Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Sofosbuvir for treating chronic hepatitis C

ERRATUM to the Evidence Review Group Final Report

This document contains an erratum to the ERG report following the factual accuracy check by Gilead Sciences Inc.

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Academic in confidence (AIC) information in yellow.

SUMMARY

Scope of the manufacturer submission

The manufacturer's submission (MS) reflects the scope of the appraisal issued by the National Institute for Health and Care Excellence (NICE). This was to consider sofosbuvir in combination with ribavirin with or without peginterferon alfa for the treatment of chronic hepatitis C.

Summary of submitted clinical effectiveness evidence

The clinical effectiveness evidence in the MS comes from:

- Eight RCTs (four phase 3, four phase 2)
- Five non-randomised studies (two phase 3, three phase 2)

These studies report evidence for the following combinations of patients' hepatitis C virus (HCV) genotype and treatment history:

- HCV genotype 1, treatment naive (three phase 2 RCTs, one phase 3 non-randomised trial);
- HCV genotype 2/3, treatment naive (one phase 3 RCT, one phase 2 RCT and one phase 2 non-randomised trial) – the phase 3 RCT is a head-to-head trial of sofosbuvir against standard of care (ribavirin plus peginterferon alfa);
- HCV genotype 2/3, treatment experienced (one phase 3 RCT, one phase 2 non-randomised trial);
- HCV genotype 2/3, treatment naive and experienced (two phase 3 RCTs of which one was converted to a non-randomised multi-cohort trial);
- HCV genotypes 1/2/3, treatment naive and experienced, with HCV and HIV co-infection (one phase 3 non-randomised trial);
- Patients with any HCV genotype, awaiting a liver transplant (one phase 2 non-randomised trial) – this trial was not used to inform the economic analysis.

Sofosbuvir is indicated in combination with other medicinal products for the treatment of chronic hepatitis C in adults. The average length of a course of treatment is 12 or 24 weeks according to patients' HCV genotype and history of prior treatment with interferon.

The primary outcome is sustained virologic response, expressed as the proportion of patients (%) who achieved an undetectable level of HCV RNA 12 weeks after the end of treatment (SVR12). SVR12 is reported for each of the patient groups listed above and in some cases also for subgroups of patients within these.

SVR12 rates in sofosbuvir regimens of the included studies ranged from 50% to 100%, depending upon the regimen, duration of therapy, and treatment history of the patients:

- HCV genotype 1, treatment naïve: SVR12 ranged from 52% to 93%.
- HCV genotype 2/3 combined: SVR12 ranged from 50% to 100% (in studies on mixed treatment naive and experienced, and treatment naive patients respectively).
- HCV genotype 2 subgroup: SVR12 ranged from 86% to 100% (in studies on treatment experienced and treatment naive patients respectively).
- HCV genotype 3 subgroup: SVR12 ranged from [redacted] to 100% (in studies on treatment experienced and treatment naive patients respectively).
- HCV genotypes 1/2/3, treatment naive and experienced, with HCV and HIV co-infection (a subgroup specified in the NICE scope): SVR ranged from 67% to 93%.

Only one RCT provided a direct head-to-head comparison of sofosbuvir against standard of care (peginterferon alfa + ribavirin) as specified in the NICE scope, for HCV genotype 2/3 treatment naive patients; SVR12 was found to be 67% following sofosbuvir + ribavirin for 12 weeks and also 67% following peginterferon alfa-2a + ribavirin for 24 weeks.

