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Boceprevir for the treatment of genotype 1 chronic hepatitis C

Produced by Southampton Health Technology Assessments Centre

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Rider on responsibility for the report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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D Mendes (Research Fellow) critically appraised the health economic systematic review and the economic evaluation and drafted the report; K White (Research Fellow) critically appraised the clinical effectiveness systematic review and drafted the report; K Cooper (Senior Research Fellow) critically appraised the health economic systematic review and the economic evaluation and drafted the report; J Bryant (Principal Research Fellow) critically appraised the clinical effectiveness systematic review, drafted the report and project managed the review.

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LIST OF ABBREVIATIONS

AE	Adverse event(s)
BOC	Boceprevir
CEA	Cost effectiveness analysis
CHMP	Committee for Medicinal Products for Human Use of the European Medicines Agency
CRD	Centre for Reviews and Dissemination
DC	Decompensated cirrhosis
DSA	Deterministic Sensitivity Analysis
EMA	European Medicines Agency
EPO	Erythropoietin
ERG	Evidence Review Group
FAS	Full Analysis Set
HCC	Hepatocellular carcinoma
HCHS	Hospital and Community Health Services
HCV	Hepatitis C Virus
HRQoL	Health Related Quality of Life
ICER	Incremental Cost Effectiveness Ratio
ITT	Intention to Treat
ICTRP	WHO International Clinical Trials Registry Platform
LT	Liver transplant
LY	Life years
mITT	Modified Intent to Treat
MS	Manufacturer's Submission
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NR	Null responder
OR	Odds Ratio
PEG	Pegylated interferon
PR	Pegylated interferon and ribavirin
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
RGT	Response Guided Therapy
RR	Relative Risk
SOC	Short course of treatment
SPC	Summary of Product Characteristics
SVR	Sustained Virologic Response
TE	Treatment naïve
TN	Treatment experienced
TW	Treatment week
WTP	Willingness to pay

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 Clinical Excellence (NICE). This was to consider boceprevir in combination with peginterferon alfa and ribavirin for the treatment of genotype 1 chronic hepatitis C.

Summary of submitted clinical effectiveness evidence

The clinical effectiveness evidence in the MS comes from:

- Three Phase III randomised controlled trials: one trial (SPRINT-2) compares boceprevir (BOC) in combination with PEG2b/R to PEG2b/R alone in treatment naïve patients; two trials were in treatment experienced patients, one (RESPOND-2) comparing BOC in combination with PEG2b/R to PEG2b/R alone, and the other (P05685) comparing BOC plus PEG2a/R to PEG2a/R alone.
- Two additional Phase II studies were used to support the Phase III evidence and to assess the safety of boceprevir.

The primary outcome is sustained virologic response (SVR). In previously untreated patients, the percentage achieving SVR increased from 38% with PEG2b/R alone to 63% in the boceprevir response guided therapy group (BOC/PR RGT) and 66% in the boceprevir full treatment group (BOC/PR48), ($p<0.001$). In previously treated patients for whom treatment with PEG/R alone did not result in SVR, the percentage achieving SVR increased from 21% with PEG2b/R alone to 59% with BOC/PR RGT and 66% for BOC/PR48 ($p<0.001$); and from 21% with PEG2a/R alone to 64% with BOC/PEG2a/R ($p<0.001$).

Other results included achievement of SVR by response to treatment at weeks 4 and 8, and end of treatment response and relapse rates. In treatment naïve patients, both those interferon-responsive and poorly responsive at 4 weeks achieved higher SVR rates with boceprevir than control patients; no significant differences were seen in SVR by treatment week 8 response. Similar results were shown in treatment experienced patients for SVR at treatment week 4 response, except for those poorly responsive in the study of BOC/PEG2a/R; higher SVR rates were also seen in patients with detectable HCV-RNA at treatment week 8. End of treatment response rates were statistically significantly increased with boceprevir in treatment naïve

patients and treatment experienced patients. Relapse rates were statistically significantly reduced in both treatment naïve and treatment experienced patients with boceprevir, except for BOC/PR RGT in treatment experienced patients.

Adverse events that occurred in a much higher proportion of patients who received boceprevir than patients who received standard of care were anaemia, dysgeusia and neutropenia.

Summary of submitted cost effectiveness evidence

The MS includes:

i) a review of published economic evaluations of pharmacological treatments for chronic HCV genotype 1 infection.

ii) an economic evaluation undertaken for the NICE STA process. The cost effectiveness of boceprevir in combination with pegylated interferon alpha and ribavirin (BOC/PEG/R) is compared with the combination PEG/R for the treatment of chronic HCV genotype 1 infection in adult patients with compensated liver disease, either treatment naïve or treatment experienced for whom previous therapy has failed.

A systematic search of the literature was conducted by the manufacturer to identify economic evaluations of pharmacological treatment of chronic HCV genotype 1 infection. Forty three studies were included for full review, i.e. 19 cost-effectiveness studies, 3 cost studies, and 21 HRQoL studies. The review did not contain any studies that compared boceprevir to its alternatives.

The economic evaluation uses a Markov model to estimate the cost-effectiveness of BOC/PEG/R compared with PEG/R in adult chronic HCV genotype 1 patients with compensated liver disease, either treatment naïve or treatment experienced. The model adopted a lifetime horizon to capture lifetime costs and health outcomes, with a yearly cycle length after the initial 72 weeks, during which treatment and follow-up are modelled using a weekly cycle. In the economic model, patients are distributed across different degrees of fibrosis (F0-F4) and then may progress to more severe stages of liver disease. After successful treatment, patients achieve SVR, which is considered a cure for F0-F3 (non-cirrhotic) patients.

The model structure and parameter inputs for resource use, health related quality of life and transition between health states are similar to that developed by SHTAC for the previous NICE appraisal for pegylated interferon and ribavirin.

Results are presented for lifetime costs and QALYs and incremental cost-effectiveness ratios (ICERs) for a cohort representing the total UK HCV population. For the base case, an ICER of £11,601 per QALY gained is reported for treatment naïve patients and £2,744 per QALY gained for treatment experienced patients. Results are also presented for the subgroups F0-3, F4, and null responders (NR) and for a cohort with a shortened course of treatment.

The manufacturer deterministic sensitivity analysis showed that the base case ICER was most sensitive to the efficacy estimates (probability of achieving SVR), health state utilities, costs and the discount rates. The probabilistic sensitivity analysis estimates there is a 92.5% and 100% probability of BOC/PEG/R being cost-effective, relative to PEG/R alone, at a threshold willingness to pay of £20,000 per QALY gained, for naïve and treatment-experienced patients, respectively. The MS states that the use of boceprevir was found to be a cost-effective use of NHS resources.

Commentary on the robustness of submitted evidence

Strengths

- The MS contains systematic searches for the clinical and cost effectiveness studies of boceprevir. It appears unlikely that these have missed any studies that would have met the inclusion criteria.
- The systematic review meets the Centre for Reviews and Dissemination (CRD) criteria for methodological quality.
- The economic model presented in the MS used an appropriate approach for the disease area.
- The economic model used a similar structure and parameter inputs to that used in previous economic models developed for NICE.

Weaknesses and Areas of uncertainty

- The MS does not report details of the process used to conduct the systematic review although meeting criteria for methodological quality.

- Subgroup analyses for patients with and without cirrhosis should be regarded as speculative as the clinical trials included few patients with cirrhosis.
- There are differences between the SPC for boceprevir and the treatment regimens used in the clinical trials. Retrospective analyses of subgroups in line with the UK licence based on data from the clinical trials should be viewed with caution.
- Null responders were not represented in the clinical trials of treatment experienced patients. Data for this group has been estimated and therefore these results should also be viewed with caution.
- Higher rates of anaemia are reported in patients receiving boceprevir compared with those receiving current standard of care. As erythropoietin is not used routinely in England to manage anaemia, discontinuation rates may be higher in clinical practice than those seen in clinical trials.
- It should be noted that the MS does not report confidence intervals (CIs) and p-values in some analyses, making interpretation of findings difficult as it is not possible to tell whether differences between groups are statistically significant. However, clarification was supplied from the manufacturer on request.
- It is unlikely that the trial population reflects the UK population treated in secondary care in terms of its distribution by level of fibrosis. The population treated in secondary care in the UK has a larger proportion of cirrhotic patients (F4) than the trials.
- The characteristics of the patient groups considered in the marketing authorisation (F0-3 and F4) differ from the trials' participant groups (F0-2 and F3-4) in terms of their initial fibrosis level. The cirrhotic group is not adequately powered to provide effectiveness estimates for this subgroup.
- Different definitions of early responders and stopping rules for naïve and experienced patients were used in the clinical trials SPRINT-2 and RESPOND-2, and these differ from the ones indicated in the SPC.
- The methods for deriving efficacy estimates are not clearly described in the MS. The probabilities of achieving SVR for the BOC/PEG/R arm by initial level of fibrosis seem to have been derived from the boceprevir clinical trials, whereas the probabilities of achieving SVR for the PEG/R arm seems to have been derived from a meta-analysis performed by the manufacturer.
- The transition probabilities used for progression between fibrosis levels seemed significantly higher than those used in previous models.

Summary of additional work undertaken by the ERG

The ERG corrected the model for the errors identified during the critical appraisal of the MS. These had a minimal impact on the cost effectiveness results.

The ERG undertook additional analyses varying the starting fibrosis distribution in the population, the SVR treatment effect, the cost of boceprevir and the transition probabilities of progressing between fibrosis health states. Of these analyses, changes to the transition probabilities had the most effect on the model results. When the MS model was run with transition probabilities similar to those used in the previous SHTAC model, the ICER increased from £11,601 to £26,645 and from £2,744 to £6,902 per QALY gained for the treatment-naïve and treatment-experienced groups, respectively.

