype IL28B polymorphism' should be corrected to 'non-CC IL28 polymorphism'
8	3.4	Clarification The last sentence in this section would benefit from the following additional text highlighting that there is no benefit in extending treatment with sofosbuvir plus peginterferon alpha and ribavirin beyond12 weeks. '*Results showed that sustained virological responses between 96 and 98% after treatment with sofosbuvir were achieved in each treatment arm reinforcing that for sofosbuvir plus peginterferon alpha and ribavirin there is no SVR benefit in extending treatment beyond 12 weeks*.'
13	3.16	Factual inaccuracy The following sentence within this section is incorrect: '*In around 65% of treatment-experience people, initial response was lost during previous treatment, in 28% response was lost after the end of previous treatment and 7% were interferon intolerant'* The 65% figure actually refers to those patients who relapsed during previous treatment, 28% were non-responders and 7% were interferon intolerant.
15 -16	3.20 – 3.21	Clarification No mention is made to study 1910 in these sections. Details of study 1910 were submitted, with the agreement of NICE, in response to factual accuracy check of the ERG. Additional information is provided above in response to the question *Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence* (see section 4).
17	3.24	Clarification For clarification it would be helpful to add the following sentence to after the first sentence in

Page	Section	Comment
		this section: '*In the phase III trials patients were not aware of their SVR status when completing the quality of life questionnaires*'
19	3.26	Clarification The current statement '*no studies were included that examined the efficacy of sofosbuvir within its licensed indication for treatment-experienced people with genotype 1 HCV'* is misleading and fails to recognise the evidence submitted in the original submission and in response to the ERG clarification requests detailing the FDA considerations nor the Pol *et al.* 2014 data submitted, with the agreement of NICE, in response to the ERG clarification requests. We would like to suggest that the current text is amended as follows: '*While no studies were included that examined the efficacy of sofosbuvir within its licensed indication for treatment-experienced people with genotype 1 HCV within the initial MS submission information was provided on the considerations of the FDA. In addition details of a small study in this patient population was provided in response to the ERG clarification requests. '*
19	3.26	Clarification and factual inaccuarcy The statement relating to the breaking of the randomisation for VALENCE would benefit from clarification as to actual number of patients who switched from 12 to 24weeks of treatment with sofosbuvir along with a factual correction that these patients were not included in the final analysis. At the time of the amendment unblinding the study, 11 GT3 patients had already completed 12 weeks of treatment; the remaining 250 GT3 patients were treated for 24 weeks. The 11 GT3 patients who received 12 weeks of SOF + RBV (unlicensed treatment duration) were excluded from the final efficacy analyses because of the different treatment duration. The primary endpoint of SVR12 was not influenced by the discontinuation of the placebo arm as no patients, as expected, in this group achieved SVR12. Therefore it is incorrect to state that comparisons against the placebo group need to be interpreted with caution. We would like to suggest that text is amended to highlight that the 11 GT3 patients who

Page	Section	Comment
		received 12 weeks of SOF + RBV (unlicensed treatment duration) were excluded from the final efficacy analyses because of the different treatment duration.
23	3.39	Clarification The current statement '*The manufacturer did not conduct an economic analysis for treatment experienced patients with genotype 1 HCV'* is misleading as it fails to highlight that economic analysis for GT1 treatment-experience patients was provided in response to the ERG clarification questions. The results of this analysis showed that SOF + PEG-IFN-2a + RBV is cost-effective in GT1 treatment-experienced patients against telaprevir (£8,203/QALY), boceprevir (£683/QALY) and PEG-IFN-2a + RBV (£12,641/QALY). We would request that in order to be factually correct the current text is amended accordingly and suggest the following: *'The manufacturer did not conduct an economic analysis for treatment experienced patients with genotype 1 HCV in their initial submission because there was no clinical evidence available to populate the economic model for this population. Analysis based on the FDA model for genotype 1 treatment experienced patients was however provided in response to clarification questions.* Results show that SOF + PEG-IFN-2a + RBV is cost-effective in GT1 treatment-experienced patients against telaprevir (£8,203/QALY), boceprevir (£683/QALY) and PEG-IFN-2a + RBV (£12,641/QALY).
26	3.46	Clarification The current statement '*results suggest that sofosbuvir had less than a 50% probability of being cost effective in 6 of the base case comparisons'* omits reference to the number of base cases where sofosbuvir had a greater that 50% probability of being cost-effective. In order to accurately reflect the cost effective probability we would recommend the following text is added: '*results suggest that sofosbuvir had less than a 50% probability of being cost effective in 6 of the base case comparisons and greater than 50% probability of being cost-effective in 9 of the base case comparisons'*