The NICE scope specifies that subgroup analysis of SVR12 rates according to patients' response to prior therapy should be considered. Three studies provided relevant subgroup analyses:

- interferon non-responders versus those with relapse or virologic breakthrough (one trial – found no differences in SVR12 between the subgroups);
- interferon-ineligible patients versus those classified as interferon-intolerant or interferon-unwilling (one trial - found no differences in SVR12 between the subgroups);
- interferon-intolerant patients versus interferon-non-responders and those with relapse or virologic breakthrough ([redacted]

- No clinical trial data are available for the efficacy of sofosbuvir in comparison to the protease inhibitors boceprevir and telaprevir in treating genotype 1 patients as specified in the NICE scope.
- No clinical trial data are available for treatment experienced patients with HCV genotype 1 infection; this is an unmet need group, without alternative non-interferon therapy options.
- Where SVR12 rates are available for specific genotypes (i.e. consistent with the licensed indications for sofosbuvir), these are mostly from subgroup analyses which in some cases have small sample sizes.
- Analyses of subgroups were not powered statistically to detect differences among subgroups.
- The economic model structure is modified from a structure used in previous HTAs for HCV and replaces 'mild', 'moderate', and 'severe' cirrhosis health states with 'non-cirrhotic' and 'cirrhotic'. As a consequence, SVRs are required for each of these health states but there is a paucity of data in the literature to fulfil the requirements of the model. The clinical efficacy data may therefore not be robust.
- Direct evidence of sofosbuvir versus comparators is lacking and in most cases efficacy data come from single arms of a variety of RCTs (or non-RCTs).
- The ERG was unable to check all efficacy and transition probability data used in the MS and some calculations were not sufficiently well presented to allow replication.
- The model is not well validated against external data. This is particularly the case with the comparison with boceprevir + peginterferon alfa-2b + ribavirin where the MS model outcomes do not agree with previously presented results for this treatment.

Summary of additional work undertaken by the ERG

- Validation work was undertaken to compare the results of the sofosbuvir model to previous HTA models.
- PSA was re-run for all indications and comparators considered in the base case as the ERG found a slight error in the settings of the model slider control used to set the probability of cost-effectiveness at the £20,000 and £30,000 WTP thresholds.
- The model was re-run to examine variation to the final ICERs caused by using alternative estimates of SVR for peginterferon-alfa + ribavirin in the HCV genotype 1 treatment naive interferon eligible population.

2.3 Critique of manufacturer's definition of decision problem

Population

The population described in the decision problem – adults with chronic hepatitis C – is appropriate for the NHS and matches the broad chronic hepatitis C population described in final scope issued by NICE and the licensed indication for sofosbuvir, which is for use in adults only.[7]

Intervention

The intervention, sofosbuvir (SOF), is indicated in combination with other medicinal products for the treatment of chronic hepatitis C in adults. Sofosbuvir can be administered together with ribavirin (RBV) (dual therapy) or together with RBV and peginterferon-alfa (triple therapy). Sofosbuvir is not licensed as a monotherapy for chronic hepatitis C.[7] Sofosbuvir triple therapy is permitted with either peginterferon alfa-2a (PEG2a) or peginterferon alfa-2b (PEG2b) (which are considered equally efficacious[8;9]). However, in clinical studies, sofosbuvir triple therapy has so far only been combined with PEG2a. In this report, unless stated otherwise, the abbreviations SOF, PEG2a and RBV refer to the following standard dosing regimens of these therapies as specified in the summary of product characteristics (SmPC) for sofosbuvir[7] and peginterferon alfa-2a:[10]

- SOF: oral tablet, 400 mg once daily with food.
- RBV (Copegus®): oral tablet, twice daily to give a total weight-based dose per day of 1000 mg (if < 75 kg) or 1200 mg (if ≥ 75 kg) (note that Rebetol® is used specifically with PEG2b and as such is only referred to in this report where regimens containing PEG2b are being discussed).
- PEG2a, subcutaneous injection, 180µg once per week.