1 INTRODUCTION TO ERG REPORT

This report is a critique of the manufacturer's submission (MS) to NICE from Merck Sharp and Dohme on the clinical effectiveness and cost effectiveness of Boceprevir (BOC) for the treatment of chronic Hepatitis C (genotype 1). It identifies the strengths and weakness of the MS. A clinical expert was consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the MS was requested from the manufacturer by the ERG via NICE on 18 August 2011. A response from the manufacturer via NICE was received by the ERG on 8 September 2011 and this can be seen in the NICE evaluation report for this appraisal.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The MS provides a clear and accurate overview of chronic Hepatitis C.

2.2 Critique of manufacturer's overview of current service provision

The MS provides an accurate overview of current service provision.

2.3 Critique of manufacturer's definition of decision problem

Population

The population described in the decision problem is appropriate for the NHS.

Intervention

The description of the intervention in the decision problem is appropriate for the NHS. The product was granted marketing authorisation in July 2011. Standard dose of boceprevir, which must be administered in combination with peginterferon alfa and ribavirin (PEG/R), is 800 mg orally three times daily with food.

Comparators

The main comparator in the MS decision problem is combination therapy PEG/R which is the current standard of care for individuals with genotype 1 hepatitis C virus (HCV) in the UK.

Outcomes

The outcomes included in the MS are appropriate and clinically meaningful to patients.

Economic analysis

The economic evaluation in the MS decision problem appears to be appropriate, being a cost utility analysis from the NHS and Personal Social Services (PSS) perspective.

Other relevant factors

The MS states that subgroups are not applicable. However, the NICE scope states that 'if evidence allows, subgroups based on IL28b should be considered separately and the previously treated population should be divided into relapsed, partial and non-responders'. Prespecified subgroups that are reported in the MS include black and non-black patients, and patients with and without cirrhosis.

The MS states special considerations, including issues relating to equity or equality are not applicable and this is in line with the decision problem in the NICE scope.

3 CLINICAL EFFECTIVENESS

3.1 Critique of manufacturer's approach to systematic review

3.1.1 Description of manufacturer's search strategy

The manufacturer's literature searches were checked by an information scientist. Overall, the search strategies were considered sound, containing just a few minor inconsistencies. ERG adaptation of the strategies produced no further useful results. The databases and hosts used, dates of execution, and search strategies were all clearly recorded in the MS. Acceptable search filters were employed. Searches were re-run by the ERG on the Cochrane database producing identical results. Due to differing host systems between those employed in the MS and by the ERG, searches on Medline and Embase were not directly comparable with variation in search syntax giving slight differences in return of numbers. It is noted that all searches were limited to English Language. Searches re-run by the ERG on NHSEED were comparable. The

ERG searched the following trials registries: controlled-trials.com, UKCRN Portfolio and ICTRP (WHO International Clinical Trials Registry Platform). The FDA and EMEA websites were also checked for further information. The results were checked by an ERG reviewer. No additional trials identified were relevant to the decision problem.

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

The MS clearly states the inclusion and exclusion criteria (MS p.35) and these reflect the final scope issued by NICE and the licensed indication. Quality of the RCTs was not stated as an inclusion or exclusion criterion. Setting was not stated in the final scope and was not used as an inclusion criterion.

A flow diagram showing the number of studies from the database searches that were included and excluded at each stage of the review is presented (MS p. 36). The diagram does not include publications identified through manual searches of conference proceedings from two conferences; numbers included and excluded from these searches are detailed separately on p. 36 of the MS and sufficient information is given about these. Reasons for excluding studies at the full publication review stage are provided, along with the number excluded for each reason.

Studies had to be randomised controlled trials to meet the inclusion criteria. The manufacturer does not explicitly consider issues of bias or study quality at the stages of study searching, screening and selection. A critical appraisal of the included RCTs, however, is presented in Section 5.4 of the MS and Appendix 3.

3.1.3 Identified studies

The MS identified five RCTs (four from the database searches and one from the manual searches), shown in Table 1. All of the studies were sponsored by the manufacturer (four were sponsored by Schering-Plough which is now a part of Merck and one was sponsored by Merck). Two RCTs were of treatment naïve patients (one was a phase II[1] and one was a phase III trial[2]). Three RCTs were of treatment experienced patients (one was a phase II trial[3] and two were phase III trials[4;5]). All the identified RCTs meet the inclusion criteria for the review and the MS appears to have included all relevant RCTs. The ERG searches did not identify any further relevant studies.

Table 1: List of identified studies

Trial Name	Phase	Intervention	Comparator
Treatment naïve patients			
SPRINT-2[2]	III	BOC plus PEG2b/R as: • BOC/PR RGT* • BOC/PR48	PEG2b/R (PR48) (plus placebo)
SPRINT-1[1]	*II*	*BOC plus PEG2b/R*	*PEG2b/R*
Treatment experienced patients			
RESPOND-2[4]	III	BOC plus PEG2b/R as: • BOC/PR RGT* • BOC/PR48	PEG2b/R (PR48) (plus placebo)
P05685[5]	III	BOC plus PEG2a/R	PEG2a/R
RESPOND-1[3]	*II*	*BOC plus PEG2b with or without ribavirin*	*PEG2b/R*

*RGT response guided therapy

The RESPOND-1[3] phase II study was excluded post-hoc from further discussion in the review of clinical effectiveness. The manufacturer is transparent about the reasons for this and they are detailed on p. 39 of the MS. Four of the treatment arms in the SPRINT-1 trial[1] were also excluded from the review of clinical effectiveness, and the manufacturer states the reason for this too (the arms did not include a lead-in period). The MS presents results from the three remaining arms in the SPRINT-1[1] phase II trial "for interest" (MS p. 40), but as this limited reporting of outcomes for particular groups breaks randomisation, we do not discuss this trial further in the ERG report and only focus on the findings of the three phase III trials. The MS does not include any non-randomised studies.

The five RCTs identified in the MS are briefly summarised in Table B2 on MS p. 38, with more detailed information about the trial designs, interventions and populations tabulated on MS p. 44 to 48, in addition to the primary and secondary outcomes measured. Other features of the study design of the phase III trials are described on MS p. 41 to 43. The arms of each trial and intervention received are shown graphically in Figures B2 to B5 (MS p. 49 and 50). More detail about the primary and secondary outcomes is given in a table on MS p. 58 to 60. Patient numbers, including the number screened and randomised, are shown in a flow chart for each trial (MS p. 68 to 71). Statistical analysis information is tabulated (MS p. 62 to 66), including details of the power/sample size calculations and the full analysis set (FAS) and modified intent to treat (mITT) analyses.

Electronic copies of the RCT publications were provided to the ERG for three studies (Bacon et al., 2011[4]; Kwo et al., 2010[1]; Poordad et al., 2011[2]) and electronic conference abstracts were provided for two studies (Flamm et al., 2011[5]; Schiff et al., 2008[3]). A poster was also provided for trial P05685 (Flamm et al., 2011[5]). The MS also draws on data contained in the clinical study reports for the RCTs, but these reports were not provided.

In the RCTs, the only difference between groups at baseline highlighted in the MS is that patients in the BOC/PR RGT group in the RESPOND-2[4] trial had a higher viral load at baseline than patients in the PR48 group. This difference was statistically significant (p=0.04) (MS p. 53 and Bacon et al., 2011[4]). Significance values are not provided in the MS or the original papers, however, for any other comparison of patient baseline characteristics in neither this study nor the other RCTs, so it is not possible to determine whether the groups differed in any other statistically significant way.

The phase III trials appear comparable in terms of most of the patient characteristics reported. A slightly higher proportion of White patients were randomised in RESPOND-2[4] and P05685[5] than in SPRINT-2.[2] However, the proportion of black patients randomised did not differ greatly between studies – around 11% to 15% of patients were black in each arm of each study, except for the BOC/PEG2a/R group in P05685[5] (9% of whom were black). Proportionally more patients in the treatment experienced trials had a Metavir fibrosis score of 3 and 4 and had cirrhosis than patients in the treatment naive trials.

The MS lists two ongoing studies (p. 15 and 16). One (PROVIDE, trial P05514) is a clinical study of the effects of treatment with triple therapy among patients who did not achieve SVR with PEG/R in the boceprevir trials. Comparators for this study are not described in the MS, but an ERG search of a clinical trials register clarified that this is a single-arm trial. The other study examines the treatment of anaemia with erythropoietin in HCV patients. The MS does not provide a reference to this study. It also does not specify whether the population is patients with genotype 1 HCV or another genotype. An ERG search identified this study as possibly trial P06086 (a phase III trial which is sponsored by Schering-Plough) and clarified that to be eligible for this trial, patients must have genotype 1 HCV. The ERG did not find any other ongoing relevant trials.

3.1.4 Description and critique of the approach to validity assessment

The MS provides a quality assessment of the identified RCTs in Appendix 3 (MS p. 305 to 309) and a summary of the quality assessment for each RCT is tabulated on MS p.73. The manufacturer's quality assessment follows the NICE criteria and is appropriate. Table 2 shows the assessment of study quality for each RCT by the manufacturer and ERG. As this table shows, the ERG agrees partly with the MS assessment of study quality.

