Sofosbuvir for chronic hepatitis C

ERG additional exploratory analyses

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Geoff Frampton
Vicky Copley
Keith Cooper
Emma Loveman

Correspondence to [redacted]

Date completed 06/05/2014

ERG additional exploratory analyses in response to discussions at the first premeeting teleconference (24-04-2014)

The ERG was requested by NICE to undertake 10 additional exploratory analyses that may inform the discussions at the appraisal committee meeting and these are presented below. The ERG also conducted an additional exploratory analysis to demonstrate the overall impact of the changes on ICERs.

1. The manufacturer applied response rates/transition probabilities for comparator treatments that were used in previous appraisals. There are many older interferon-based studies and the resulting response rates in those studies varied with risk factors, treatment experience and genotype. The ERG was requested to investigate a range of alternative SVR estimates based on these studies of comparator treatments for consideration of the differential effect of response to other treatments compared with sofosbuvir.

ERG response:

The ERG has commented on the SVR rates used in the manufacturer's model in the ERG report (p. 71). As described in section 4.4 of the ERG report these are a source of uncertainty in the manufacturer's approach. The main points are summarised here.

For HCV genotype 1 treatment-naive patients, the manufacturer has used the estimates for SOF+PEG2a+RBV from the single-arm NEUTRINO trial. Other trial estimates are available but have small numbers of patients. The estimates for BOC+PEG2b+RBV SVR differ from those used in the boceprevir STA, where the BOC+PEG2b+RBV SVR was 68.2% for non-cirrhotic patients and 41.7% for cirrhotic patients. These boceprevir STA estimates were taken from the SPRINT-2 trial and a meta-analysis of peginterferon trials. The estimates for telaprevir were taken from the ADVANCE trial. There are other trials for telaprevir but these have small numbers of patients. The estimates for PEG2a+RBV are from McHutchinson.[1] There are other estimates of PEG2a+RBV SVR available from other peginterferon trials. For example in the Hadziyannis and colleagues[2] trial the SVR in a non-cirrhotic group was approximately 56% (estimated from a figure) and in a cirrhotic group was approximately 38%. In the Roberts and colleagues[3] trial the SVRs were 55% and 24% for the two groups respectively.

The ERG has examined the variation in the final ICER arising with the use of alternative estimates of SVR for PEG2a+RBV in the HCV genotype 1 treatment-naive interferon-eligible population (see ERG report additional analyses). Applying the boceprevir STA SVR values noted in the preceding paragraph (68.2% non-cirrhotic and 41.7% cirrhotic) for BOC+PEG2b+RBV in the sofosbuvir model decreases the ICER, i.e. SOF+PEG2a+RBV becomes more cost-effective compared to BOC+PEG2b+RBV. (The SVRs used in the sofosbuvir model base case for BOC+PEG2b+RBV are 64.1% and 55.0%.)

For HCV genotype 3 treatment-naive patients, the manufacturer has used the estimates for sofosbuvir from single arms of the ELECTRON and PROTON studies. The number of patients in each trial was small and the patients were pooled to give a total population of 39 in the sofosbuvir non-cirrhotic group. The patients in the cirrhotic group (n=12) were from LONESTAR-2 although this is the incorrect (treatment-experienced) patient population. For peginterferon, although there are other trials available, SVR data are not available for cirrhotic and non-cirrhotic population subgroups. The ERG has concerns about the robustness of the sofosbuvir SVR data used in this indication and has conducted two scenario analyses.

The first scenario uses a SOF+PEG2a+RBV SVR of 90.7% for the non-cirrhotic population. This is the lower end of the 95% confidence interval for the estimate of 97.4% used in the manufacturer's base case. The second scenario examines a cirrhotic SVR for SOF+PEG2a+RBV of 92.3%. This is higher than the value used in the manufacturer's base case (83.3%) in order to better reflect a population which is not treatment-experienced. The value of 92.3% was chosen as this is the SVR for the cirrhotic population for SOF+RBV (24 weeks) in this indication in the MS (MS Table 51, p. 197). Results of the two scenarios are given in Table 1.

The ICER for sofosbuvir in the HCV genotype 3 treatment-naive interferon-eligible indication increases from £20,613 per QALY gained in the base case to £23,772 in the scenario which uses an SVR of 90.7% for the non-cirrhotic population SOF+PEG2a+RBV arm (Table 1). SOF+PEG2a+RBV remains cost-effective at a willingness-to-pay threshold of £30,000 per QALY gained in this scenario.

The ICER in the second scenario decreases compared to the base case as this scenario assumes a better treatment efficacy of SOF+PEG2a+RBV in the cirrhotic population (Table 1). In this scenario SOF+PEG2a+RBV is a cost-effective treatment at a lower willingness-to-pay threshold of £20,000 per QALY gained.

In summary, changing two of the SVR estimates used in the HCV genotype 3 treatment-naive interferon-eligible indication changes final ICERs slightly compared to baseline although not in a consistent direction. The SVR estimates used in the model base case for SOF+PEG2a+RBV in this indication remain a cause of concern as they are drawn from multiple studies and based on small numbers.

