Sofosbuvir for chronic hepatitis C

ERG report on the manufacturer's additional analyses requested by NICE for the second Appraisal Committee Meeting

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Keith Cooper
Geoff Frampton
Emma Loveman

Correspondence to Geoff Frampton
Senior Research Fellow
Southampton Health Technology Assessments Centre (SHTAC)
[redacted]

Date completed 09/07/2014

1. Introduction

In the Appraisal Consultation Document (ACD) for sofosbuvir for treating chronic hepatitis C, NICE requested further analyses from the manufacturer for sofosbuvir in combination with ribavirin, with or without peginterferon alfa, compared against peginterferon alfa and ribavirin in people with genotype 1 and genotype 3 chronic hepatitis C.

The manufacturer outlined their response to these requests in an additional document and provided an updated version of the economic model. The analyses were presented in a series of scenario analyses. The ERG was requested to provide an independent assessment of these analyses.

2. ERG's comments on the manufacturer's additional analyses

The manufacturer has presented their analyses as four "scenarios" which capture some of the analyses requested by NICE. These are summarised here, together with the ERG's comments. Where appropriate, the ERG has conducted new analyses and these are presented in section 3 below.

Manufacturer's scenario 1: Transition probabilities from Cardoso et al. (2010) + Utility rate from Vera-Llonch et al. (2013) + Mortality rates + Ribavirin cost

The manufacturer provided a new base case analysis applying four changes from the original base case:

1) Using transition probabilities identified from Cardoso et al. (2010) as requested for the SVR-cirrhotic health state to the hepatocellular carcinoma (HCC) health state. The manufacturer also applied an additional change to the transition probability to HCC from the non-SVR-cirrhotic (compensated cirrhosis) health state.
2) Using the utility increment after reaching SVR from Vera-Llonch et al. (2013).
3) Varying all-cause mortality assuming a 61%:39% male to female distribution in line with Wright et al. (2006).
4) Applying the generic cost of ribavirin based on £43.50 for a 56-tablet pack.

ERG comments

1) The transition probability applied for the SVR-cirrhotic health state to HCC has been checked by the ERG and is correct.

In the original base case the transition probability from the compensated cirrhosis health state to HCC was 0.014. In this scenario the manufacturer has applied a different transition probability of 0.0631. The manufacturer took this from the Cardoso et al. (2010) study which the manufacturer states is more appropriate given the requested transition probability from SVR-cirrhosis to HCC was also taken from that study. The probability is however much higher than in the original base case, and is also higher than the transition probability to the decompensated cirrhosis state (0.039 in the base case). The anticipated effect on the ICERs is favourable to sofosbuvir (see ERG analysis 6 which illustrates this point).

2) The updated analysis uses the utility from Vera-Llonch et al. (2013) as requested. The ACD also requested utility values taken from the included clinical trials to be applied. The manufacturer justifies not applying these utilities because the participants were not aware that they had achieved an SVR at the time the HRQoL assessment was applied in the trials. The ERG has not re-run this analysis as it is unclear whether the SF-36 data obtained from the trials would be reflective of post-SVR utilities.

3) A sensitivity analysis was requested by NICE relating to the proportion of males and females in the all-cause mortality data. This has instead been included by the manufacturer as part of their revised base case.

In addition, NICE requested the inclusion of alternative SVR12 estimates from Hadziyannis et al. (2004) in the revised base case but this has not been applied in Scenario 1. This is, however, given as a separate sensitivity analysis in Scenario 2 (see below).

The manufacturer has not applied the full set of assumptions requested by NICE in the ACD in their new base case. The ERG has re-run the revised base case and

sensitivity analyses in line with the changes requested by NICE (see Section 3 below). The manufacturer provides probabilistic results in the form of cost-effectiveness acceptability curves (CEACs) and scatterplots for each of their analyses. However, they have not presented probabilistic ICERs. The ERG re-ran the manufacturer's base case analyses which confirmed that probabilistic ICERs were similar to the deterministic results.

Manufacturer's scenario 2: SVR rates from Hadzyannis et al. (2004)

As noted above, this analysis was requested by NICE to be included in the revised base case. The manufacturer argues that Hadziyannis et al. (2004) is not an appropriate study for providing SVR data because it grouped METAVIR fibrosis scores as F0-F2 and F3-F4 whereas the NEUTRINO trial defined non-cirrhotic and cirrhosis as F0-3 and F4. In the original base case the manufacturer employed SVR rates from the study by McHutchison et al. (2009) and in the updated analyses the manufacturer states that this was because it was the largest study available and the most representative of current practice. Nevertheless, the manufacturer has provided a scenario analysis using the Hadziyannis et al. (2004) study.