Table 2: **Manufacturer and ERG assessment of trial quality**

		SPRINT-2 (P05216)	RESPOND-2 (P05101)	P05685
1. Was randomisation carried out appropriately?	MS:	Yes	Yes	Yes
	ERG:	Yes	Yes	Unclear
Comment:				
2. Was concealment of treatment allocation adequate?	MS:	Yes	Yes	Yes
	ERG:	Yes	Yes	Unclear
Comment:				
3. Were groups similar at outset in terms of prognostic factors?	MS:	Yes	Yes	Yes
	ERG:	Unclear	Unclear	Unclear
Comment: P-values were not provided in any of the RCTs to show whether any differences in baseline characteristics between groups were statistically significant, except for baseline high viral load in RESPOND-2 (which was significant).				
4. Were care providers, participants and outcome assessors blind to treatment allocation?	MS:	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes
Comment:				
5. Were there any unexpected imbalances in drop-outs between groups?	MS:	No	No	No
	ERG:	Unclear	Unclear	Unclear
Comment: There is an imbalance in treatment discontinuation, reasons for discontinuation and loss to follow-up between some groups in the trials. FAS analyses were conducted that adjust for this.				
6. Is there any evidence that authors measured more outcomes than reported?	MS:	No	No	No
	ERG:	No	No	No
Comment:				
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	MS:	Yes	Yes	Yes
	ERG:	Yes	Yes	Unclear
Comment: All the trials included FAS analyses rather than full ITT analyses, but this is unlikely to have impacted the results (see comment in Section 3.1.5 in this report). P05685: FAS analyses were performed, but there is no information in the MS or papers about how data were imputed for patients missing data during treatment (but this is stated for the follow-up period).				

3.1.5 Description and critique of manufacturer's outcome selection

The primary outcome, which is defined as achievement of SVR among patients who received at least one dose of any study medication, matches the decision problem. Secondary outcomes appropriate to the decision problem are end of treatment response rates and relapse rates. The MS also describes three subgroup analyses/comparisons as secondary outcomes:

- Achievement of SVR by response to treatment at weeks 4 and 8.
- Achievement of SVR among patients with and without cirrhosis.
- Comparison of SVR rates between boceprevir arms and boceprevir response guided therapy (RGT) arms.

Adverse events (AE) are reported in the AE section (MS p. 98 to 113). Mortality is specified as an outcome in the final scope, and this is included in the AE section. Degree of virological response and health-related quality of life are also specified as outcomes in the final scope, but these are not measured in the original papers and are not reported in the MS.

The MS does not report outcomes for previous non-responders and relapsers to peginterferon alfa and ribavirin, even though this is stated to be of interest in the final scope and is reported in the original papers of the trials of treatment experienced patients (REPOND-2[4] and P05685[5]).

3.1.6 Description and critique of the manufacturer's approach to trial statistics

In all the phase III trials, two-sided Cochran-Mantel-Haenszel chi-square tests were used to compare groups in the primary and secondary outcome analyses. Outcomes for each of the boceprevir treatment arms were compared with those of the control arm in each trial. Comparisons of outcomes between different boceprevir treatment arms were not conducted. Multivariate logistic regression analyses were also conducted in the SPRINT-2[2] and RESPOND-2[4] trials to examine the baseline characteristic and treatment group predictors of SVR.

Results for all relevant outcomes are reported, but ORs, Absolute Difference, 95% confidence intervals and p-values are missing for a number of the outcomes (in some cases this information is available in the original papers). Response rates, relapse rates and achievement of SVR according to subgroup are presented as n and %. The N included in the analysis is provided for all outcomes, but some of the subgroup Ns in Tables B12, B13 and B17 do not add up to the

total N for the analysis (clarification was requested from the manufacturer). Interim data are not presented.

Intention-to-treat (ITT) analyses of all patients randomised were not carried out in any of the studies. Instead, full analysis set (FAS) analyses were conducted that included randomised patients who had received at least one dose of any study drug. The discrepancy in the number of patients randomised and the number included in the FAS analyses in each study is very small, and so this approach is unlikely to have impacted the results.

FAS results are presented for the primary outcome, response rates and the subgroup analysis of patients with or without cirrhosis. The MS states that the analyses of SVR achievement by response at weeks 4 and 8, and the relapse rate analyses are also FAS analyses, but the original papers state that these analyses exclude patients missing relevant data and the Ns in the MS suggest this too. The MS provides discussion and justification of clinically important differences.

3.1.7 Description and critique of the manufacturer's approach to the evidence synthesis

The tabulated data in the clinical effectiveness review reflect the data in the trials except for a few minor incorrect values, but these do not change the interpretation of the data. Numerous data in Table B25 in the AE section (MS p. 106 and 107) differ to the poster for trial P05685[5], but this also makes little difference to the interpretation. The narrative review reflects the data in the trials, with a few exceptions:

- The analysis of the proportion of patients who relapsed in SPRINT-2[2] is described as a FAS analysis (MS p. 83), but the paper states that these analyses were based only on patients with data available at follow-up.
- MS p. 86 states that in RESPOND-2[4] the proportion of patients with cirrhosis "achieving SVR was higher in the boceprevir-containing arms compared to PEG2b/R alone", but the confidence intervals presented in the paper suggest that there is no difference in the likelihood of achieving SVR between these groups, and the groups Ns are small.
- MS p.86 also states that a higher proportion of patients with cirrhosis in the PR48 arm in SPRINT-2[2] achieved SVR than in the boceprevir arms; however, the confidence intervals suggest there is no difference in the likelihood of achieving SVR between these groups, and the group Ns are small.

An overall problem with the narrative review is that much of the interpretation is based on comparison of percentage values between groups without reference to ORs, RRs (for AE), confidence intervals or significance tests.

A meta-analysis is provided that includes two of the studies (RESPOND-2[4] and P05685[5]). The meta-analysis examines the proportion of patients with cirrhosis or who were null-responders who achieved SVR. The included trials appear to be comparable. The MS states that "no important heterogeneity between studies was found" (MS p. 95), but is it unclear if this means that no statistically significant heterogeneity was found (clarification was requested from industry).

A fixed effects model was used in the meta-analysis, but the MS does not give a justification for this choice. The MS also does not report relative or absolute differences. No summary measure of the treatment effect is given and the results seem to be simple averages by treatment group (clarification was requested from industry). Confidence intervals are provided for this. The MS does not provide any other statistics. Sensitivity analyses were not conducted.

Clarification was received from industry which provided some of the missing p values and corrected group Ns. It also reported the methods of the meta-analysis, which appears to be an accepted and valid approach, together with summary meta-analysis results. (The summary measure is Relative Risk for overall SVR and is reported as 3.10). However, there may be concerns about combining different pharmacological agents (PEG2a and PEG2b), especially as it is not clear if the addition of boceprevir alters pharmacokinetics or other responses to interferon.

3.2 Summary statement of manufacturer's approach

The quality of the MS based on CRD criteria[6] for a systematic review as assessed by the ERG is shown in Table 3.

Table 3: Quality assessment (CRD criteria) of MS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes. Inclusion and exclusion criteria are reported
2. Is there evidence of a substantial effort to search for all relevant research? Ie all studies identified	Yes. Extensive searches were conducted for clinical and cost effectiveness and adverse events.
3. Is the validity of included studies adequately assessed?	Yes. The validity of the included RCTs was assessed using standard CRD criteria for assessing the quality of RCTs and is presented in a summary table and appendix only (Table B 9, Appendix 3). No narrative discussion is presented.
4. Is sufficient detail of the individual studies presented?	Yes. Study characteristics are described for the included RCTs and presented in several tables.
5. Are the primary studies summarised appropriately?	Yes. The primary studies are appropriately summarised. The RCTs are summarised through narrative means and tabulation of results for treatment naïve and treatment experienced patients for all outcomes (FAS analysis). Uncertain if all analyses presented are FAS. A meta-analysis is reported for treatment experienced patients with cirrhosis and prior null responders achieving SVR but methods and results are not clear. (Clarification was requested from the manufacturer.) Summary strengths and weaknesses are briefly mentioned, and the clinical interpretation reports the relevance of the evidence base to the UK licence.

The systematic review is of good quality according to CRD criteria and the submitted evidence reflects the decision problem defined in the MS. However, no details are given for any of the processes used in the systematic review; it is not reported whether inclusion/exclusion, data extraction and quality assessment were undertaken by a single reviewer or independently by two reviewers.

Overall the risk of systematic error in the systematic review appears to be low.

3.3 Summary of submitted evidence

In this section of the report the ERG provides a summary of the evidence presented in the MS from the included Phase III studies only.[2;4;5] Data have been checked by the ERG and summarised for the primary outcome and key secondary outcomes for the FAS analysis. Some points of clarification were requested from the manufacturer and these are noted below.

3.3.1 SVR (FAS)

The primary outcome was SVR (defined as undetectable levels of HCV RNA 24 weeks after completion of therapy) in patients who received at least one dose of any study medication (FAS population).

Treatment naïve patients (*SPRINT-2 trial*[2])

A significant improvement in SVR was observed in both non-black and black cohorts as well as the combined population compared with the control population (63.3% patients achieved SVR in the BOC/PR RGT arm, 66.1% in the BOC/PR48 compared with 37.7% in the control PR48 arm, both p<0.001, as shown in Table 4). (See MS Table B10, p75)

Table 4: **Achievement of SVR in Treatment Naïve patients (FAS)**

	SPRINT-2 (combined cohorts)		
	Group 1 (PR48) N = 363	**Group 2 (BOC/PR RGT) N = 368**	**Group 3 (BOC/PR48) N = 366**
SVR n (%)	137 (37.7)	233 (63.3)	242 (66.1)
Absolute Difference from control, % (95% CI) P value	--	25.6 (18.6-32.6) p < 0.001	28.4 (21.4-35.3) p < 0.001

Treatment experienced patients (RESPOND-2[4]*, P05685*[5]*)*

The proportion of patients achieving SVR was significantly higher in the boceprevir treatment arms compared with control in both the Phase III RCTs in treatment experienced patients as shown in Table 5. SVR was achieved in 58.6% patients in the boceprevir RGT and 66.5% in the BOC/PR48 arm compared with 21.3% in the control PEG2b/R arm (both p<0.001) in the RESPOND-2 trial.[4] Similar results were found in the P05685 trial in which SVR was achieved in 64.2% patients in the BOC/PEG2a/R arm compared with 20.9% in the control PEG2a/R arm, p<0.001.[5] (See MS Table B11).