Table 1. ICERs arising from alternative SVR estimates, GT3 TN IE patients

Indication	Comparison	Submitted ICER (£/QALY)	Non-cirrhotic SVR 90.7% (£/QALY)	Cirrhotic SVR 92.3% (£/QALY)
GT3 TN IE	SOF vs. PEG2a+RBV (24 wks)	20,613	23,772	18,187

GT: Genotype; IE: Interferon-eligible; QALY: Quality Adjusted Life Year; TE: Treatment-experienced; TN: Treatment-naïve; UI: Unsuitable for interferon; wks: weeks

2. The ERG was requested to further explore the natural history of the condition and its effect on the ICERs. The natural history of HCV is recognised as very variable with prospective studies going out 35 years showing a rate of cirrhosis of <10% in some cases. While the duration of infection with HCV has an impact on progression, many other risk factors play a role in the chance for future complications and the progression of fibrosis is nonlinear across the grades of fibrosis. The ERG was asked to consider:

- What proportion of patients are likely to be cirrhotic/have HCC/need a transplant?
- If the model is sensitive to these transition probabilities?
- If so, to investigate a range of transition probabilities to different health states based on these studies of comparator treatments to allow consideration of the differential effect of response to other treatments compared with sofosbuvir.

ERG response:

Estimates for cirrhosis vary in phase 3 clinical trials, where between 17% - 35% of patients had cirrhosis. Our experts agreed that these are generally representative of clinical practice. However, the proportion may vary according to whether patients have had previous treatment or not. Hartwell and colleagues[4] used a distribution for new and existing patients with cirrhosis, based upon a London teaching hospital with 32% cirrhosis for existing patients and 10% for new patients.

A scenario analysis which uses the proportion cirrhotic given in Hartwell and colleagues[4] is shown in Table 2. This analysis assumes that 32% of treatment-experienced patients are cirrhotic, and that 10% of treatment-naive patients are cirrhotic (in comparison the base case assumes that 19% of genotype 1 treatment-naive patients are cirrhotic; and that 24% of patients are cirrhotic in genotype 3, irrespective of treatment experience).

Table 2 shows that in some comparisons the ICERs decrease with respect to the base case when these alternative estimates of the proportion cirrhotic are used. In other comparisons the ICERs increase. This behaviour depends to some extent on treatment history (treatment-experienced patients are more likely to show a decline in ICER) but also reflects the differential SVRs which are specific to a particular comparison.

In one comparison (genotype 3, treatment-naive, interferon-eligible) sofosbuvir is no longer cost-effective at a willingness to pay threshold of £30,000 per QALY gained, although it is cost-effective at this threshold in the manufacturer's base case (Table 2).

Table 2. Revised ICERs with an alternative proportion cirrhotic at treatment outset. Comparisons in bold text are not cost-effective at a WTP of £30,000 per QALY gained with the alternative proportion cirrhotic.

Indication	Comparison	Submitted ICER (£/QALY)	Revised ICER (£/QALY)
GT2 TN IE	**SOF vs. PEG2a+RBV (24 wks)**	**46,324**	**53,674**
GT2 TN UI	SOF vs. no treatment	8,154	9,650
GT2 TE IE	SOF vs. no treatment	9,274	7,350
	SOF vs. PEG2a+RBV (48 wks)	12,519	10,590
GT2 TE UI	SOF vs. no treatment	8,591	6,463
GT3 TN IE	**SOF vs. PEG2a+RBV (24 wks)**	**20,613**	**30,175**
GT3 TN UI	SOF vs. no treatment	21,478	25,986
GT3 TE IE	SOF vs. no treatment	8,557	7,335
	SOF vs. PEG2a+RBV (48 wks)	12,246	10,830
GT3 TE UI	SOF vs. no treatment	28,569	27,096
GT1 TN IE	SOF vs. telaprevir	11,836	14,661
	SOF vs. boceprevir	7,292	9,046

Indication	Comparison	Submitted ICER (£/QALY)	Revised ICER (£/QALY)
	SOF vs. PEG2a+RBV (48 wks)	14,930	18,219
GT1 TN UI	**SOF vs. no treatment**	**49,249**	**51,341**
GT4/5/6	SOF vs. PEG2a+RBV (48 wks)	26,797	25,036

GT: Genotype; IE: Interferon-eligible; QALY: Quality Adjusted Life Year; TE: Treatment-experienced; TN: Treatment-naïve; UI: Unsuitable for interferon; wks: weeks

The source of the probabilities for the transition from non-cirrhotic to compensated cirrhosis is a study by Grishchenko and colleagues.[5] Previous HTA studies used different probabilities for this transition, based upon the work of Wright and colleagues.[6] The Grischenko and colleagues study is based upon a large (n=315) representative sample of UK cases from a Trent HCV cohort and provides transition probabilities by three ages at treatment. The authors of that study considered that the estimates of disease progression will be representative of progression rates of patients presenting for treatment in the UK. For this cohort, the predicted probability of progression to cirrhosis after 20 years of infection is 12%, and the mean age at infection was 22 years. The study also analysed two other cohorts (UK National Register cohort and St Mary's) and the predicted probability of progression to cirrhosis after 20 years for these cohorts are 6% and 20%.