Page	Section	Comment
29/39	3.52	Clarification The statement '*The ERG noted that this transition was not included in the manufacturer's economic model'* is misleading and makes no reference to the fact that the potential for the transition from SVR cirrhotic back to compensated cirrhosis was included in the sensitivity analysis. In addition no reference is made to the fact that further data was provided in response to the ERG clarification requests although we note that this is mentioned later in the ACD in section 4.13.
33	3.59	Factual inaccuracy The first sentence '*The ERG pointed out the that the manufacturer's economic model* allows for 12 week regimens for sofosbuvir plus ribavirin only *for treatment-naive people with genotype 1 HCV who are interferon eligible and treatment-naive people with genotype 2 HCV (regardless of interferon eligibility'* is incorrect and should read: *'The ERG pointed out the that the manufacturer's economic model* allows for a 12 week regimen~~s for~~ of sofosbuvir plus peginterferon alpha and ribavirin ~~only~~ *for treatment-naive people with genotype 1 HCV who are interferon eligible and a 12 week regimen of sofosbuvir plus ribavirin for treatment-naive people with genotype 2 HCV (regardless of interferon eligibility'*
35	3.62	Factual inaccuracy The sentence '*The ERG used estimated from Robert et al. (2009) which reported a sustained virological response of 55% for people without cirrhosis and 24% for people with cirrhosis'* is incorrect and the cited figures should be 51% and 6% respectively. Please note that this error has already been acknowledged by the ERG and a correction issued in the ERRATUM to the ERG Final Report (page 71). We are concerned that this error has continued through to the ACD despite being recognised and reported previously.
38	4.4	Clarification We are concerned that the Committee expressed concerns about the robustness of the estimates of the clinical effectiveness of sofosbuvir. We have provided additional information

Page	Section	Comment
		above in our response the question '*Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?* and would again highlight, as stated in section 4.4 of the ACD, that the regulators and clinical specialists also supported and accepted the design of the clinical trials. We would also: • Challenge the statement that '*the number of people with cirrhosis in the clinical trials was small'*. Within the phase III trials 20% of patients had cirrhosis – this number is reflective of the proportion of patients seen in clinical practice and is substantially greater than that usually seen with clinical trial programmes (including those technologies previously appraised by NICE). We would ask that the Committee re-consider the current statement and revise this to appropriately reflect the proportion of patients included within the trials • Clarify that 6% of patients included in the Phase III trials were receiving opioid substitution therapy (methadone and buprenorphine) (see section 6.10.2 of the Gilead submission document). Patients with HCV taking opiate substitution therapy achieve cure rates similar to those not taking opiate substitution therapy. In a retrospective analysis of GT1 adult treatment-naïve patients (NEUTRINO) the percentage of patients achieving an SVR12 was 92% in patients receiving opioid substitution therapy and 90% in those patients not receiving opioid substitution therapy (92% vs. 90% respectively)[13].
39	4.5	We are disappointed that the Committee do not appear to have considered the data available for GT1 TE patients (please see our response for section 3.39)
39/40	4.6	<u>Clarification</u> We disagree with the Committees comment that the four trials in patients with GT2 and 3 had small patients numbers. Patient numbers in each trial are as follows:

[13] Mangia A et al. AASLD 2013, poster 1115

<table>
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<tr><th>Trial</th><th>Number of patients</th></tr>
<tr><td>FISSION</td><td>499</td></tr>
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<tr><td>POSITRON</td><td>278</td></tr>
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<tr><td>41</td><td>4.8</td><td>
<u>Further support</u>

Further support to the Committees conclusion that the efficacy of sofosbuvir plus ribavirin HCV and HIV co-infected people is similar to that reported for patients with chronic hepatitis C mono-infection details is provided above in our response to ‘Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence’(see section 4). These data support the justification that the rates are similar. Please note this information was provided in the Gilead response to the ERG report.