Table 5: Achievement of SVR in Treatment Experienced Patients (FAS)

	RESPOND-2			P05685	
	Group 1 (PR48) N = 80	**Group 2 (BOC/PR RGT) N = 162**	**Group 3 (BOC/PR48) N = 161**	**Group 1 (PEG2a/R) N = 67**	**Group 2 (BOC/PEG2a/R) N = 134**
SVR, n (%)	17 (21.3)	95 (58.6)	107 (66.5)	14 (20.9)	86 (64.2)
Absolute Difference from control, % (95% CI) p value	--	37.4 (25.7-49.1) p < 0.001	45.2 (33.7-56.8) p < 0.001	--	43.3 (30.6-56.0) p < 0.001

3.3.2 SVR achievement by response at treatment weeks 4 and 8 (FAS)

Treatment naïve patients (*SPRINT-2 trial[2])*

SVR was highest in patients receiving boceprevir who demonstrated interferon responsiveness (≥ 1-log10 decrease in HCV-RNA) at TW 4. For the combined cohort in the SPRINT-2 trial[2] SVR in interferon-responsive patients was achieved in 78.7% to 80.6% with boceprevir compared with 51.2% for the control group (both p<0.001). In patients poorly responsive to interferon (<1-log10 decline in HCV-RNA at TW 4) SVR was achieved in 27.8% to 37.9% in boceprevir arms compared with 3.6% in the control arm (both p<0.001). In patients with undetectable HCV-RNA at TW8 there were no statistically significant differences between treatment and control groups in the percentage of patients achieving SVR. Similar results were reported for those with detectable HCV RNA at TW 8 except for the non-black cohort Group 3 (BOC/PR48) which showed a higher rate of SVR compared with control (43.1% vs 31.3%, p=0.046). (See MS Table B12.)

Treatment experienced patients (RESPOND-2[4], P05685[5])

The MS states that response at TW 4 was predictive of SVR; however, no p values for comparisons are given. In interferon-responsive patients SVR was achieved by 70.5% to 78.9% patients in the boceprevir arms compared with 24-25% in the control arm in the RESPOND-2 trial[4] and study P05685.[5] In patients poorly responsive to interferon 32.6% to 38.9% patients in the boceprevir arms achieved SVR compared with none in the control arm.[4;5]

The MS also states that response at TW 8 was also predictive of SVR but again no p values are given. Addition of boceprevir improved achievement of SVR in patients with undetectable and detectable HCV RNA at TW 8 (but no p values given). (See MS Table B13)
(NB Clarification was sought from the manufacturer regarding n/N figures as it seems possible that not all patients are accounted for in Tables B12 and B13; also no p values are given for Table B13; clarification shows there are no statistically significant differences between groups in SVR by TW8 for undetectable HCV in the RESPOND-2 trial.)

3.3.3 End of treatment response rates and relapse rates (FAS)

Treatment naïve patients (SPRINT-2 trial[2])

Higher rates of response at the end of treatment in terms of undetectable HCV-RNA were observed with boceprevir (71% patients in boceprevir RGT, 76% in BOC/PR48) compared with control (53% in PEG/R, $p<0.001$ for both groups).[2] Between the end of treatment and end of the follow-up period, 9% patients relapsed in both the boceprevir treatment arms compared with 22% patients in the control group ($p<0.001$ for both groups). It should be noted that this is not a FAS analysis and is based only on patients with data available at follow-up. (See MS Table B14).

Treatment experienced patients (RESPOND-2[4], P05685[5])

Higher response rates at the end of treatment in terms of undetectable HCV-RNA were observed in boceprevir containing regimens compared with control in both Phase III studies; 70% in the boceprevir RGT and 77% in the BOC/PR48 arm compared with 31% in the control arm (Respond-2[4]); 74% in the BOC/PEG2a/R group compared with 42% in the control group.[5] However, as no p values are given for comparisons it is not clear whether this is statistically significant. Relapse occurred in 15% patients in the boceprevir RGT and 12% in the BOC/PR48 arm compared with 32% patients in the control arm in the Respond-2 trial, and 12% patients in the BOC/PEG2a/R group compared with 33% patients in the control group in the P05685 trial.[5] Again no p values are given for statistical comparisons. (See MS Table B 15).
(NB Clarification was requested from the manufacturer regarding p values; clarification shows that the relapse rate for the BOC/PR RGT group in RESPOND-2 is not statistically significantly different from the relapse rate seen in the control group.)

3.3.4 SVR in patients with and without cirrhosis (FAS)

Achievement of SVR in patients with and without cirrhosis is reported in the MS in Tables B16 and B17. It is stated in the MS (page 86) that as the number of patients with cirrhosis in the Phase III trials was low, results are difficult to interpret. In addition it is not clear whether the studies are powered to detect differences between groups. Therefore these results are not reported here.

3.3.5 Comparison of boceprevir arms (BOC/PR RGT vs BOC/PR48)

The MS states that there are no statistically significant differences between the boceprevir PR fixed 48 week duration arm compared with the boceprevir RGT treatment arm in either treatment naïve and treatment experienced patients (as shown in MS Tables B10 and B11). However, the MS also states that a difference in the proportion of patients who achieved SVR was observed between the RGT and BOC/PR48 week duration arms among patients with cirrhosis in the RESPOND-2 study.[4] As no p values are given (clarification requested from the manufacturer) and the subgroups analysis for cirrhotic patients is post-hoc and based on few patients, it is not clear what inference can be drawn from these results.

3.3.6 Boceprevir efficacy data in line with UK SPC

The SPC recommends different treatment regimens from those used in the Phase III clinical trials for both treatment naïve and treatment experienced patients and also different treatment regimens for specific categories of patients in terms of degree of fibrosis (Metavir score F0-3 and F4) and null response. Data from the trials that most closely match the SPC recommendations are presented in the MS in Tables B18, B19 and B20. Although relevant to clinical practice this is an unpublished retrospective analysis and is therefore not included here. Additionally, it should be noted that null responders (defined as patients with <2 log10 decline in HCV-RNA at TW 12 of their previous treatment regimen) were not included in the Phase III trials in treatment experienced patients (RESPOND-2 and P05685).

3.3.7 Summary of adverse events

The manufacturer carried out a separate literature search to identify triple therapy studies that examined AE. Any study reporting AE was eligible; inclusion was not limited to RCTs. The five RCTs[1-5] identified for the clinical effectiveness review were the only studies that met the

inclusion criteria for the AE review. Additionally, the manufacturer identified a pooled analysis[7] of the AE in the SPRINT-2,[2] SPRINT-1[1] and RESPOND-2[4] trials and used this in the review instead of the individual papers.

The MS provides an overview of the safety of boceprevir in combination with peginterferon alfa and ribavirin. All the RCTs, except RESPOND-1,[3] directly compare the incidence of AE between combination therapy patients and patients treated with triple therapy. In RESPOND-1,[3] a change in treatment protocol part way through the study (all patients were switched to boceprevir triple therapy) meant that comparative data is not available. Instead, the MS reports AE among patients before and after patients switched to boceprevir triple therapy. The MS presents group Ns, percentages and the relative risk statistics for each AE but does not provide the associated confidence intervals or p values. It is therefore not clear whether the differences between groups highlighted by the MS are statistically significant. Furthermore, it is not clear how the analyses were conducted.

The most common AE reported in the trials are tabulated (MS Tables B23 - 26). The MS states that anaemia, dysgeusia, neutropenia, rash, fatigue and drug discontinuation occurred more frequently with boceprevir triple therapy than combination therapy. As Table 6 shows, there were particularly large differences between boceprevir triple therapy groups and combination therapy groups in rates of anaemia, dysgeusia and neutropenia. Haemoglobin results showed a higher rate of Grade 2 and Grade 3 anaemia in the boceprevir triple therapy patients in comparison to the combination therapy patients. Data in the MS also indicate that diarrhoea, nausea, vomiting, thrombocytopenia, myalgia, leukaemia and dose modification due to an AE may be more common in patients treated with boceprevir triple therapy than combination therapy, but myalgia, leukaemia and dose modification are not commented on in the narrative review.

(NB clarification was requested from the manufacturer on AE data, and confidence intervals and risk differences for each AE were provided. Confidence intervals suggest that differences in rates of nausea and myalgia between boceprevir triple therapy patients and combination therapy patients were not statistically significant. Note also that the manufacturer clarified that ‘leukaemia’ should read ‘leukopenia’.)