Although the ERG feels that the values obtained from Grishchenko and colleagues[5] are representative of natural history progression of HCV in the UK population, as noted above other estimates of progression are available. ICERs of a scenario which examines lower probabilities of progression from non-cirrhotic to compensated cirrhosis at age 40 are given in Table 3 for the HCV genotype 1 and genotype 3 indications. The lower 95% confidence interval values of the PSA distribution used in the model for these transition probabilities were examined (0.005 and 0.00874 for HCV genotype 1 and 3 respectively, compared to 0.01 and 0.014 assumed in the base case).

Table 3 shows that sofosbuvir is no longer cost-effective at a willingness-to-pay threshold of £30,000 per QALY gained in the genotype 3 treatment-experienced interferon-unsuitable indication in this scenario, although it is cost-effective in the base case. Other cost-effectiveness results do not change substantively from the base case.

Table 3. Revised ICERs with a lower transition probability from non-cirrhotic to compensated cirrhosis at age 40 years. Comparisons in bold text are not cost-effective at a WTP of £30,000 per QALY gained with alternative transition probabilities.

Indication	Comparison	Submitted ICER (£/QALY)	Revised ICER (£/QALY)
GT3 TN IE	SOF vs. PEG2a+RBV (24 wks)	20,613	22,862
GT3 TN UI	SOF vs. no treatment	21,478	24,984
GT3 TE IE	SOF vs. no treatment	8,557	10,415
	SOF vs. PEG2a+RBV (48 wks)	12,246	14,368
GT3 TE UI	**SOF vs. no treatment**	**28,569**	**33,649**

Indication	Comparison	Submitted ICER (£/QALY)	Revised ICER (£/QALY)
GT1 TN IE	SOF vs. telaprevir	11,836	14,338
	SOF vs. boceprevir	7,292	9,458
	SOF vs. PEG2a+RBV (48 wks)	14,930	17,851
GT1 TN UI	**SOF vs. no treatment**	**49,249**	**61,077**

GT: Genotype; IE: Interferon-eligible; QALY: Quality Adjusted Life Year; TE: Treatment-experienced; TN: Treatment-naïve; UI: Unsuitable for interferon; wks: weeks

3. The ERG was asked to investigate the impact on the results of using other estimates to inform the transition probabilities for the HIV co-infected subgroup, considering that initial response rates will not necessarily translate into the same health benefits seen in mono-infected people. For example, one report stated that over 50% of deaths in people co-infected with HIV were attributed to AIDS complications rather than chronic HCV infection.

ERG response:

The ERG notes that the probabilities which are currently used in the model for the co-infected population for the transition from non-cirrhotic to compensated cirrhosis at age 40 are higher than those for the mono-infected population (ERG Report Table 22). Co-infection specific SVRs are also used but other transition probabilities are not different from those applied to the mono-infected population.

Using these probabilities sofosbuvir is not cost-effective at a threshold of £30,000 per QALY gained in the HIV co-infected population when compared to PEG2a+RBV (MS Appendix Table 202, p. 499). However the HIV co-infected population is likely to have higher mortality than the mono-infected population, whether or not SVR is achieved, and this is not currently modelled. For example, in a study of Spanish patients with HIV and HCV Hernando and colleagues[7] found an excess of all-cause and liver-related mortality compared with the general population. The ERG notes that the effect of this differential mortality on the ICERs given in MS Appendix Table 202 will depend on the balance between the excess mortality seen in patients with and without SVR. In other words, whether the excess mortality post-SVR will be similar to the excess mortality when no SVR is achieved.

A 2013 study by Van Der Helm and colleagues[8] concluded that it is necessary to evaluate the effects of HCV therapy on HIV progression. On the basis of this conclusion the ERG considers that the evidence required to accurately evaluate the cost-effectiveness of sofosbuvir in a co-infected population is not currently available.

4. The ERG was requested to conduct a sensitivity analysis varying the relapse rate of people who have achieved SVR12 with sofosbuvir treatment and report what effect it has on the ICERs for each subgroup. While a longer course of therapy can be "considered" for genotype 1 HCV and indeed may occur in practice, only a 12 week course was modelled.

ERG response:

Clinical expert advice to the ERG is that a relapse following SVR12 is very unlikely (clinical opinion is that relapse after successful sofosbuvir therapy is considered not to occur after 8

weeks following end of treatment). Note that reinfection is entirely possible though. One patient in one of the clinical trials (in the SOF+RBV 12-week arm of FISSION) was observed to relapse after achieving SVR12. This would equate to a relapse rate in this trial arm of 1/170 = 0.6%. However, it should be noted that no relapses after achievement of SVR12 occurred in any of the other studies of sofosbuvir included in the MS, suggesting that the true rate of relapse would be less than 0.6%.

Incorporating a relapse rate of 0.6% to the SVRs applied in the economic model makes little difference to final ICERs. For example, if the base case SOF+PEG2a+RBV SVR of 91.7% used for non-cirrhotic patients in the HCV genotype 1 treatment-naïve, interferon-eligible population is adjusted down to reflect relapse at 0.6%, the revised SVR is 91.1% and the final ICER increases by only a few hundred pounds. The main cost-effectiveness findings do not change.