It should also be noted that as previously highlighted the current guidelines recommend that HCV/HIV co-infected patients should be treated the same as mono-infected patients and the recently published ‘2014 EASL (European Association of the Study of the Liver) Recommendations on the Treatment of Hepatitis C’ highlights the following:
• Indications for HCV treatment in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection (Recommendation A1)
• The same treatment regimens can be used in HIV co-infected patients as in patients without HIV infection, as the virological results of therapy are identical (Recommendation A1)
• No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs (Recommendation A2)

Please note that the British HIV Association Guidelines for HCV/HIV co-infection are currently being updated to reflect a similar position to the European guidelines.
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Page	Section	Comment
42	4.9	Clarification The current statement '*It noted that the adverse events reported in the main sofosbuvir clinical studies….were generally consistent with those reported in other studies for hepatitis C'* is misleading and implies that sofosbuvir has similar adverse events to other treatments. Sofosbuvir does not have any AEs. In our submission document the safety and tolerability data from the Phase 3 studies demonstrate that sofosbuvir is well tolerated and has a side effect profile which is similar to placebo and significantly superior to the current standard of care (see section 6.9.3 of the Gilead submission). We would ask that the text is amended as follows: *'It noted that the adverse events reported in the main sofosbuvir clinical studies….were related to the use of pegylated interferon and/or ribavirin with adverse events for these medicines generally consistent with those reported in other studies for hepatitis C'*
43	4.12	Additional analysis Additional analysis allowing people aged 35 and 55 years to enter the model has been provided and illustrates that impact on the ICERs of age at treatment start is not substantial. In addition, with the advent of new interferon sparing treatments it is likely that patients will initiate treatment much earlier and based on this analysis starting treatment at 35 years of age is more cost-effective compared with ages of 40 to 45 and 55.
44	4.13	Additional analysis Additional analysis exploring the effect of the transition probability from Cardoso et al. has been provided. Clarification The text stating that the transition probability of 0.05 is from Cardosa et al (2010) is incorrect.

Page	Section	Comment
		The transition probability used by Gilead in response to the ERG clarification request is assumed correct based on published literature according to Chhatwal et al. 2013[14] based on Cardoso et al. 2010.
44	4.14	Additional analysis Additional analysis exploring the impact on the ICER of alternative SVR estimates (including those from Hadziyannis et al) has been provided.
45	4.15	Additional analysis Additional analysis using the average cost for generic ribavirin (RBV) based on eMIT: £42.50 for a 56-tablet pack size.[15] has been provided
45	4.16	Clarification Clarification is required on the source of the figure of 30% of people who may need extended treatment. This figure is not supported by previous statements within the ACD which state figures of 1-2% and 20% (ACD Section 3.58). In addition as and as stated earlier in our response to *'Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence'* Gilead's discussions with leading English clinicians suggest that this group comprises no more than 10% of English patients. It should be noted that this group are unable to tolerate IFN and therefore the only comparator is no treatment.
46/47	4.18	Additional analysis Additional analysis using a utility increment after reaching sustained virological response (SVR) of 0.041 from Vera-Llonch et al. (2013)[16] has been provided. The Committee also requested the utility increment for patients that reached SVR to be taken from the sofosbuvir

[14] Chhatwal J, Ferrante S, Brass C et al. Cost effectiveness of boceprevir in patients previously treated for chronic hepatitis C genotype 1 infection in the United States. Value in Health 2013; 16: 973-86

[15] eMIT, 02/2014, NPC: DEC223, Ribavirin 400 mg tablets/Packsize 56

[16] Vera-Llonch M, Martin M, Aggarwal J, et al. Health-related quality of life in genotype 1 treatment-naïve chronic hepatitis C patients receiving telaprevir combination treatment in the ADVANCE study. Aliment Pharmacol Ther 2013; 38: 124–33.

Page	Section	Comment
		clinical trials. This is not appropriate since patients were not aware of SVR status when completing SF36. Despite this, some improvement in health-related quality of life was noted[17]. This was also noted in section 3.24 of the ACD.