Table 6: Adverse events that occurred in a much higher proportion of patients who received boceprevir than patients who received standard of care

Adverse event	Pooled analysis		Trial P05685	
	PEG2b/R n (%)	BOC/PEG/2b/R n (%)	PEG2a/R n (%)	BOC/PEG2a/R n (%)
Anaemia	158 (28.9)	755 (48.8)	22 (32.8)	67 (50.0)
Dysgeusia	82 (15.0)	568 (36.7)	10 (14.9)	52 (38.8)
Neutropenia	96 (17.6)	350 (22.6)	12 (17.9)	42 (31.3)

The MS states that "boceprevir was generally well tolerated when used in combination with PEG/R" (p. 109), but the incidence of AE, and particularly anaemia, in the boceprevir groups does not concur with this. A clinical expert's advice to the ERG also indicates that this may not be a reasonable conclusion. In the trials, most patients with anaemia were treated with erythropoietin alone or erythropoietin combined with ribavirin dose reduction. In clinical practice, anaemia would first be treated by a reduction in ribavirin and if this were not successful treatment would be stopped. Erythropoietin is rarely used in the UK. Therefore the impact of increased risk of anaemia on outcomes for patients treated with boceprevir in clinical practice is unknown; treatment responses in clinical practice could be less than those reported in the clinical trials.

3.4 Summary

Results of the three phase III RCTs show statistically significantly increased rates of SVR with boceprevir compared with current standard of care.

In treatment naïve patients (SPRINT-2[2]) there was an increase in the proportion of patients achieving SVR of about 26% in patients receiving BOC/RGT PR and about 28% in patients receiving BOC/PR48. This result was extended to both subgroups of non-black and black cohorts. In treatment experienced patients (RESPOND-2[4]) there was an increase of about 37% in patients receiving BOC/RGT PR and about 45% in patients receiving BOC/PR48. Similar results were also shown for PEG2a/R in treatment experienced patients (P05685[5]). Response guided therapy allowed some patients to reduce total treatment duration to 28 weeks of therapy.

In treatment naïve patients, both those interferon-responsive and poorly responsive at 4 weeks achieved higher SVR rates with boceprevir triple therapy than control patients. No significant differences in SVR were seen for response at 8 weeks. Similar results were shown in treatment experienced patients for SVR at treatment week 4 response, except for those poorly responsive in the study of BOC/PEG2a/R; higher SVR rates were also seen in patients with detectable

HCV-RNA at treatment week 8. End of treatment response rates were statistically significantly increased with boceprevir in treatment naïve patients and treatment experienced patients. Relapse rates were statistically significantly reduced in both treatment naïve and treatment experienced patients with boceprevir-containing regimens, except for BOC/PR RGT in treatment experienced patients.

In a pooled analysis anaemia and dysgeusia were reported in ≥10% more patients receiving boceprevir than those receiving PEG/R. Around half of patients (48.8%) in the boceprevir groups experienced anaemia, an increase of about 20% in comparison to controls.

On the whole it appears that the MS contains an unbiased estimate of treatment effect within the stated scope of the decision problem.

In general the manufacturers' interpretation of the evidence is appropriate and justified. It acknowledges the following issues of relevance/uncertainty:

- the clinical trials included few patients with cirrhosis and therefore the results from the post-hoc subgroup analysis for this group should be regarded as speculative.
- differences exist between the SPC and treatment regimens used in the trials, and results for the retrospective SPC subgroup analysis should also be used with caution due to the low numbers involved.
- null responders were not represented in the clinical trials of treatment experienced patients; data has been estimated for this group and again should be viewed with caution.
- the higher rates of anaemia seen in patients receiving boceprevir may result in higher discontinuation rates in England as erythropoietin is not used routinely to manage anaemia.

4 ECONOMIC EVALUATION

4.1 Overview of manufacturer's economic evaluation

The manufacturer's submission to NICE includes:

iii) a review of published economic evaluations of pharmacological treatments for chronic HCV genotype 1 infection.

iv) an economic evaluation undertaken for the NICE STA process. The cost effectiveness of boceprevir in combination with pegylated interferon alpha and ribavirin (BOC/PEG/R) is compared with the combination PEG/R for the treatment of chronic HCV genotype 1 infection in adult patients with compensated liver disease, either treatment naïve or previously treated who have failed previous therapy.

Manufacturer's review of published economic evaluations

A systematic search of the literature was conducted by the manufacturer to identify economic evaluations of pharmacological treatment of chronic HCV genotype 1 infection. See section 4.2 of this report for the ERG critique of the literature review. The review did not identify any studies that compared boceprevir to its alternatives.

CEA Methods

The economic evaluation uses a Markov model to estimate the cost-effectiveness of BOC/PEG/R compared with PEG/R in adult chronic HCV genotype 1 patients with compensated liver disease, either treatment naïve or treatment experienced for whom previous treatment had failed. The model adopted a lifetime horizon to capture lifetime costs and health outcomes, with a yearly cycle length after the initial 72 weeks, during which treatment and follow-up are modelled using a weekly cycle.

Results are presented for lifetime costs and QALYs and incremental cost-effectiveness ratios (ICERs) for a cohort representing the total UK HCV population with genotype 1. The MS presents sub-group analyses according to patients' fibrosis level (F0-F3 and F4 of the Metavir scoring system). Additional analyses are presented for treatment-experienced null responders (NR) and for earlier responders who became eligible for a shorter course of treatment.

In the economic model, patients are distributed across different degrees of fibrosis (F0-F4) and then may progress to more severe stages of liver disease or remain in the current health state. Over time, liver disease will become more severe (from initial F0 to the latest F4 fibrosis state) and non-cirrhotic patients (F0-F3) will gradually become cirrhotic (F4), when they will be at high risk of developing decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC), which might then require liver transplantation (LT). Patients with DC, HCC, or LT are at increased risk of death compared with the general population, and the mortality rates in the first year after DC and LT are higher than those for the subsequent years.

Health related quality of life (HRQoL) is included in the model through disease severity (health states) and treatment-related AE. Utility values associated to each health state are affected by decrements applied due to treatment and AE (anaemia). Anaemia was the only AE related to treatment accounted for in the MS. These utility values were the same as those used in a model developed for previous NICE guidance on Hepatitis C,[8;9] referred to in this report as the previous SHTAC model.

The approach to quantifying resource use is similar to the one used by Hartwell and colleagues[9] (p. 208 of the MS). The costs were included for health state costs, on-treatment monitoring and drug costs, and AE costs. Dosing data, frequency and intensity of monitoring is also similar to that used in the previous SHTAC model.[8;9] The same health state costs were also used but inflated to 2010 values (MS page 218).

Deterministic sensitivity analyses (DSA), scenario analyses, and probabilistic sensitivity analyses (PSA) were performed. DSA results are presented in Tables B62 and B63 for treatment naïve and treatment experienced patients (p. 264-275 MS); whereas scatterplots and cost-effectiveness acceptability curves (CEACs) of the PSA are shown on pages 276-279 for naïve patients, experienced patients, null responders and for the overall population.

For validation purposes, the MS states that model estimates were evaluated against several outcomes: incidence of compensated cirrhosis, DC, HCC, LT and HCV-related death. The model estimate for 20-year cirrhosis probability was also compared with values from previous models (MS p. 225 and Table B49).

CEA Results

Results from the economic model are presented (section 6.7, page 257 of the MS) as incremental cost per QALY gained for BOC/PEG/R compared with PEG/R. Model estimates are also presented (pages 228-256 of the MS) for clinical outcomes [life years (LY), quality adjusted life years (QALY), incidence of DC, HCC, LT and HCV-deaths], QALY gain and costs by health state, and resource use by category of cost.

Base case results are reported in tables B58-B61 of the MS (pages 259 and 260) for treatment naïve and treatment experienced patients. For the base case, an ICER of £11,601 per QALY

gained is reported for treatment naïve patients and £2,744 per QALY gained for treatment experienced patients (See Table 7). Results in the MS are also presented for the subgroups F0-3, F4, and null responders (NR) and for a cohort with a shortened duration of treatment.

Table 7: Base case cost effectiveness results (MS Tables B58-B61)

	Costs, £	Incremental costs, £	QALYs	Incremental QALYs	ICER (£/QALY)
Treatment naïve patients					
BOC/PEG/R	32,699	10,570	15.30	0.91	11,601
PEG/R	22,128	-	14.38	-	-
Treatment experienced patients					
BOC/PEG/R	38,339	5,478	14.47	2.00	2,744
PEG/R	32,861	-	12.48	-	-

The manufacturer DSA results showed that the base case ICER was most sensitive to the efficacy estimates (probability of achieving SVR), health state utilities, costs, and the discount rates. The MS PSA results estimate there is 92.5% and 100% probability of BOC/PEG/R being cost-effective, relative to PEG/R alone, at a threshold willingness to pay of £20,000 per QALY gained, for naïve and treatment-experienced patients, respectively. The MS states that the use of boceprevir was found to be a cost-effective use of NHS resources (p. 257).

4.2 Critical appraisal of the manufacturer's submitted economic evaluation

Manufacturer's review of published economic evaluations

A systematic search of the literature was conducted by the manufacturer to identify economic evaluations of pharmacological treatments of chronic HCV genotype 1 infection. The inclusion and exclusion criteria for the systematic review are listed in section 6.1.1 of the MS, page 126. The inclusion criteria state that cost-effectiveness studies (including cost-utility analyses) of pegylated or non-pegylated interferon α-2a or α -2b monotherapy or in combination with ribavirin, boceprevir, or telaprevir in adult patients with genotype 1 HCV would be included. The exclusion criteria state that studies set in a non-European context, reported only as conference abstracts, posters or abstracts, or assessing HCV patients co-infected with HIV, Hepatitis B, substance dependent or illegal drug users were excluded. Forty three studies were included for full review, i.e. 19 cost-effectiveness studies, 3 cost studies, and 21 HRQoL studies.