All the possible treatment durations for each subgroup are appropriately inputted into the model but the model structure does not enable the proportions receiving 12 weeks or 24 weeks of therapy to be varied, since patients receiving each regimen are considered as separate starting populations.

5. The ERG was asked to ascertain what percentage of patients receive 24 weeks of treatment versus 12 weeks and to conduct a sensitivity analysis around this assumption.

<u>ERG response</u>:

The MS and sofosbuvir studies do not provide any information on the proportions of patients who would receive 12 weeks or 24 weeks of therapy. There are three subgroups where this would be relevant:

- HCV genotype 1, SOF+PEG+RBV
- HCV genotype 2, SOF+RBV
- HCV genotype 3, SOF+PEG+RBV

The ERG sought advice from our 2 clinical experts:

- The first expert felt that it is unlikely that more than 1-2% of the patients would be considered better off with longer therapy (these would probably be patients with all possible adverse factors (cirrhosis, wrong IL28 genotype, sub-genotype, metabolic syndrome etc).
- The second expert gave a much higher figure, suggesting around 20% of patients may require 24 weeks of therapy, especially those who are interferon intolerant, including the more severe cirrhotic patients. However the expert cautioned that it is very difficult to predict what will happen when the all-oral regimens become available.
- One expert commented that HCV genotype 3 has the lowest response rates and the most doubt as to which would be the best regimen. The alternative here though would be between 24 weeks SOF+RBV and 12 weeks SOF+PEG+RBV; the expert had not seen any evidence that 12 weeks of SOF+PEG+RBV has better results for this genotype.

The ERG notes that only the 12 week regimen of SOF+PEG2a+RBV is an option in the economic model for the HCV genotype 1 treatment naïve, interferon-eligible population. It

is not possible to select a 24-week regimen. 12 week regimens of SOF+RBV are also the only option presented in the model for the HCV genotype 2 treatment naïve interferon-eligible and interferon-unsuitable populations, irrespective of treatment experience. The 24 week regimen of SOF+RBV is, however, available as an input option in various genotype 3 indications. The 12-week SOF+PEG2a+RBV option is used in the base case for the genotype 3 interferon-eligible group. ICERs obtained with the 24 week SOF+RBV regimen for this group are given in Table 4. In two of the three comparisons examined, the 24-week regimen is not cost-effective at a willingness-to-pay threshold of £30,000 per QALY gained.

Table 4. Revised ICERs for a 24 week SOF+RBV regimen in GT3 IE patients. Comparisons in bold text are not cost-effective at a WTP of £30,000 per QALY gained with the 24 week regimen.

Indication	Comparison	Submitted ICER (£/QALY)	ICER with 24 week SOF regimen (£/QALY)
GT3 TN IE	**SOF vs. PEG2a+RBV (24 wks)**	**20,613**	**46,713**
GT3 TE IE	SOF vs. no treatment	8,557	28,438
	SOF vs. PEG2a+RBV (48 wks)	**12,246**	**48,687**

GT: Genotype; IE: Interferon-eligible; QALY: Quality Adjusted Life Year; TE: Treatment-experienced; TN: Treatment-naïve; UI: Unsuitable for interferon; wks: weeks

6. The ERG was asked to conduct a sensitivity analysis around the age of people entering the model. The manufacturer used an average age of 45, but the average age of participants per trial ranged from 46 (mean, ELECTRON trial) to 59 years (median, P7977-2025 trial), with the overall age range across all relevant arms of the included trials being 19-77 years.

ERG response:

Sensitivity analyses were conducted using an age of treatment of 35, and an age of treatment of 55. Results are compared with the original submitted ICERs in Table 5.

Table 5 demonstrates that a lower age at treatment (35 years) is associated with lower ICERs than the base case, while a higher age at treatment (55 years) is associated with higher ICERs than the base case. With a willingness-to-pay threshold of £30,000 per QALY gained, and at an age of treatment of 55 years, sofosbuvir is not cost-effective in four treatment comparisons. These are shown in bold text in Table 5. In two of these comparisons sofosbuvir is cost-effective in the base case (HCV genotype 3 treatment-experienced, unsuitable for interferon, and HCV genotype 4/5/6).

Table 5. ICERs by alternative ages at treatment. Comparisons in bold text are not cost-effective at a WTP of £30,000 per QALY gained for treatment at age 55.