Sofosbuvir, a first-in-class uridine nucleotide, was granted its marketing authorisation in January 2014. In line with the final scope and licensed indication,[7] the intervention described in the decision problem is sofosbuvir either as a dual therapy (SOF+RBV) or triple therapy (SOF+PEG+RBV). The MS accurately details in Table 6 (MS p. 36) that treatment length and the choice of combination therapy depends on a patient's HCV genotype and whether or not a patient is suitable for interferon treatment. For patients with HCV genotypes 1 and 3 to 6, the licensed indication is sofosbuvir triple therapy for 12 weeks. When sofosbuvir is used in triple therapy, the SmPC[7] states that the treatment duration can be extended beyond 12 weeks and up to 24 weeks, if a patient has a risk factor associated with a poorer response to interferon-based therapies, such as cirrhosis. For genotype 3, sofosbuvir dual therapy can also be used, for a treatment period 24 weeks. For genotype 2, the only licensed sofosbuvir treatment is

The MS makes a case for innovation based on the novel drug class of sofosbuvir (MS p. 16) and its efficacy, safety and tolerability (MS p. 48).

3 CLINICAL EFFECTIVENESS

3.1 Critique of manufacturer's approach to systematic review

3.1.1 Description of manufacturer's search strategy

The MS reports two separate searches for clinical effectiveness information. One search was for studies of sofosbuvir (Appendix 10.2 p. 35-36) and this informs the clinical effectiveness review. The second search was for relevant comparators (Appendix 10.4, p. 96-101) and informs a mixed treatment comparison (MTC). Apart from some minor inconsistencies, sufficient detail is given to enable the search methods for all searches (clinical, MTC, cost and HRQoL) to be reproduced.

The minimum list of databases set by NICE to be searched has been met in all instances.

In the MTC searches numerous terms were excluded from the search using the NOT operator in the search strategy. The ERG ran a search on Pubmed and confirmed that use of the NOT operator is unlikely to have caused relevant studies to be missed.

The ERG undertook searches to identify unpublished clinical trials. Four additional ongoing trials were identified (section 3.1.3).

On balance, although there are some inconsistencies, the searches reported in the MS are considered by the ERG to be fit for purpose and unlikely to have missed relevant studies.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection.

Inclusion and exclusion criteria are clearly stated in Table 8 (MS p. 53), and are consistent with the decision problem, except that any comparator is permitted. This is in contrast to the final scope (MS p. 51) which lists specific comparators. However, the MS has not included any comparators that are not in the final scope. The eligibility criteria capture all the licensed indications of sofosbuvir and the current and intended usage of sofosbuvir in the NHS (confirmed by two clinical experts). Trial phase is specified as a quality-related eligibility criterion, with phase 2 or 3 studies being considered eligible but phase 1 studies excluded. The manufacturer clarified that trial 'phase' was defined as reported by the trial authors (see NICE

in Table 1 according to which of the licensed regimens of sofosbuvir they inform, i.e. the specific combinations of HCV genotype and patients' treatment history (naive or experienced).

Table 1 Studies included in the MS grouped according to patients' HCV genotype and treatment history