<u>ERG comments</u>

The ERG notes that in the McHutchison et al. (2009) study, non-cirrhotic and cirrhosis were also grouped by METAVIR scores as F0-F2 and F3-F4 (similarly to Hadziyannis et al.) and therefore this is not an appropriate justification to not use Hadziyannis et al. data.

The Hadziyannis et al. rates have been applied by the ERG in the base case analysis along with the requested changes noted above (see Section 3).

Manufacturer's scenario 3: SOF+RBV for 24 weeks in HCV genotype 3 patients

The manufacturer provides scenarios assuming that 100% of patients who are interferon eligible will receive 24 weeks of SOF+RBV versus PEG+RBV and a scenario assuming that either 98% or 80% of patients receive SOF+PEG+RBV for 12 weeks and 2% or 20% receive SOF+RBV. As noted above, the manufacturer has not applied the full set of assumptions requested by NICE in the ACD in their new base case. Therefore, the ERG has re-run this analysis (see section 3).

Manufacturer's scenario 4: HCV/HIV co-infected

The manufacturer has provided analyses for HCV/HIV co-infected patients infected with HCV genotypes 1 and 3. For genotype 1, the data for study 1910 are used (from a poster by Rodrigues-Torres et al. 2013). Study 1910 had a regimen of SOF+PEG+RBV, with all drugs administered for 12 weeks. For genotype 3, the SVRs are taken from a study by Lagging et al. (2013). Initially, the manufacturer presented analyses for the combined cirrhotic + non-cirrhotic cohort (manufacturer's Table 1 in "Gilead's response to further analysis required by the Appraisal Committee – June 2014"; and Table 4 in "Gilead Consultation Response – 4 July 2014"). Subsequently, in response to a request for clarification from the ERG, the manufacturer provided a further analysis (received by the ERG 8th July 2014) which provides ICERs for mono- and co-infected patients separately according to their cirrhosis status.

<u>ERG comments</u>

The ERG has checked the calculation of the ICER for the overall cohort reported in Table 10 of the manufacturer's additional analyses and this appears correct. However, the ERG has not checked the accuracy of analysis results for the separate cirrhotic and non-cirrhotic cohorts. It should be noted that the individual studies that the analyses are based on have various limitations. The manufacturer states that they obtained a 35% SVR rate for mono-infected cirrhotic patients based on the paper by Lagging et al (2013). However, the Lagging et al. (2013) study reports that it contained only 7 confirmed cirrhotic patients and provided an SVR for 6 of these, which was 50%. It is not clear where the manufacturer's 35% comes from. The HCV genotypes of the cirrhotic patients (i.e. whether genotype 2 or 3) and the PEG+RBV

retreatment groups they were assigned to were not specified in the Lagging et al. (2013) paper.

3. ERG analyses

The ERG re-ran the revised base case analysis (ERG analysis 1) to reflect that requested by NICE. The ERG also re-ran the sensitivity analyses requested by NICE (ERG analyses 2-6) as these had been applied to an incorrect revised base case in the manufacturer's analyses.

ERG analysis 1: Revised base case

In the Tables below, the 'Manufacturer base case model' refers to the results from the manufacturer's original submission and the 'ERG analysis model' refers to the analyses conducted by the ERG using the following criteria requested by NICE:

1) A transition from the SVR-cirrhotic health state to the HCC health state, using the transition probability estimates from Cardoso et al. (2010).
2) SVR estimates for peginterferon alfa and ribavirin from Hadziyannis et al. (2004) (F0-F2 56%; F3-4 38%).
3) A utility increment after SVR (0.041) from Vera-Llonch et al. (2013).
4) Alternative costs for ribavirin (average cost for generic ribavirin based on eMIT: £42.50 for a 56-tablet pack).

Table 1 and Table 2 show the scenario analysis model results with the changes 1-4 for the combined cohort and the cirrhotic and non-cirrhotic cohorts respectively. For all analyses the ICERs are less favourable for sofosbuvir than the base case model results provided by the manufacturer. For two comparisons the ICER increases to above the £30,000 per QALY threshold, where it was below this threshold in the base case.