Indication	Comparison	Submitted ICER (£/QALY)	Age at treatment 35 (£/QALY)	Age at treatment 55 (£/QALY)
GT2 TN IE	**SOF vs. PEG2a+RBV (24 wks)**	**46,324**	**47,254**	**60,976**
GT2 TN UI	SOF vs. No treatment	8,154	7,497	9,306

Indication	Comparison	Submitted ICER (£/QALY)	Age at treatment 35 (£/QALY)	Age at treatment 55 (£/QALY)
GT2 TE IE	SOF vs. No treatment	9,274	8,578	10,478
	SOF vs. PEG2a+RBV (48 wks)	12,519	11,518	14,316
GT2 TE UI	SOF vs. No treatment	8,591	7,903	9,790
GT3 TN IE	SOF vs. PEG2a+RBV (24 wks)	20,613	20,516	28,836
GT3 TN UI	SOF vs. No treatment	21,478	19,406	24,820
GT3 TE IE	SOF vs. No treatment	8,557	7,697	10,071
	SOF vs. PEG2a+RBV (48 wks)	12,246	10,943	14,607
GT3 TE UI	**SOF vs. No treatment**	**28,569**	**26,251**	**32,223**
GT1 TN IE	SOF vs. telaprevir	11,836	10,752	14,783
	SOF vs. boceprevir	7,292	6,717	9,170
	SOF vs. PEG2a+RBV (48 wks)	14,930	13,465	18,731
GT1 TN UI	**SOF vs. No treatment**	**49,249**	**46,555**	**57,500**
GT4/5/6	**SOF vs. PEG2a+RBV (48 wks)**	**26,797**	**25,687**	**31,516**

BC: Base case; GT: Genotype; LB: Lower bound; QALY: Quality Adjusted Life Year; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; UB: Upper bound; UI: Unsuitable for interferon; wks: weeks

7. There is uncertainty around how representative the HRQoL results are of the wider trial populations. There was a decrement on treatment in the trials suggesting a worsening of QoL with sofosbuvir-based regimens that returned to baseline 12 weeks after treatment completion. The utility increment attributed to achieving an SVR propagated through the model has a significant effect on the ICER in patients with different genotype and levels of liver disease. The ERG was asked to investigate whether this benefit has been established in other trials and what (if any) is the range of benefit and the effect on the ICER.

ERG response:

The ERG found a HRQoL study for HCV patients receiving telaprevir combination therapy - the ADVANCE study (Vera-Llonch 2013[9]). The study included treatment-naive patients with HCV genotype 1 who received 12 weeks of telaprevir with either 24 or 48 weeks of PEG2a+RBV, or 48 weeks of PEG2a+RBV without telaprevir. The EQ-5D-3L (EQ-5D) questionnaire was completed at baseline and at weeks 4, 12, 24, 36, 48 and 72. Data from 722 patients were included; 20.2% of patients had bridging fibrosis or cirrhosis. The mean EQ-5D index decreased during the first 12 weeks and returned to baseline by week 72 across treatments. SVR at week 72 was associated ($p < 0.0001$) with improved EQ-5D index [mean; SVR+ (0.90, CI 0.88-0.92), SVR- (0.86, CI 0.83-0.88)], a 4% difference.

Scenario analyses were conducted using two alternative estimates of the utility increment after SVR. The first scenario assumes no utility increment after SVR. The second scenario

assumes a utility increment of 0.041 after SVR as given in Vera-Llonch and colleagues.[9] Results are given in Table 6.

With no utility increment after SVR, five of the comparisons shown in Table 6 are not cost-effective at a willingness-to-pay threshold of £30,000 per QALY gained. Three of these comparisons are cost-effective at this threshold in the base case: genotype 3 treatment-naive interferon-unsuitable; genotype 3 treatment-experienced interferon-unsuitable; and genotype 4/5/6. Thus, the cost-effectiveness results are sensitive to the utility increment applied. With a utility increment of 0.041 after SVR, three treatment comparisons are not cost-effective at a willingness-to-pay threshold of £30,000 per QALY gained. One of these (HCV genotype 3 treatment-experienced interferon-unsuitable) is cost effective in the base case.

Table 6. Revised ICERs for different utility increments after SVR. Comparisons in bold text are not cost-effective at a WTP of £30,000 per QALY gained with utility increment of 0.

Indication	Comparison	Submitted ICER Incr = 0.05 (£/QALY)	Revised ICER Incr = 0 (£/QALY)	Revised ICER Incr = 0.041 (£/QALY)
GT2 TN IE	**SOF vs. PEG2a+RBV (24 wks)**	**46,324**	**69,160**	**49,251**
GT2 TN UI	SOF vs. no treatment	8,154	13,168	8,754
GT2 TE IE	SOF vs. no treatment	9,274	20,438	9,969
	SOF vs. PEG2a+RBV (48 wks)	12,519	15,141	9,225
GT2 TE UI	SOF vs. no treatment	8,591	13,894	9,225
GT3 TN IE	SOF vs. PEG2a+RBV (24 wks)	20,613	29,461	21,791
GT3 TN UI	**SOF vs. no treatment**	**21,478**	**33,487**	**22,960**
GT3 TE IE	SOF vs. no treatment	8,557	13,434	9,156
	SOF vs. PEG2a+RBV (48 wks)	12,246	19,228	13,103
GT3 TE UI	**SOF vs. no treatment**	**28,569**	**46,006**	**30,661**
GT1 TN IE	SOF vs. telaprevir	11,836	20,168	12,787
	SOF vs. boceprevir	7,292	12,732	7,899
	SOF vs. PEG2a+RBV (48 wks)	14,930	25,000	16,097
GT1 TN UI	**SOF vs. no treatment**	**49,249**	**92,795**	**53,793**
GT4/5/6	**SOF vs. PEG2a+RBV (48 wks)**	**26,797**	**52,907**	**29,409**

GT: Genotype; IE: Interferon-eligible; QALY: Quality Adjusted Life Year; TE: Treatment-experienced; TN: Treatment-naïve; UI: Unsuitable for interferon; wks: weeks; incr: utility increment after SVR

8. The ERG was asked to confirm whether the manufacturer's model included treatment discontinuation due to adverse effects for sofosbuvir and comparators (apart from through

costs), as the Markov trace doesn't seem to be affected by discontinuations. The ERG was asked to conduct an exploratory analysis to consider the impact of various treatment discontinuation rates for comparators.