The checklist suggested by NICE has been applied to the included cost effectiveness studies (Appendix 11 on page 321 of the MS). However, no interpretation or conclusions of this quality

assessment were provided in the MS. In section 6.1.2, a summary of the characteristics of the CE studies (Table B28) and of the costs and HRQoL studies (Table B29) are listed, but no critique of these studies or comment on their relevance to the UK was provided, nor the rationale for the development of a *de novo* analysis.

None of the published economic evaluations identified compared boceprevir to alternative pharmacological treatments for the treatment of chronic HCV genotype 1 infection.

Critical appraisal of manufacturer's submitted economic evaluation

The ERG have considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in Table 8 below, drawn from common checklists for economic evaluation methods (e.g. Drummond and colleagues[10]).

Table 8: Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment
Is there a well-defined question?	Yes	Statement of the decision problem shown in MS p32.
Is there a clear description of alternatives?	Yes	Boceprevir in combination with peginterferon alfa and ribavirin versus combination therapy (peginterferon alfa and ribavirin), MS p32.
Has the correct patient group / population of interest been clearly stated?	Yes	Adults with genotype 1 chronic hepatitis C: - who have not been previously treated - who have previously been treated
Is the correct comparator used?	Yes	Peginterferon alfa and ribavirin.
Is the study type reasonable?	Yes	Cost-utility analysis.
Is the perspective of the analysis clearly stated?	Yes	NHS and PSS.
Is the perspective employed appropriate?	Yes	
Is effectiveness of the intervention established?	Yes	Effectiveness estimates derived from RCT data.
Has a lifetime horizon been used for analysis?	Yes	
Are the costs and consequences consistent with the perspective employed?	Yes	See ERG critique of costs and consequences in section 4.2.6 and 4.2.7.
Is differential timing considered?	Yes	Costs and benefits discounted at 3.5% per year.
Is incremental analysis performed?	Yes	Given in table 58-61 in MS.
Is sensitivity analysis undertaken and presented clearly?	Yes	One way sensitivity analysis is presented in Table B62 and B63 in MS. PSA presented in section 6.7.8 (Figures B21 – B22)

NICE reference case

The NICE reference case requirements have also been considered for critical appraisal of the submitted economic evaluation in Table 9.

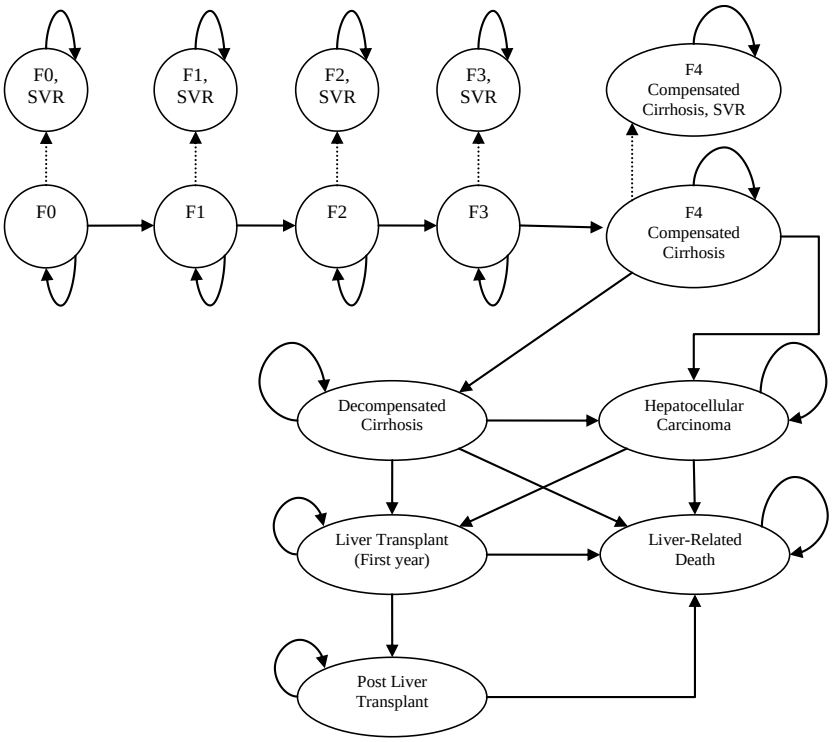
Table 9: NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Y	
Comparator: Alternative therapies routinely used in the UK NHS	Y	
Perspective on costs: NHS and PSS	Y	
Perspective on outcomes: All health effects on individuals	Y	*See ERG critique on patient outcomes in section 4.2.5*
Type of economic evaluation: Cost effectiveness analysis	Y	Cost utility analysis
Synthesis of evidence on outcomes: Based on a systematic review	Y	*Clinical trial data presented.*
Measure of health benefits: QALYs	Y	*See ERG critique on patient outcomes in section 4.2.5*
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	Y	
Method of preference elicitation for health state values: Choice based method (e.g. TTO, SG, not rating scale)	Y	
Source of preference data: Representative sample of the public	Y	
Discount rate: 3.5% pa for costs and health effects	Y	
Notes: ? = uncertain; N/A=not applicable		

4.2.1 Modelling approach / Model Structure

The CEA uses a Markov model to estimate the costs and benefits associated with treatments for hepatitis C. The model has a lifetime horizon with weekly cycle length for the first 72 weeks and a yearly cycle length thereafter. The perspective adopted for the analysis is that of the NHS and PSS. The costs and health consequences in the model are discounted at a rate of 3.5%. (See Figure 1).

Figure 1: State-transition diagram for chronic hepatitis C and liver disease model (MS Figure B 20, p155).



The MS presents a schematic for the model in Figure B 20 (p155). This consists of 16 health states. Patients in the model start in states F0-F4, which represent the degree of fibrosis using the Metavir scoring system. Patients then may either remain in their current health state or move to a more severe health state of liver disease. During the initial treatment phase of the model, patients receive antiviral drug therapy. During each weekly cycle, a patient may discontinue treatment, according to stopping rules specified by that treatment strategy, and other medical reasons, such as AE. The model assumes that, in the absence of successful treatment, reversion to a less severe health state is not possible. Patients can achieve SVR which the MS states is considered a cure for HCV in patients who are non-cirrhotic. Those who achieve SVR will not progress to a more severe health state during therapy or thereafter.

If a patient develops DC and/or HCC then they may subsequently receive a LT. Those surviving the first year after LT enter a long-term health state, the "Post-Liver Transplant" state (PLT). Patients who receive a LT are assumed to not be at risk of further liver disease. All other patients face the same mortality risk as the general population, except those with DC, HCC, and LT patients who have excess mortality compared with the general population.

4.2.2 Patient Group

The MS concerns adult patients chronically infected with HCV genotype 1 whether or not previously treated with PEG/R. This patient group conforms to the scope of this analysis and reflects the licensed indication. The manufacturer used the distribution of the UK HCV genotype 1 population by age from the Health Protection Agency (HPA) 2009 report (Table B30, page 143 of the MS) and assumed that 68% of patients are male and 2.18% black (estimates derived from Mann and colleagues (2008) study[11] on minority groups with Hepatitis C in England).

The patients' distribution per level of fibrosis was also used (Table B31). In response to the ERG's clarification request (Question B1), the manufacturer explained that this distribution had been derived from the baseline characteristics of the cohorts included in the SPRINT-2 and RESPOND-2 trials, and the derivation conducted to produce the estimates are shown in Table B31 of the MS. The trial population is unlikely to reflect the UK population treated in secondary care in terms of its distribution by level of fibrosis. According to our clinical expert, the population treated in secondary care in the UK has a larger proportion of cirrhotic patients (F4) than the trials. The ERG is uncertain whether the cirrhotic group is adequately powered to provide effectiveness estimates for this subgroup.

The MS presents results for subgroups of patients with initial fibrosis levels F0 to F3 and F4, as well as separate analyses for patients eligible to short course of treatment (SOC2), and null responders (NR) – defined as patients with <2log decline in HCV-RNA level from baseline at week 12 of their previous treatment. The rationale for the selection of the subgroups analysed was not provided in MS. Two of the subgroups selected by the manufacturer are similar to those analysed by Hartwell and colleagues[9] (patients who are eligible for shortened course of treatment and null responders). Clarification was requested regarding the differences between the initial fibrosis level of the patient groups defined in the marketing authorisation (F0-3 and F4) and those from the trials (F0-2 and F3-4). The manufacturer clarified that the subgroups included in the MS (F0-3 and F4) are consistent with those in the license that arose from the decision of the European Medicines Agency (EMA) to recommend a specific treatment strategy for cirrhotic (F4) patients. The estimates for these subgroups were obtained by averaging data across all patients with Metavir score F0-F3 and separately for F4 patients. The clinical trials are not powered for the analysis of these subgroups (see section 3.3.4 of this report); and so it is difficult to interpret any results presented for them.

4.2.3 Interventions and comparators

The comparator considered in the model is combination therapy PEG/R in compliance with the scope developed by NICE which is the treatment currently routinely used in the UK NHS.

Treatment regimens and stopping rules

Three main treatment regimens are recommended in the SPC for boceprevir[12] according to patients' initial level of fibrosis and response to treatment (as shown in Figure 2 below). Response-guided therapy (RGT) is recommended for non-cirrhotic patients [with initial fibrosis level of F0 to F3, whether treatment naïve (TN) or treatment experienced (TE)] whereas 48 weeks is the recommended treatment duration with the full course of treatment with boceprevir (44 weeks) for cirrhotic patients (F4, TN or TE) and for null responders (NR).