Table 1 – ICERs/QALY for genotypes 1 and 3: combined cohort

Indication	Treatment strategies	ICERS (£/QALY) Manufacturer base case model	ICERS (£/QALY) ERG analysis model
GT1 TN IE	SOF+PR vs. TPV+PR (RGT)	11,836	18,704
	SOF+PR vs. BOC+PR (RGT)	7,292	12,172
	SOF+PR vs. PR (48 wks)	14,930	30,993
GT1 TN UI	SOF+RBV vs. NT	49,249	58,113
GT3 TN IE	SOF+PR (12 wks) vs. PR (24 wks)	20,613	28,666
GT3 TN UI	SOF+RBV vs. NT	21,478	26,611
GT3 TE IE	SOF+PR (12 wks) vs. No treatment	8,557	10,773
	SOF+PR (12 wks) vs. PR (48 wks)	12,246	16,979
GT3 TE UI	SOF+RBV vs. NT	28,569	34,261

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

Table 2 – ICERs/QALY for genotypes 1 and 3: non-cirrhotic and cirrhotic cohorts

		ICERS (£/QALY) Manufacturer base case model		ICERS (£/QALY) ERG analysis model	
Indication	**Treatment strategies**	**Non-cirrhotic cohort**	**Cirrhotic cohort**	**Non-cirrhotic cohort**	**Cirrhotic cohort**
GT1 TN IE	SOF+PR vs. TPV+PR (RGT)	18,819	846	24,509	4,680
	SOF+PR vs. BOC+PR (RGT)	11,471	-500	15,653	2,274
	SOF+PR vs. PR (48 wks)	23,119	2,433	38,460	12,891
GT1 TN UI	SOF+RBV vs. NT	53,841	35,258	58,118	58,093
GT3 TN IE	SOF+PR (12 wks) vs. PR (24 wks)	42,240	4,281	46,036	8,318
GT3 TN UI	SOF+RBV vs. NT	30,119	8,936	31,851	15,133
GT3 TE IE	SOF+PR (12 wks) vs. NT	13,645	1,271	14,380	2,895
	SOF+PR (12 wks) vs. PR (48 wks)	17,960	3,539	20,694	8,093
GT3 TE UI	SOF+RBV vs. NT	33,777	17,983	35,744	29,704

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

ERG analysis 2: Age of patients at the start of treatment

The Committee requested a sensitivity analysis assuming patients start treatment at the ages of 35 and 55. The results for this sensitivity analysis for the manufacturer's base case and the ERG analysis are shown in Table 3. This sensitivity analysis causes a small change in the ICERs, with sofosbuvir having more favourable ICERs for younger patients.

Table 3 – ICERs/QALY for a combined cohort with age 35 and 55

Indication	Treatment strategies	Manufacturer base case model	ERG analysis model: Age 40-45	ICERs(£/QALY) ERG analysis model: Age 35	ERG analysis model: Age 55
GT1 TN IE	SOF+PR vs. TPV+PR (RGT)	11,836	18,704	17,566	22,611
	SOF+PR vs. BOC+PR (RGT)	7,292	12,172	11,586	14,706
	SOF+PR vs. PR (48 wks)	14,930	30,993	28,836	37,734
GT1 TN UI	SOF+RBV vs. NT	49,249	58,113	56,664	66,258
GT3 TN IE	SOF+PR (12 wks) vs. PR (24 wks)	20,613	28,666	29,508	38,283
GT3 TN UI	SOF+RBV vs. NT	21,478	26,611	24,877	29,520
GT3 TE IE	SOF+PR (12 wks) vs. NT	8,557	10,773	10,026	12,162
	SOF+PR (12 wks) vs. PR (48 wks)	12,246	16,979	15,651	19,517
GT3 TE UI	SOF+RBV vs. NT	28,569	34,261	32,470	37,257

BOC: Boceprevir; ICER: Incremental cost-effectiveness ratio; IE: Interferon eligible; GT: Genotype; PR: PEGINF2a/b + RBV; RBV: Ribavirin; QALY: Quality-adjusted life years; RGT: Response guided therapy; SOF: Sofosbuvir; SVR: Sustained virological response; TE: Treatment-experienced; TN: Treatment-naïve; TPV: Telaprevir; UI: Unsuitable for interferon; wks: Weeks

ERG analysis 3: SOF+RBV for 24 weeks for genotype 3 treatment-naive or experienced patients