ERG response:

Treatment discontinuations due to adverse effects (and other reasons) are reflected in the SVR12 estimates used in the model, as they would (in a conservative analysis) be captured in the denominator of the SVR12. For this reason they would not appear on the Markov trace.

The MS presents rates of discontinuation for sofosbuvir studies (MS Tables 45-54) but these are not reported at the level of the non-cirrhotic/cirrhotic subgroups that inform the model. The ERG has checked for HCV genotypes 1, 2 and 3 whether the SVR12 values for the non-cirrhotic and cirrhotic subgroups from sofosbuvir studies could be considered conservative.

In the sofosbuvir studies, for HCV genotypes 2 and 3 the denominators of the non-cirrhotic and cirrhotic subgroups reported in the MS (MS Tables 47-54) appear to include withdrawals (or in some cases there were no withdrawals). The subgroup SVR12 values for these genotypes therefore appear to be conservative with regard to the numbers analysed. However, the ERG notes that the comparison of non-cirrhotic and cirrhotic subgroups for HCV genotype 3 is problematic because the MS has presented SVR12 for the non-cirrhotic subgroup based on treatment-naive patients (ELECTRON + PROTON) and for the cirrhotic subgroup based on treatment-experienced patients (LONESTAR-2) (MS Table 51). Thus, as noted above (question 1), cirrhotic status is confounded with treatment history in this comparison.

For genotype 1, withdrawal rates ranged from 1% overall in QUANTUM (denominator not reported) (MS Table 46) to 2.1% (7/327) in NEUTRINO (MS Table 45) and 8% (2/25) in the relevant randomised arm of SPARE (Osinusi and colleagues[10]). It is unclear in these three cases whether the non-cirrhotic and cirrhotic subgroups provided conservative estimates of SVR12 since it is difficult to ascertain from the available information how the subgroup sample sizes relate to the full study populations.

If it is assumed that the sofosbuvir SVRs used in the economic model do not reflect withdrawal rates then they will be somewhat overstated as the denominator population will not include the withdrawals. A further assumption of an 8% withdrawal rate leads to an SVR of 84.3% in the sofosbuvir HCV genotype 1 non-cirrhotic interferon-eligible population, compared to an SVR of 91.7% in the base case (MS Table 45, p. 185). This is sufficient to increase the ICER to £10,082 compared to boceprevir; to £18,047 compared to telaprevir; and to £17,004 compared to PEG2a+RBV (Base case ICERs for these comparisons are given in Table 6). Thus, in this arguably worst case, the ICERs increase but do not exceed £30,000 per QALY gained.

The MS does not report discontinuation rates for the comparator studies. The ERG assumes that the manufacturer would have applied the appropriate (i.e. most conservative) analysis in comparator subgroups, as these would yield the lowest SVR12 rates.

9. The ERG was requested to provide a sensitivity analysis which includes a discount rate of 3.5% for costs and 1.5% for health benefits for the non-cirrhotic population.

ERG response:

Table 7 gives results of a scenario analysis which uses a discount rate of 3.5% for costs, and a discount rate of 1.5% for health benefits (these discount rates are both set to 3.5% in the base case). The manufacturer's model applies the same discount rates to the cirrhotic and non-cirrhotic populations. The ERG agrees that this is appropriate and accordingly this scenario does not apply differential discount rates to the different cirrhotic subgroups. Table 7 shows that all treatments are cost-effective at a willingness-to-pay threshold of £30,000 per QALY gained when a discount rate of 1.5% is used for health benefits and a discount rate of 3.5% is used for costs.

Table 7. Revised ICERs with the discount rate set to 3.5% for costs and 1.5% for health effects

Indication	Comparison	Submitted ICER (£/QALY)	Revised ICER (£/QALY)
GT2 TN IE	SOF vs. PEG2a+RBV (24 wks)	46,324	29,765
GT2 TN UI	SOF vs. no treatment	8,154	5,241
GT2 TE IE	SOF vs. no treatment	9,274	5,961
	SOF vs. PEG2a+RBV (48 wks)	12,519	8,242
GT2 TE UI	SOF vs. no treatment	8,591	5,521
GT3 TN IE	SOF vs. PEG2a+RBV (24 wks)	20,613	12,857
GT3 TN UI	SOF vs. no treatment	21,478	13,756
GT3 TE IE	SOF vs. no treatment	8,557	5,484
	SOF vs. PEG2a+RBV (48 wks)	12,246	8,029
GT3 TE UI	SOF vs. no treatment	28,569	18,293
GT1 TN IE	SOF vs. telaprevir	11,836	7,916
	SOF vs. boceprevir	7,292	4,808
	SOF vs. PEG2a+RBV (48 wks)	14,930	9,894

GT: Genotype; IE: Interferon-eligible; QALY: Quality Adjusted Life Year; TE: Treatment-experienced; TN: Treatment-naïve; UI: Unsuitable for interferon; wks: weeks

10. The manufacturer has assumed in the model that patients who have cirrhosis will not progress if they achieve an SVR. The risk of decompensation or developing HCC may diminish once a person with cirrhosis has an SVR, but a risk remains. As this could have a significant effect on the ICER, the ERG was asked to incorporate a 25%, 50% and 75% reduction in complications for the cirrhotic cohort.