Population	Trial name	Trial arms
HCV genotype 1, treatment naïve	QUANTUM (5-arm RCT, phase 2) + single cohort	1. SOF+RBV 12 weeks 2. SOF+RBV 24 weeks 3-5. *Arms excluded from MS and ERG report (drug outside scope)* 6. *Single cohort 'retreatment group' in MS but excluded from ERG report (patients had atypical treatment history on an experimental drug)*
	ATOMIC (3-arm RCT, phase 2) [a]	1. SOF+PEG+RBV 12 weeks 2. SOF+PEG+RBV 24 weeks 3. *Arm included in MS but excluded from ERG report (unlicensed SOF monotherapy)*
	SPARE (2-arm RCT, phase 2, and one non-randomised cohort) GT 1 only	1. SOF+RBV 24 weeks single cohort 2. SOF+RBV 24 weeks randomised arm 3. SOF+low-dose (600mg) RBV 24 weeks randomised arm *(technically unlicensed RBV dosing - arm included in MS and also in ERG report for supporting information, based on clinical expert advice)*
	NEUTRINO (single cohort)	1. SOF+PEG+RBV 12 weeks
HCV genotype 2/3 treatment naïve	FISSION (2-arm RCT, phase 3)	1. SOF+RBV 12 weeks 2. PEG+ 800mg RBV 24 weeks
	ELECTRON (4-arm RCT, phase 2, and 4 non-randomised cohorts)	1. Randomised arm: SOF+RBV 12 weeks 2-3. *Randomised arms mentioned narratively in MS but excluded from ERG report (unlicensed durations of PEG)* 4. Randomised arm: SOF+PEG+RBV 12 weeks 5-6. *Non-randomised cohorts mentioned narratively in MS but excluded from ERG report (unlicensed SOF regimens)* 7-8. *Non-randomised cohorts excluded from MS and ERG report (unlicensed SOF regimens)*
	PROTON (3-arm RCT and single cohort)	*1-3. Randomised arms of response-guided SOF therapy excluded from MS and ERG report (unlicensed SOF regimens)* 4. SOF+PEG+RBV 12 weeks
HCV genotype 2/3 treatment experienced	FUSION (2-arm RCT, phase 3)	1. SOF+RBV 12 weeks + matching placebo 4 weeks 2. SOF+RBV 16 weeks
	LONESTAR-2 (single cohort)	1. SOF+PEG+RBV 12 weeks
HCV genotype 2/3 treatment naive and experienced	POSITRON (2-arm RCT, phase 3)	1. SOF+RBV 12 weeks 2. Placebo 12 weeks
	VALENCE (initially 2-arm RCT, phase 3, subsequently modified to 3-	Initial randomised design: 1. SOF+RBV 12 weeks (HCVgenotype 2/3) 2. Placebo 12 weeks (HCV genotype 2/3)

The SOF+RBV 12-week regimen was also provided in a randomised arm of the ELECTRON trial and the reported SVR12 is 100% (95% CI 69-100%), although it should be noted that sample size was relatively small (N=10).

The SOF+PEG2a+RBV 12-week regimen was provided in one arm each from the ELECTRON trial and PROTON study, although these studies, especially ELECTRON, had relatively small sample sizes. The SVR12 rates were, respectively 100% (95% CI 72-100%; N=11) and 92% (95% CI 74-79%; N=25) (95% CIs for each trial not provided in the MS – obtained from the study publications[18;21]).

SVR24 rates in these three studies were identical to the SVR12 rates reported above except for the PEG2a+RBV arm of the FISSION trial, in which SVR24 was reported as 65% as compared to the SVR12 of 67%.

HCV genotype 2/3, combined treatment experienced and treatment naive

SVR12 rates for this indication are available from the POSITRON RCT and the VALENCE study (Table 9). It should be noted that VALENCE started out as an RCT combining HCV genotype 2 and 3 patients but randomisation was subsequently broken to create three cohorts, to enable HCV genotype 3 patients to be treated for a longer duration (i.e. 24 weeks). These studies compared the SOF+RBV 12-week regimen against either an inactive placebo (POSITRON) or against SOF+RBV 24-week therapy (VALENCE). The POSITRON RCT reports outcomes for a mixed HCV genotype population containing roughly equal numbers of patients with genotype 2 (48-53% per arm) and genotype 3 (47-52% per arm); in the VALENCE study SVR12 data are reported separately for patients with HCV genotypes 2 and 3.

The SOF+RBV 12-week regimen resulted in SVR12 rates of 78% (95% CI 72-83%; N=207) in mixed genotype 2/3 patients (POSITRON), [redacted]) genotype 2 patients (VALENCE) and [redacted]) in genotype 3 patients (VALENCE). It should be noted that the sample size for genotype 3 was relatively small and the 12-week regimen is not licensed for this genotype.

The SOF+RBV 24-week regimen given to genotype 3 patients in the VALENCE trial resulted in an SVR rate of [redacted]).