The committee requested an analysis assuming that an increased proportion of interferon-eligible people may receive SOF+RBV for 24 weeks. Table 4 and Table 5 show the ICERs for the manufacturer's base case and the ERG analyses of SOF+PEG+RBV for 12 weeks in genotype 3 treatment naïve and treatment experienced interferon-eligible groups, for cirrhotic, non-cirrhotic and combined cohorts. Table 6 and Table 7 show the ICERs for SOF+RBV for 24 weeks for cirrhotic, non-cirrhotic and the combined cohorts. The ICERs more than double for both comparisons when the duration of therapy is extended and increase to £64,458 and £58,388 for the HCV genotype 3 treatment naive and treatment experienced cohorts respectively. This illustrates the range of ICERs assuming that 0-100% of patients receive 24 weeks treatment with SOF+RBV.

Table 4 – ICERs/QALY for genotype 3: combined cohort

Indication	Treatment strategies	ICERS (£/QALY) Manufacturer base case model	ICERS (£/QALY) ERG analysis model
GT3 TN IE	SOF+PR (12 wks) vs. PR (24 wks)	20,613	28,666
GT3 TE IE	SOF+PR (12 wks) vs. PR (48 wks)	12,246	16,979

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

Table 5 – ICERs/QALY for genotype 3: non-cirrhotic and cirrhotic cohorts

Indication	Treatment strategies	ICERS (£/QALY) Manufacturer base case model		ICERS (£/QALY) ERG analysis model	
		Non-cirrhotic cohort	Cirrhotic cohort	Non-cirrhotic cohort	Cirrhotic cohort
GT3 TN IE	SOF+PR (12 wks) vs. PR (24 wks)	42,240	4,281	46,036	8,318
GT3 TE IE	SOF+PR (12 wks) vs. PR (48 wks)	17,960	3,539	20,694	8,093

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

Table 6 – ICERs/QALY for genotype 3 interferon experienced assuming SOF+RBV for 24 weeks

Indication	Treatment strategies	ICERS (£/QALY) Manufacturer base case model	ICERS (£/QALY) ERG analysis model
GT3 TN IE	SOF+RBV (24 wks) vs. PR (24 wks)	46,713	64,458
GT3 TE IE	SOF+RBV (24 wks) vs. PR (48 wks)	48,687	58,388

ICER: Incremental cost-effectiveness ratio; IE: Interferon eligible; GT: Genotype; PR: PEGINF2a + RBV; RBV: Ribavirin; QALY: Quality-adjusted life years; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; wks: Weeks

Table 7 – ICERs/QALY for genotype 3 TE assuming SOF+RBV for 24 weeks: non-cirrhotic and cirrhotic cohorts

Indication	Treatment strategies	ICERS (£/QALY) Manufacturer base case model		ICERS (£/QALY) ERG analysis model	
		Non-cirrhotic cohort	Cirrhotic cohort	Non-cirrhotic cohort	Cirrhotic cohort
GT3 TN IE	SOF+RBV (24 wks) vs. PR (24 wks)	106,843	12,839	113,877	21,830
GT3 TE IE	SOF+RBV (24 wks) vs. PR (48 wks)	49,621	45,814	54,051	79,247

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

ERG analysis 4: Variation in all-cause mortality

The Committee requested an analysis varying the all-cause mortality by assuming that the population entering the model comprises 61% men and 39% women. The results for this scenario are shown in Table 8. Changes to the all-cause mortality make small changes to the ICERs.

Table 8 – ICERs/QALY for genotypes 1 and 3: combined cohort varying all-cause mortality

Indication	Treatment strategies	ICERS (£/QALY) ERG analysis model	ICERS (£/QALY) ERG analysis model, adjusted mortality
GT1 TN IE	SOF+PR vs. TPV+PR (RGT)	18,704	18,229
	SOF+PR vs. BOC+PR (RGT)	12,172	12,338
	SOF+PR vs. PR (48 wks)	30,993	31,348
GT1 TN UI	SOF+RBV vs. NT	58,113	58,748
GT3 TN IE	SOF+PR (12 wks) vs. PR (24 wks)	28,666	28,931
GT3 TN UI	SOF+RBV vs. NT	26,611	26,922
GT3 TE IE	SOF+PR (12 wks) vs. No treatment	10,773	10,931
	SOF+PR (12 wks) vs. PR (48 wks)	16,979	17,200
GT3 TE UI	SOF+RBV vs. NT	34,261	34,654