ERG response:

Applying a relative reduction to the risk of HCC for the cirrhotic population after SVR is arguably less transparent than applying a probability in its own right to this transition. This is because the resulting probability will also be dependent on the probability assumed for the transition from cirrhotic to HCC in the non-SVR population. The ERG notes that in the base case this probability is assumed to be 0.014 per year, obtained from a study by Fattovich and colleagues.[11]

In its clarification letter the manufacturer presents analyses which include a transition from the SVR-Cirrhotic health state to the HCC health state. These use a probability ultimately from Cardoso and colleagues[12] but obtained by the manufacturer from a citation by Chhatwal and colleagues.[13] This probability is 0.005, i.e. 36% of the Fattovich-sourced value in the natural history model.[11] The manufacturer's conclusion from these analyses is that they do not substantively change model findings, even when the probability at the upper 95% confidence interval is applied. The ERG agrees with this assessment.

However, as described in the ERG report, the ERG could not replicate the probability of 0.005 using the figures given in Cardoso and colleagues.[12] Instead, the probability calculated by the ERG from these data[12] for the SVR-Cirrhotic to HCC transition is 0.0123 (95% confidence interval 0.0028-0.0218), i.e. 88% of the Fattovich-sourced value in the natural history model.[11] ICERs obtained by the ERG using these transition probabilities are given in Table 8.

Table 8 shows that three comparisons are not cost-effective at a willingness-to-pay threshold of £30,000 per QALY gained if a point estimate of 0.0123 per year for the SVR-Cirrhotic to HCC transition is used. Only one of these comparisons is cost-effective in the manufacturer's base case (genotype 3 treatment-experienced interferon-unsuitable). Four comparisons are not cost-effective if the value of this transition probability is set to 0.0218 per year (Table 8). Thus the cost-effectiveness findings are somewhat sensitive to the value of this transition probability, but not greatly so.

Table 8. ICERs from the model which includes transition from SVR-Cirrhotic to HCC using rates from Cardoso and colleagues.[12] Comparisons in bold text are not cost-effective at a WTP of £30,000 per QALY gained when transition probability is set to 0.0123 per year.

Indication	Comparison	Submitted ICER (£/QALY)	BC ICER: 0.0123 (£/QALY)	LB ICER: 0.0028 (£/QALY)	UB ICER: 0.0218 (£/QALY)
GT2 TN IE	**SOF vs. PEG2a+RBV (24 wks)**	**46,324**	**54,487**	**48,163**	**60,887**
GT2 TN UI	SOF vs. No treatment	8,154	9,471	8,457	10,455
GT2 TE IE	SOF vs. No treatment	9,274	10,610	8,904	11,592
	SOF vs. PEG2a+RBV (48 wks)	12,519	14,138	12,896	15,317
GT2 TE UI	SOF vs. No treatment	8,591	9,951	8,904	10,967
GT3 TN IE	SOF vs. PEG2a+RBV (24 wks)	20,613	26,411	21,847	31,618
GT3 TN UI	SOF vs. No treatment	21,478	25,349	22,345	28,434
GT3 TE IE	SOF vs. No treatment	8,557	10,339	8,957	11,757

Indication	Comparison	Submitted ICER (£/QALY)	BC ICER: 0.0123 (£/QALY)	LB ICER: 0.0028 (£/QALY)	UB ICER: 0.0218 (£/QALY)
	SOF vs. PEG2a+RBV (48 wks)	12,246	14,656	12,786	16,578
GT3 TE UI	**SOF vs. No treatment**	**28,569**	**32,535**	**29,478**	**35,529**
GT1 TN IE	SOF vs. telaprevir	11,836	14,086	12,342	15,860
	SOF vs. boceprevir	7,292	8,609	7,593	9,611
	SOF vs. PEG2a+RBV (48 wks)	14,930	17,769	15,566	20,032
GT1 TN UI	**SOF vs. No treatment**	**49,249**	**54,166**	**50,402**	**57,693**
GT4/5/6	SOF vs. PEG2a+RBV (48 wks)	26,797	28,369	27,178	29,413

BC: Base case; GT: Genotype; LB: Lower bound; QALY: Quality Adjusted Life Year; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; UB: Upper bound; UI: Unsuitable for interferon; wks: weeks

11. The ERG also evaluated a scenario which considered jointly the inclusion of a transition from SVR-Cirrhotic to HCC; alternative utility increments after SVR; and the use of an alternative estimate of efficacy for PEG2a+RBV in the HCV genotype treatment naïve, interferon-eligible population. The annual probability of the transition from SVR-Cirrhotic to HCC is assumed to be 0.0123 as discussed above.[12] The alternative estimate of efficacy of PEG2a+RBV is obtained from the study by Hadziyannis and colleagues,[2] previously considered in scenario analysis described in the ERG report. Two utility increments after SVR were applied: a worst-case value of 0; and a value of 0.041 obtained from the study of Vera-Llonch and colleagues.[9] Results of this scenario are given in Table 9.