3.4 Summary

Included studies

The manufacturer's systematic review of clinical effectiveness is of a reasonable quality and contained 13 studies examining the efficacy of sofosbuvir in treating chronic hepatitis C that had been used to inform the licensing recommendations. Seven studies compared different treatment regimens of sofosbuvir combined with RBV or PEG2a+RBV and/or different treatment durations, and four studies had single arms. Most of these studies do not directly address NICE's final scope, but do provide data on SVR rates for patients treated with sofosbuvir, across different genotypes and treatment combinations, and helped to determine treatment durations for the marketing authorisation.

Only one study directly meets NICE's final scope: FISSION, which compared SOF+RBV for 12 weeks against current standard of care (PEG2a+RBV for 24 weeks in treatment naïve genotype 2 and 3 patients). Additionally, one study (POSITRON), on a mixed population of HCV genotype 2/3 treatment experienced and treatment naive patients, that compared sofosbuvir with a true (i.e. inactive) placebo would meet the scope if the placebo arm is assumed to approximate best supportive care (i.e. no treatment).

The head-to-head trial showed that SOF+RBV for 12 weeks had similar efficacy (was statistically non-inferior) to PEG2a+RBV for 24 weeks (SVR12 67% in both groups); in subgroup analyses SOF+RBV for 12 weeks was more effective than PEG2a+RBV for 24 weeks in treating genotype 2 but not genotype 3 patients. (Note SOF+RBV is licensed for treatment in genotype 3 patients over 24 rather than 12 weeks.)

SVR12 frequencies in sofosbuvir regimens of the included studies ranged from 50% to 100%, depending upon the sofosbuvir regimen, duration of therapy, and treatment history of the patients.

Subgroup analyses

One study investigated sofosbuvir in chronic hepatitis C patients co-infected with HIV, finding that SVR12 ranged from 67% in HCV genotype 3 treatment naive patients receiving 12 weeks of SOF+RBV to 93% in combined HCV genotype 2/3 treatment experienced patients receiving 24 weeks of SOF+RBV. Limitations are that the trial is ongoing, did not include HCV mono-

The ERG notes an error in the SVRs reported for the GT2 TE IFN eligible group as reported in the SmPC. The SVR reported for the FUSION RCT appears to be the 16 week SVR. Using the 12 week SVR would lead to the non-cirrhotic SVR being 90.3% (from 91.5%) and the cirrhotic SVR being 72% (from 82.4%). This is further complicated by the MS reporting the non-cirrhotic SVR from the FUSION trial differently than the SmPC (MS Table 26, p110 reports 25/26, SmPC reports 26/29) and it is therefore unclear which is the correct estimate. (The ERG found that these alternative SVRs do not substantively change model outcomes.) The MS reports the use of data from Shoeb and colleagues[48] for PEG2a in GT2 TE IFN eligible and GT3 TE IFN eligible. However the ERG has been unable to identify these data in the Shoeb and colleagues publication and has been unable to source any alternative data.

For sofosbuvir the MS applies data from the relevant clinical effectiveness trials, as reported in section 3. In some cases estimates are combined from more than one trial using a simple average (e.g GT2 TN IFN eligible combines estimates from VALENCE and FISSION) and for some genotype subgroups the estimates were taken from non-RCTs (e.g GT1 TN IFN eligible from NEUTRINO). In the case of the genotype 3, treatment naive IFN eligible group two non-RCT estimates were combined using a simple average. As noted above, in most cases the estimates were from single arms and/or subgroups only.