[17] Younossi et al. Minimal impact of sofosbuvir and ribavirin on health related quality of life in Chronic Hepatitis C (CH-C). Journal of Hepatology 2014

Appendix 1: ICERs for genotypes 1-6

Table 1 – ICERs for GT1- 6: (Base case model)

Indication	Treatment strategies	ICERS (£/QALY) Base case model
GT1 TN IE	SOF+PR (12 wks) vs. TPV+PR (RGT)	11,836
GT1 TN IE	SOF+PR (12 wks) vs. BOC+PR (RGT)	7,292
GT1 TN IE	SOF+PR (12 wks) vs. PR (48 wks)	14,930
GT1 TE IE	SOF+PR (12 wks) vs. TPV+PR (RGT)	8,203*
GT1 TE IE	SOF+PR (12 wks) vs. BOC+PR (RGT)	683*
GT1 TE IE	SOF+PR (12 wks) vs. PR (48 wks)	12,641*
GT1 TN UI	SOF+RBV (24 wks) vs. NT	49,249**
GT2 TN IE	SOF+RBV (12 wks) vs. PR (24 wks)	£46,324
GT2 TN UI	SOF+RBV (12 wks) vs. NT	£8,154
GT2 TE IE	SOF+RBV (12 wks) vs. PR (48 wks)	£12,519
GT2 TE UI	SOF+RBV (12 wks) vs. NT	£8,591
GT3 TN IE	SOF+PR (12 wks) vs. PR (24 wks)	20,613
GT3 TN UI	SOF+RBV (24 wks) vs. NT	21,478
GT3 TE IE	SOF+PR (12 wks) vs. PR (48 wks)	12,246
GT3 TE UI	SOF+RBV (24 wks) vs. NT	28,569
GT4-6 TN	SOF+PR (12 wks) vs.PR (48 wks)	26,797

BOC: Boceprevir; ICER: Incremental cost-effectiveness ratio; IE: Interferon eligible; GT: Genotype; PR: PEGIFN2a/b + RBV; RBV: Ribavirin; RGT: Response guided therapy; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; TPV: Telaprevir; UI: Unsuitable for interferon; wks: Weeks

***** *ICERs supplied upon request within ERG clarification requests (12 March 2014), based upon FDA modelling data.*

***** *section 4.4 of the SOF SmPC states that 'SOF/RBV for 24 wks in GT1UI should only be used for patients who are intolerant to or ineligible for interferon therapy, and are in urgent need of treatment'. With the recent interim NHS England commissioning policy advocating use of SOF + Daclatasvir/Ledipasvir (for compassionate use) it is anticipated that this regimen would only be used in highly exceptional circumstances. (<1%)*

Table 2 – Weighted ICER for GT1 TN/TE based upon market share data[18]

Treatment strategies	Market share (GT1)	ICERs (£/QALY) GT1 TN	ICERs (£/QALY) GT1 TE
SOF+PR (12 wks) vs. TPV+PR (RGT)	38%	11,836	8,203
SOF+PR (12 wks) vs. BOC+PR (RGT)	33%	7,292	683
SOF+PR (12 wks) vs. PR (48 wks)	29%	14,930	12,641
Weighted ICER		**11,539**	**7,487**

BOC: Boceprevir; ICER: Incremental cost-effectiveness ratio; GT: Genotype; PR: PEGIFN2a/b + RBV; RBV: Ribavirin; RGT: Response guided therapy; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; TPV: Telaprevir; wks: weeks

Table 3 - Prevalence of HCV patients per genotype[19]

	Prevalence
Genotype 1	45.5%
Genotype 2	6.0%
Genotype 3	44.6%
Genotype 4/5/6	3.9%

[18] GT1 patient share data from Ipsos UK HCV Monitor Q2-Q4 2013 datasets (138 patients)
[19] Genotype distribution from the PHE genotype surveillance report 2008-2012, Published Jan 2014 p9

Table 4 - Prevalence of TN and TE patients split by Interferon eligible (IE) and unsuitable for interferon (UI)[20][21]

	% TN	% IE	%UI	% TE	%IE	%UI
Genotype 1	71%	91%	9%	29%	80%	20%
Genotype 2	63%	91%	9%	37%	80%	20%
Genotype 3	61%	91%	9%	39%	80%	20%
Genotype 4/5/6	65%	91%	9%	35%	80%	20%

IE: Interferon eligible; TE: Treatment-experienced; TN: Treatment-naïve; UI: Unsuitable for interferon

Table 5 - Weighted Global ICER

Weighted average	ICER (£/QALY)
Genotype 1	10,753
Genotype 2	31,361
Genotype 3	18,671
Genotype 4/5/6	26,797
Global ICER	**16,199.07**

[20] Split of treatment naïve and treatment experienced patients of patients under care from Ipsos UK HCV Monitor dataset
[21] % of patients contraindicated to IFN or intolerant to IFN from Ipsos UK HCV Monitor dataset