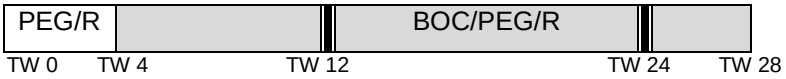
RGT comprises two different regimes: one of 28 weeks (shortened course of 24 weeks of BOC/PEG/R for TN early responders) and another of 48 weeks duration (shortened course of 32 weeks of BOC/PEG/R for TN late responders and for TE non-cirrhotic patients). Early responders are defined as patients who have HCV-RNA undetectable at weeks 8 and 24, whereas late responders are those who have HCV-RNA detectable at week 8 and undetectable at week 24.

In the case where cirrhotic patients and null responders cannot tolerate the whole 48 week period of treatment, they should follow treatment regime 2 (32 weeks of BOC/PEG/R).

Discontinuation of treatment with BOC/PEG/R is recommended if patients have HCV-RNA ≥ 100 IU/ml at week 12, or if the patient has detectable HCV-RNA at week 24. These stopping rules are represented in solid black lines in Figure 2 below at weeks 12 and 24 and apply to the three treatment regimens.

Figure 2: Treatment regimens and stopping rules as per SPC[12]

Treatment regime 1 (RGT) – TN F0-3 early responders



Treatment regime 2 (RGT) – TN F0-3 late responders & TE F0-3 patients

Treatment regime 3 – F4 & NR

In response to the ERG clarification request of why there are different treatment strategies and stopping rules in the trials and the SPC, the manufacturer explained that EMA's CHMP decided to recommend longer treatment durations for some patient groups given the uncertainty surrounding the shortened duration treatments. Furthermore, the CHMP decided on the 12 week futility rule for both TN and TE patients to ensure that only patients with very low (or undetectable) HCV-RNA remain on treatment beyond week 12. Monitoring HCV RNA by testing at weeks 12 and 24 is already part of the standard of care during therapy with PEG/R.

4.2.4 Clinical Effectiveness

The aim of treatment is to prevent patients from progressing to more severe health states. The measure of treatment effect (for both the intervention and comparator) is the proportion of patients achieving a SVR with each treatment. SVR was defined as undetectable viral RNA in the blood 24 weeks after the end of treatment (p.8 MS) and was the primary outcome of the relevant clinical trials.[2;4] The probabilities of achieving SVR were applied to the natural progression of the disease (i.e., transition probabilities among the modelled health states) in order to estimate the difference between the impact of the intervention and that of the comparator.

The methods for deriving efficacy estimates are not clearly described in the MS. According to the manufacturer's response to the clarification request B4, the SVR rates for TN and TE patients receiving BOC/PEG/R were obtained from the SPRINT-2[2] and the RESPOND-2[4] trials

respectively, whereas the SVR rates for patients receiving PEG/R were estimated through a meta-analysis by Mills and colleagues[13] for TN patients and for TE patients from a meta-analysis of RESPOND-2[4] and P05685[5] trials presented in section 5.6 of the MS (page 94 and 95). The estimates used have been derived from potentially different patient populations, and thus potential differences in baseline characteristics might be contributing to the estimated differences in treatment effect.

SVR is considered a cure for non-cirrhotic (F0-F3) patients, i.e. these patients will not progress to more severe disease. For cirrhotic (F4) patients, the base case analysis in the economic model assumes SVR is also a cure (a null probability of developing DC or HCC for cirrhotic patients achieving SVR was input in the model) though the MS states the contrary, i.e. that cirrhotic patients achieving SVR are at risk of DC and HCC (page 154 of the MS). Hartwell and colleagues depicted the transition from SVR to HCC in the diagram of their model; however this transition probability was not reported.[9] According to our clinical expert, cirrhotic patients who achieve SVR are still at risk of developing decompensation or HCC but the risk is significantly reduced compared to cirrhotic patients who do not achieve SVR. The long-term follow up of the HALT-C trial (HCV antiviral long term treatment against cirrhosis) suggests that at 7.5 years after treatment death or transplantation was about 2% in the SVR group versus 20% in the non-response group. HCC was reduced but not so dramatically.[14]

The probabilities of treatment discontinuation before and after each stopping rule as well as the probabilities of failing each stopping rule for each treatment arm were also incorporated in the model. The manufacturer stated that these estimates were derived from the boceprevir clinical trials (section 6.3 page 160 of the MS); however details of their derivation were not provided.

The manufacturer only included treatment AE for anaemia. In a pooled safety analysis, anaemia and dysgeusia were the only AEs reported in more than 10% more patients in the BOC/PEG/R arms than in the pooled PEG/R control arms (MS page 11). Treatment AE are incorporated in the model through the proportion of patients developing anaemia, mean duration of anaemia, proportion of patients receiving treatment (with EPO), and duration of EPO treatment.

The natural progression of the disease was modelled using disease-specific transition probabilities between health states. Several sources were used, as summarised in Table B34 (page 168 of the MS), and some of these had been used in the previous SHTAC model.[9] Though the rationale for not using the same sources as the previous SHTAC model is given

(page 166 of the MS), no explanation is presented for the selection of these data sources nor any quality assessment of them or discussion of their relevance. For example, the rationale for choosing Planas and colleagues,[15] rather than Fattovich and colleagues[16] for the probabilities of transition from decompensated cirrhosis to HCC and death,[9] is unclear.

Overall, the transition probabilities used seem appropriate. Some discrepancies compared with the same sources used in the previous SHTAC model[9] were found (see Table 10 below for the most significant discrepancies) and the derivation of these estimates from the cited sources was not described. The probabilities used by the manufacturer for the transitions from lower fibrosis severity levels to more severe ones (pF0-F1=0.117, pF1-F2=0.085, pF2-F3=0.121, pF3-F4=0.115) differ significantly from those used in the previous SHTAC model[9] from mild to moderate disease and from moderate disease to compensated cirrhosis (mean estimates: 0.025 and 0.037, respectively).

Table 10: Transition probabilities discrepancies between the submitted model and the previous SHTAC model

Transition probabilities	MS Model	Hartwell et al. model[9]	Comment
pDC_HCC	0.068	0.014	Different from Hartwell et al 2011: 0.014 derived from Fattovich et al[16]
pDC_DTH	0.140	0.130	Similar to Hartwell et al 2011: 0.130 derived from Fattovich et al[16]
pPDC_DTH	0.103	0.130	

4.2.5 Patient outcomes

Health-related quality of life (HRQoL) estimates are applied to the model health states and decrements to these were used to reflect the effect of treatment and its AE, and this is consistent with the previous SHTAC model.[9]

The MS reports the strategy and results of searches conducted specifically for HRQoL estimates (page 189 of the MS) but none of the studies found (Table B36) was used and there is no discussion of their appropriateness for the current analysis.

The methods for deriving HRQoL estimates were clearly described, by stating that a similar approach to NICE TA105[17] and TA200[18] was adopted, i.e. the same utility values were applied to the health states considered in the MS. As shown in table B38 of the MS (page 203), the

manufacturer assumed that the utility values used for the mild and moderate HCV infection health states can be applied to the F0-1 and F2-3 states of the MS model. These utilities had been derived from the UK Mild HCV trial[19] (using the EQ-5D) and valued using the UK general population tariff.[20] None of the HRQoL studies found through the manufacturer systematic review is methodologically more appropriate to the NICE Reference Case than the one used.

Overall, the patient outcome estimates used by the manufacturer conform to the NICE Reference Case and are consistent with the approach adopted previously for NICE guidance.[9]

4.2.6 Resource use

Three categories of resource use were included by the manufacturer: treatment (including drug acquisition and on-treatment monitoring), health states/ disease progression and AE.

The manufacturer searched the literature for studies on resource use and costs (results presented in Table B44, pages 215-217 of the MS), but no discussion of the appropriateness or relevance of the three studies found was provided. The manufacturer followed the approach used for NICE TA200[18] to estimate both treatment and health state resource use.

The estimation of dosage and frequency of administration of boceprevir was based on the SPC.[12] Only one course of treatment is expected and it may take 24 weeks for naïve early responders, 32 weeks for experienced early responders and late responders (whether naïve or experienced), and 44 weeks for cirrhotic patients. The assumptions made regarding the dosing and frequency of administration of the PEG/R combination therapy are the same as the ones made for previous NICE guidance,[8;9] based on clinical guidelines and discussion with clinical experts. The uncertainty around the estimation of PEG/R dosage due to the assumption of an average body weight of 79 Kg was not explored; however it does not seem likely to have a significant impact on results as the blended cost of PEG/R seems to vary little for different patient weights (MS Table B42 page 210). Overall these assumptions seem reasonable as they are consistent with the analyses previously conducted.[8;9]

The resource use involved in on-treatment monitoring and management was derived from the previous SHTAC model[9], accounting as well for one additional HCV viral load test to be performed at treatment week 8 (in alignment with the SPC). Overall, the most relevant resource use related to treatment monitoring appears to have been covered. Monitoring-related resource

use considered for NICE TA106[17] also included resources for the surveillance of patients failing, refusing or unsuitable for treatment; however, these are not included in the current MS. Therefore, if the proportion of patients withdrawing treatment is higher due to anaemia for patients receiving boceprevir in combination with PEG/R, there may be additional costs too.

The resource use associated with each health state was derived from the resource use in the previous SHTAC model[8;9] as similar health states were used in both models. The same assumptions were made, for instance applying the resource use of managing cirrhotic patients who have achieved SVR for 5 years.