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

ERG analysis 5: Generic cost of ribavirin

The manufacturer disagreed with the inclusion of the generic cost of ribavirin, stating that according to the MHRA website generic ribavirin should only be used as part of a combination with interferon or peginterferon alfa-2b. Whilst there is limited published information concerning generic ribavirin, the ERG has not been able to find any generic ribavirin products for use with peginterferon alfa-2a. Furthermore, the ERG notes that the manufacturer's model analyses have been conducted using peginterferon alfa-2a, and it is therefore not appropriate to use a generic ribavirin in these analyses. The ERG has produced an analysis using the non-generic cost for ribavirin (Table 9). The effect of using a generic cost for ribavirin differed between the analyses: for those comparisons against no treatment, using the generic cost of ribavirin reduced the ICER of sofosbuvir, whilst for those comparisons against PEG+RBV, telaprevir or boceprevir, using the generic cost of ribavirin increased the ICER of sofosbuvir by up to £3,000 per QALY.

Table 9 – ICERs/QALY for genotypes 1 and 3: combined cohort with non-generic ribavirin

Indication	Treatment strategies	ICERS (£/QALY) ERG analysis model	ICERs (£/QALY) ERG analysis model with non-generic ribavirin
GT1 TN IE	SOF+PR vs. TPV+PR (RGT)	18,704	15,484
	SOF+PR vs. BOC+PR (RGT)	12,172	9,477
	SOF+PR vs. PR (48 wks)	30,993	28,408
GT1 TN UI	SOF+RBV vs. NT	58,113	59,815
GT3 TN IE	SOF+PR (12 wks) vs. PR (24 wks)	28,666	28,499
GT3 TN UI	SOF+RBV vs. NT	26,611	27,513
GT3 TE IE	SOF+PR (12 wks) vs. No treatment	10,773	11,245
	SOF+PR (12 wks) vs. PR (48 wks)	16,979	15,936
GT3 TE UI	SOF+RBV vs. NT	34,261	35,353

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

ERG analysis 6: Transition from the cirrhotic health state to the HCC health state

The manufacturer incorporated a change to the transition from the cirrhotic health state to the HCC health state, although this change was not requested by the Committee. The manufacturer used a transition probability from Cardoso et al. (2010) of 0.0631, whilst the transition probability of 0.014 in the base case model was from Fattovich et al. (1997). The manufacturer justified changing the transition probability for consistency with Cardoso et al. (2010). The ERG conducted a sensitivity analysis to demonstrate the effect of changing this transition probability on the model results (Table 10). Results show that changing the transition probability to 0.0631 has a large impact on the model results in favour of sofosbuvir.

Table 10 – ICERs/QALY for genotypes 1 and 3: combined cohort using transition probability compensated cirrhosis to HCC of 0.0631

Indication	Treatment strategies	ICERS (£/QALY) ERG analysis model	ICERs (£/QALY) ERG analysis model with TP from cirrhosis to HCC from Cardoso et al 2010)
GT1 TN IE	SOF+PR vs. TPV+PR (RGT)	18,704	15,223
	SOF+PR vs. BOC+PR (RGT)	12,172	10,214
	SOF+PR vs. PR (48 wks)	30,993	24,758
GT1 TN UI	SOF+RBV vs. NT	58,113	47,126
GT3 TN IE	SOF+PR (12 wks) vs. PR (24 wks)	28,666	21,692
GT3 TN UI	SOF+RBV vs. NT	26,611	20,834
GT3 TE IE	SOF+PR (12 wks) vs. No treatment	10,773	8,897
	SOF+PR (12 wks) vs. PR (48 wks)	16,979	13,727
GT3 TE UI	SOF+RBV vs. NT	34,261	27,199

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

4. Summary

The manufacturer has conducted additional analyses as requested by the NICE Committee. However the ERG is concerned that the manufacturer has not followed the criteria requested by the Committee. The manufacturer has included an additional change to the transition probability for compensated cirrhosis to HCC and has not included the alternative SVR12 estimates from Hadziyannis et al. (2004) in the revised base case. The ERG considers that both these changes to the Committee's criteria result in cost effectiveness results more favourable to sofosbuvir. In addition, the manufacturer has included altered mortality estimates in their revised base case; however, this change has little impact on cost effectiveness results.

The manufacturer highlighted that generic ribavirin should only be used as part of a combination with interferon or peginterferon alfa-2b. The ERG notes that the model results presented by the manufacturer are for peginterferon alfa-2a (due to its higher market share) and so it may not be appropriate to include the cost for generic ribavirin in the revised base case.