Table 9 shows that seven comparisons are not cost-effective at a willingness-to-pay threshold of £30,000 per QALY gained in the combined scenario which uses a utility increment of zero after SVR. Four comparisons are not cost-effective at this threshold in the combined scenario which uses a utility increment of 0.041 after SVR.

Table 9. Revised ICERs for the combined scenario. Comparisons in bold text are not cost-effective at a WTP of £30,000 per QALY gained with utility increment set to 0.

Indication	Comparison	Submitted ICER (£/QALY)	Revised ICER Incr = 0 (£/QALY)	Revised ICER Incr = 0.041 (£/QALY)
GT2 TN IE	**SOF vs. PEG2a+RBV (24 wks)**	**46,324**	**86,589**	**58,383**
GT2 TN UI	SOF vs. no treatment	8,154	16,289	10,242
GT2 TE IE	SOF vs. no treatment	9,274	18,383	11,484
	SOF vs. PEG2a+RBV (48 wks)	12,519	24,407	15,297
GT2 TE UI	SOF vs. no treatment	8,591	17,135	10,763

Indication	Comparison	Submitted ICER (£/QALY)	Revised ICER Incr = 0 (£/QALY)	Revised ICER Incr = 0.041 (£/QALY)
GT3 TN IE	**SOF vs. PEG2a+RBV (24 wks)**	**20,613**	**40,919**	**28,211**
GT3 TN UI	**SOF vs. no treatment**	**21,478**	**42,435**	**27,330**
GT3 TE IE	SOF vs. no treatment	8,557	17,499	11,161
	SOF vs. PEG2a+RBV (48 wks)	12,246	24,816	15,822
GT3 TE UI	**SOF vs. no treatment**	**28,569**	**55,733**	**35,170**
GT1 TN IE	SOF vs. telaprevir	11,836	26,377	15,376
	SOF vs. boceprevir	7,292	16,417	9,415
	SOF vs. PEG2a+RBV (48 wks)	**14,930**	**47,723**	**28,213**
GT1 TN UI	**SOF vs. no treatment**	**49,249**	**109,526**	**59,587**
GT4/5/6	**SOF vs. PEG2a+RBV (48 wks)**	**26,797**	**58,568**	**31,271**

GT: Genotype; IE: Interferon-eligible; QALY: Quality Adjusted Life Year; TE: Treatment-experienced; TN: Treatment-naïve; UI: Unsuitable for interferon; wks: weeks; incr: utility increment after SVR

References

(1) McHutchison JG, Lawitz EJ, Shiffman M, Muir AJ, Galler GW, McCone J et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009; 361:580-593.

(2) 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.

(3) 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.

(4) Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. *Health Technol Assess* 2011; 15:i-210.

(5) Grishchenko M, Grieve RD, Sweeting MJ, De Angelis D, Thomson BJ, Ryder SD et al. Cost-effectiveness of pegylated interferon and ribavirin for patients with chronic hepatitis C treated in routine clinical practice. *Int J Technol Assess Health Care* 2009; 25:171-80.

(6) Wright M, Grieve R, Roberts J, Main J, Thomas HC. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol Assess* 2006; 10:1-113.

(7) Hernando V, Perez-Cachafeiro S, Lewden C, Gonzalez J, Segura F, Oteo JA et al. All-cause and liver-related mortality in HIV positive subjects compared to the general population: differences by HCV co-infection. *J Hepatol* 2012; 57(4):743-751.

(8) van der Helm J, Geskus R, Sabin C, Meyer L, Del AJ, Chene G et al. Effect of HCV infection on cause-specific mortality after HIV seroconversion, before and after 1997. *Gastroenterology* 2013; 144(4):751-760.

(9) Vera-Llonch M, Martin M, Aggarwal J, Donepudi M, Bayliss M, Goss T et al. Health-related quality of life in genotype 1 treatment-naive chronic hepatitis C patients receiving telaprevir combination treatment in the ADVANCE study. *Aliment Pharmacol Ther* 2013; 38(2):124-133.

(10) Osinusi A, Meissner EG, Lee YJ, Bon D, Heytens L, Nelson A et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. *JAMA* 2013; 310(8):804-811.

(11) Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997; 112(2):463-472.

(12) Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavarin therapy on hepatocellular carcinoma: indicence and survival in hepatitis C patients with advanced fibrosis. *J Hepatol* 2010; 52:652-7.

(13) Chhatwal J, Ferrante SA, Brass C, El Khoury AC, Burroughs M, Bacon B et al. Cost-effectiveness of boceprevir in patients previously treated for chronic hepatitis C genotype 1 infection in the United States. *Value Health* 2013; 16(6):973-986.