Appendix 2: Suitability of trials utilised in naïve comparisons and direction of bias

GT1 TN IFN eligible			
SOF+PR (12 w) vs. TEL+PR (Response guided therapy)			
SOF trial	**TEL trial**	**Direction of bias**	**Comments**
NEUTRINO	ADVANCE	Clinical data in favour of TEL	- %cirrhotic in the ADVANCE trial is 6% (compared with 17% in NEUTRINO) - %black patients lower in ADVANCE (7% vs.17% in NEUTRINO) The population in the ADVANCE trial appears to be easier to treat than the one included in NEUTRINO. The difference between cirrhotic and non-cirrhotic is taken into account in the model as separate inputs are considered for these two subgroups. For the difference in the proportion of black patients, the SVR rates observed in ADVANCE could be expected to be lower if assessed in a similar population as the NEUTRINO trial. The current base case is therefore conservative.
SOF+PR (12 wks) vs. BOC+PR (Response guided therapy)			
SOF trial	**BOC trial**	**Direction of bias**	**Comments**
NEUTRINO	Anemia Management Study	Clinical data in favour of BOC	- % cirrhotic in the Anemia management study trial is 10% (compared to 17% in NEUTRINO) - % F3/F4 in the Anemia management study is only 14% (i.e. 86% are F0-F2) The population in the Anemia management study trial appears to be easier to treat than that in NEUTRINO. However, it has not been possible to verify the definition of cirrhosis in the BOC trial. As the difference between cirrhotic and non-cirrhotic is taken into account in the model by considering separate inputs, if we assume that cirrhosis combines F3 and F4 in the BOC study, then the results could be in favour of BOC. The estimates are consequently conservative.
SOF+PR (12 wks) vs. PR (48 wks)			
SOF trial	**PR trial**	**Direction of bias**	**Comments**
NEUTRINO	IDEAL	Clinical data in favour of	- %F3-F4 in the IDEAL trial is 11%

		PR	- SVRs were reported for F3-F4 and not for F4 only - Roberts et al 2009[22] reported SVR for F4 patients of around 6%. This value was considered too low by clinicians and the base case input was therefore based on the F3-F4 values, which is a conservative approach.
GT3 TN IFN eligible			
SOF+PR (12 wks) vs. PR (24 wks)			
SOF trial	**PR trial**	**Direction of bias**	**Comments**
ELECTRON/PROTON/ LONESTAR 2	Fission	Unclear	%cirrhotic in FISSION was 20% - compared to 55% in LONESTAR-2 (no cirrhotics in ELECTRON/PROTON). Other baseline characteristics (age, gender, ethnicity, BMI and IL-28 CC) in PROTON & ELECTRON similar to FISSION but much worse in LONESTAR-2. Therefore, patients in LONESTAR-2 appear more difficult-to-treat and SVR rate is therefore likely underestimated in the cirrhotic group.
GT3 TE IFN eligible			
SOF+RBV (12 wks) vs. PR (48 wks)			
SOF trial	**PR trial**	**Direction of bias**	**Comments**
VALENCE	Lagging (2013) [23]	Clinical data in favour of PR	- %cirrhotic in the Lagging was 8% while it was 23.2% in VALENCE - While VALENCE had 250 patients, Lagging only had 38 patients The data from Lagging seem to be biased in favour of PR as patients in Lagging appear to be easier to treat. Also, the same SVR rate was assumed for non-cirrhotic and cirrhotic; the SVR rate for cirrhotic patients on PR is therefore likely overestimated.

Abbreviations: BOC, boceprevir; IFN, interferon; NT, no treatment; PR, peginterferon alfa-2A + ribavirin; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TN, treatment-naïve; TEL, telaprevir.

[22] Roberts SK, Weltman MD, Crawford DH, McCaughan GW, Sievert W, Cheng WS et al. Impact of high-dose peginterferon alfa-2A on virological response rates in patients with hepatitis C genotype 1: a randomized controlled trial. Hepatology 2009; 50:1045-1055.

[23] Lagging M, Rembeck K, Buhl MR et al. Retreatment with peg-interferon and ribavirin in patients with chronic hepatitis C virus genotype 2 or 3 infection with prior relapse. Scandinavian journal of gastroenterology 2013;48:839-847.