For the comparator evidence the MS applies data from various clinical effectiveness studies. Overall the choice of studies appears to be reasonable given the need for the data to report non-cirrhotic and cirrhotic patients separately. In the GT1 TN IFN eligible group the source of data for the PEGIFN-2a+RBV treatment was taken from McHutchinson and colleagues.[8] The estimates used by the manufacturer for the non-cirrhotic and cirrhotic groups taken from McHutchinson and colleagues[8] relate to METAVIR scores F0-2 and F3-4 respectively (bridging fibrosis/cirrhosis). In the appendix describing the MTC a variety of studies in this patient subgroup were reported, of which McHutchinson and colleagues is the largest and therefore likely to be the most reliable source of data (although the MS does not state that this was why McHutchinson and colleagues' study was chosen). However, the manufacturer's MTC searches identified two other large RCTs; Hadziyannis and colleagues[50] and Roberts and colleagues.[51] The ERG has checked these trials for the SVR in these subgroups and rates appear to be different from those of McHutchinson and colleagues.[8] To be consistent with the MS, the ERG has used METAVIR F0-2 for non-cirrhosis and F3-4 for cirrhosis in this genotype subgroup. In the Hadziyannis and colleagues[50] 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[51] trial the SVRs were 55% and 24% for the two groups respectively. However, in the Roberts and colleagues[51] trial SVRs for each METAVIR group were presented separately and therefore a calculation of the SVRs in METAVIR F0-3 and F4 can be extracted. These rates were 51% and 6% respectively. Alternative SVR estimates for PEG2a+RBV in a genotype 1 treatment naive population are examined by the ERG in additional analyses given in section 4.3.

	(£)		costs (£)	QALYs	baseline (QALYs)	(QALYs)
PEG2a+RBV (48 weeks)	£23,192	14.045	-	-	-	-
Boceprevir+PEG2b+RBV	£39,221	14.419	£16,029	0.374	£42,858	Extended dominance
Telaprevir+PEG2a+RBV	£38,835	14.645	£15,643	0.600	£26,072	Extended dominance
SOF+PEG2a+RBV (12 weeks)	£44,123	15.092	£20,931	1.047	£19,991	£19,991

Table 31. Cost-effectiveness results, HCV genotype 1 treatment naive, interferon eligible using PEG2a+RBV SVR data from Roberts and colleagues[51]

Technologies	Total costs (£)	Total QALYs	Incre-mental costs (£)	Incre-mental QALYs	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
PEG2a+RBV (48 wks)	£23,862	13.979	-	-	-	-
Boceprevir+PEG2b+RBV	£39,221	14.419	£15,359	0.440	£34,928	Extended dominance
Telaprevir+PEG2a+RBV	£38,835	14.645	£14,973	0.666	£22,491	Extended dominance
SOF+PEG2a+RBV (12 wks)	£44,123	15.092	£20,261	1.113	£18,209	£18,209

Table 32. Cost-effectiveness results, HCV genotype 1 treatment naive, interferon eligible using PEG2a+RBV SVR data from Hadziyannis and colleagues[50]

Technologies	Total costs (£)	Total QALYs	Incre-mental costs (£)	Incre-mental QALYs	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
PEG2a+RBV (48 wks)	£22,802	14.116	-	-	-	-
Boceprevir+PEG2b+RBV	£39,221	14.419	£16,419	0.303	£54,207	Extended dominance
Telaprevir+PEG2a+RBV	£38,835	14.645	£16,033	0.529	£30,314	Extended dominance
SOF+PEG2a+RBV (12 wks)	£44,123	15.092	£21,321	0.976	£21,848	£21,848

Table 30 shows that, with the MTC SVR estimate for PEG2a+RBV, the ICER for SOF+PEG2a+RBV compared to PEG2a+RBV rises to £19,991 per QALY compared to the base case ICER of £14,930 per QALY. Thus SOF+PEG2a+RBV remains cost-effective compared to PEG2a+RBV at a willingness to pay threshold of £20,000 per QALY, but marginally so.

The Roberts and colleagues[51] PEG2a+RBV SVR estimates are associated with an ICER of £18,209 per QALY for SOF+PEG2a+RBV compared to PEG2a+RBV, again an increase compared to the base case (Table 31). Using F0-3 data for non-cirrhosis and F4 data for cirrhosis (see discussion in Section 4.2.3, p. 71) would have the effect of slightly reducing the

ICER. With the Hadziyannis and colleagues PEG2a+RBV SVR estimates[50] the ICER for SOF+PEG2a+RBV compared to PEG2a+RBV becomes £21,848 (Table 32), i.e., within this indication SOF+PEG-IFN-2a+RBV is no longer cost-effective compared to PEG2a+RBV at a willingness to pay threshold of £20,000 per QALY.

The ERG notes that the same caution is required with interpreting these results as required when interpreting the MS results because the estimates of SVRs are not based on controlled comparator studies or linked through any robust statistical analysis.

b) Total cost and QALY data from boceprevir STA: HCV genotype 1, treatment naive, interferon eligible

The ERG notes in section 4.2.8 that the total cost and total QALY outcomes for boceprevir obtained from the economic model are relatively different from the total cost and QALY figures given in the boceprevir STA base case.[1] Total discounted costs for the boceprevir arm are approximately 20% higher in the sofosbuvir submission than in the boceprevir STA. One possible reason for some of these higher costs is that the sofosbuvir model considers boceprevir in combination with PEG2b rather than in combination with PEG2a.

The ERG has re-run the model using PEG2a cost data on the boceprevir arm and assuming the same SVRs as the base case. This gives the results shown in Table 33. Boceprevir+PEG2a+RBV is subject to extended dominance by SOF+PEG2a+RBV as it has a higher ICER compared to the baseline treatment PEG2a+RBV. This compares to the base case where boceprevir is dominated by telaprevir as it is more expensive than telaprevir, and associated with fewer QALYs.

Table 33. Cost-effectiveness results, HCV genotype 1 treatment naive interferon eligible using total cost and QALY data from boceprevir STA[1]

Technologies	Total costs (£)	Total QALYs	Incre-mental costs (£)	Incre-mental QALYs	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
PEG2a+RBV (48 wks)	£24,994	13.8	-	-	-	-
Boceprevir+PEG2a+RBV	£38,195	14.4	£13,201	0.619	£21,313	Extended dominated
Telaprevir+PEG2a+RBV	£38,835	14.6	£13,841	0.845	£16,380	Extended dominated
SOF+PEG2a+RBV (12 wks)	£44,123	15.1	£19,129	1.292	£14,806	£14,806

per week, giving 119mcg per week at an assumed body weight of 79kg.[43] The cost of PEG2b is £159.51 for 120mcg.[69]

The ERG notes that the impact of these alternative costs on the final ICER will vary by indication depending upon the assumed peginterferon treatment duration, and whether peginterferon is also given in combination with sofosbuvir and/or the comparator. The revised ICERs given in Table 37 are all within £1,000 per QALY of the original base case ICERs, demonstrating no substantive change to model outcomes.

4.4 Summary of uncertainties and issues

The economic model structure is a modified version of a model structure used in previous HTA reports to NICE. The model replaces the 'mild', 'moderate' and 'severe' cirrhosis starting health states of previous models with two health states, non-cirrhotic and cirrhotic. Consequently the model requires estimates of proportion achieving SVR for each of these health states but in some genotype subgroups there are limited good quality data available and therefore the clinical efficacy data used in the model may not be robust.

Some of the model SVR estimates come from single arms of RCTs which were not linked through any statistical methods to one another while others are drawn from non-RCTs and from small subgroup analyses. In instances where multiple efficacy estimates are available for the same treatment and indication (i.e. PEG2a in GT1 treatment naïve interferon eligible patients) the model uses an estimate drawn from one source and does not examine alternative efficacy estimates in sensitivity analysis.

In several cases the ERG was unable to find the efficacy figures or transition probabilities used in the MS in the publications cited in the MS. Other calculations are not presented in sufficient detail in the MS to allow replication.

The model is not well validated against external data. The sofosbuvir economic model results show that boceprevir+PEG2b+RBV is not cost-effective compared to PEG+RBV at a willingness to pay threshold of £20,000 per QALY. This does not agree with findings presented in the boceprevir STA.

5 Innovation

The manufacturer makes the case that sofosbuvir offers a new treatment option across all chronic hepatitis C genotypes and offers a step-change in treatment efficacy, safety and