The resource use of treatment and management of AE were considered to be similar for BOC/PEG/R and PEG/R, and only the treatment of anaemia with EPO was considered as related to the addition of boceprevir. The model assumes that 25% of patients with anaemia are treated with EPO (estimate based on the 20% suggested by an advisory board of 7 senior healthcare professionals, MS page 114). According to the ERG clinical expert, this approach differs from the UK clinical practice where EPO is not routinely used and instead the dose of ribavirin is reduced. In the expert's opinion, 25% is an upper estimate of the proportion that actually receives EPO in this context in a UK secondary care setting. Not using EPO would be expected to increase the number of patients intolerant to treatment.

Overall, the relevant resource use appears to have been covered and was estimated in line with the previous SHTAC model.[9] The approach used seems to be consistent with the reference case as the NHS perspective was adopted.

4.2.7 Costs

The cost year used in the MS was 2010 and the main sources were MIMS July 2011[21] for drug costs and Hartwell and colleagues[9] for on-treatment monitoring and health state costs. The manufacturer inflated the health state costs used for previous NICE guidance[9] to 2010 values according to the Hospital and Community Health Services (HCHS) Pay and Prices Index.[22] The inflated values obtained by the ERG are similar to the ones reported in Table B46 of the MS (page 220). Table 11 shows the main discrepancies between the MS model inputs and the ERG estimates.

Table 11: Differences in health state costs between the MS and the previous SHTAC model

Health state	Cost estimates (£)			
	Hartwell et al. model[9] (2007/08)	Manufacturer Submission (inflated to 2009/10)	Manufacturer Electronic Model	ERG (inflated to 2009/10)
F2, F3	862	927.05	927	911
SVR F4	684	722.90	329	723
DC, PDC	10,964	11,587.98	11,558	11,583
LT	44,225	47,462.32	47,462	46,720

On treatment monitoring costs (Table B43 page 212 of the MS) were derived from Shepherd and colleagues[8] inflated to 2010 values. Clarification was requested on the monitoring costs input in the model for the three treatment regimens considered (cM_PR, cM_RGT and cM_PRB) as they seem to be substituted in the model by the costs in Table B43. The manufacturer confirmed that parameter inputs cM_PR, cM_RGT and cM_PRB should be ignored as these were not used to run the analyses once the weekly treatment monitoring costs approach was considered to be more appropriate.

The ERG has checked the unit costs presented for PEG/R in the MS (TB39 and TB40, page 209) with the British National Formulary (BNF), number 61, March 2011.[23] The weighted average cost of PEG/R, presented in Table B42 (page 210 of the MS) taking into consideration the market share of each product, was based on the IMS/BPI database which is not available to the ERG. The unit market shares provided in Table B41 of the MS specifically concern June 2010; and the ERG suggest a wider period should have been considered for this estimation.

The cost of boceprevir provided by the manufacturer of £100/day (page 211 of the MS) has not been published in BNF or MIMS but was confirmed in the NHS database for UK medicines information 'New Drugs Online' (consulted on 19/08/2011).

All relevant costs seem to have been considered and manufacturer's approach is consistent with NICE TA 200.[18]

4.2.8 Consistency/ Model validation

Internal consistency

The electronic model is coded in Microsoft Excel and is fully executable. It is run through clicking on the '*Run base case analysis*' button on the 'Menu' worksheet. Models inputs can be varied by changing values in the 'Parameters' worksheet. The results of the base case analyses, DSA and PSA are presented on the '*Menu*' worksheet. Deterministic one-way sensitivity analyses are run from the '*Menu*' worksheet by clicking on the '*Run DSA*' button. The PSA is run from the '*Menu*' worksheet with results graphs shown in the '*PSA graphs*' worksheet. The model is well presented and documented and user friendly. The model calculates results for the chronic HCV infection genotype 1 population by aggregating the results by each age, gender and race group.

The MS does not report any techniques used for internal validation of the economic model. The ERG have not undertaken a comprehensive check of all cells in the model, rather random checking of the model has been done for some of the key equations in the model. Changing the parameter values produced intuitive results and from random checking the 'wiring' of the model appears to be accurate. The ERG was able to replicate the results presented in the MS and the deterministic sensitivity analyses, as reported in Tables B 58 - B 61 and Tables B 62 and B63. The ERG views the model as a reasonable approach to modelling the cost effectiveness of chronic HCV infection.

External consistency

The MS discusses the external validity of the model. They state that the modelling approach is justified on the basis of the natural history of the disease and on previously developed cost-effectiveness analyses that used a similar approach. In particular the structure of the model is similar to that used in previous assessment reports and many of the model parameters, such as cost and HRQoL inputs, have also been previously used in those reports.

The MS reported having validated the model results against other published analyses. The model estimations were evaluated against the following outcomes: incidence of compensated cirrhosis, decompensated cirrhosis, HCC, and HCV-related death. MS states that 'model predictions generally fell within the range of values reported in the literature.'' However the validation estimates were not presented so the ERG is not able to verify this statement.

The ERG has validated the MS model by running the previous SHTAC model with SVR effectiveness estimates for boceprevir and the control treatment from the clinical trials. Results for health benefits from the previous SHTAC model were similar to those presented in the MS.

4.2.9 Assessment of Uncertainty

One-way sensitivity analyses

A series of deterministic analyses was carried out on the base case model. The MS provided no rationale for the choice of variable included (or excluded) in the sensitivity analysis. The following variables were subjected to sensitivity analysis: distribution of patients by fibrosis level and gender; transition probabilities between fibrosis states and health states; health costs; treatment-related, AE and disease-AE related QoL; SVR; discontinuation rates; frequency and duration AE. Sensitivity analyses were also carried for structural changes for discount rate and change to the assumption of progression between SVR and DC and HCC.

The MS provides deterministic results for the treatment-naïve and treatment experienced groups for all patients and subgroups F0-F3, F4, SOC2 (short course of treatment) in Tables B 62 and B63. The MS does not provide any discussion for the rationale of the ranges chosen for the sensitivity analyses. The MS has aggregated some of the parameters together, for example all health costs are adjusted together, rather than running for individual cost parameters. The ERG assumes that approach was taken because there are a large number of parameters in the model. For most of the parameters in the sensitivity analysis, the MS uses ranges arbitrarily chosen, for example by varying by +/- 10% for HRQoL, +/- 20% for costs, +/- 25% for SVRs. The ERG suggests a better approach would be to link the sensitivity ranges to the confidence intervals around the treatment effects from the clinical trials. In particular, the SVR for each of the treatment arms should be varied separately, rather than varying together by the same magnitude and direction.

In section 6.7.10, the MS states that the greatest variability in the ICER was associated with changes in response to treatment, i.e. the probability of achieving SVR with each treatment. With the exception of this parameter, generally the model results were robust to changes in parameter values. The deterministic analysis for SVR in response to treatment varies the SVR between +/- 25% of the mean treatment effect for both the PEG/R and BOC/PEG/R arms simultaneously. The results vary between £7,115 and £16,376 per QALY gained for the

treatment-naïve and between £1,173 and £7,026 per QALY gained for the treatment experienced group.

Scenario Analysis

In the MS base case analyses, there are results for several alternative subgroups, F0-F3 PEG/R vs. F0-F3 BOC/PEG/R; F4 PEG/R vs. F4 BOC/PEG/R; SOC2 PEG/R vs. BOC/PEG/R (SOC2 has alternative stopping rules for treatment discontinuation); NR PEG/R (TE) vs. NR (TE) BOC/PEG/R (treatment-experienced patients identified as non-responders (NR) during initial treatment). These are presented in MS Tables B 59 and B 61. There were some minor errors in some of the parameter values for the probability of SVR in the treatment experienced group and these were corrected in the manufacturer's response to clarification. The corrected results are shown in this report in Table 12.

All analyses have favourable cost effectiveness for boceprevir compared to PEG/R, (i.e. ICER < £11,000 per QALY) except for the F4 treatment-naïve analysis. For this analysis, there are only small QALY gains for the BOC group compared to the PEG/R group, and this resulted in a very high ICER (£246,958 per QALY gained). The MS states that this finding is counter-intuitive and is based on very small numbers. Furthermore, it states that the CHMP recognised that this group was in fact the one who would gain the most immediate clinical benefit.

The MS has chosen the sub-groups F0-F3 and F4 which differ from the trial groups F0-F2 and F3-F4. The ERG requested clarification on the rationale for the choice of subgroups. In their letter of clarification the manufacturer states that 'the decision to recommend different treatment strategies, stopping rules and to group patients differently according to their fibrosis level, compared to the clinical trials, was made by the EMA when granting marketing authorisation for boceprevir.'

Table 12: Incremental cost-effectiveness results for treatment-naïve and treatment experienced patients (MS B 59 and B 61), with correction of SVR parameter values

	Treatment-naive patients			Treatment-experienced patients		
Technology* (and comparators)	**Total discounted cost**	**Total discounted QALY**	**ICERs versus baseline**	**Total discounted cost**	**Total discounted QALY**	**ICERs versus baseline**
F0-F3 PEG/R	£21392	14.61	-	£30377	13.09	-
F0-F3 BOC/PEG/R	£31481	15.57	£10,565	£36664	14.98	£3,327
F4 PEG/R	£36129	10.09	-	£47438	8.60	-
F4 BOC/PEG/R	£55843	10.17	£246,958	£49487	11.11	£817
SOC2 PEG/R (All treatment)	£23121	14.22	-	£32606	12.50	-
BOC/PEG/R (All)	£32699	15.30	£8,880	£38339	14.47	£2,909
QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios						

Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis can be run by clicking on the '*Run PSA*' button on the '*Menu*' worksheet in the Excel model. The number of simulations to be run in the PSA can be set in cell K28 of the '*Menu*' worksheet. The '*PSA input*' worksheet contains a table of input values for all model parameters, which lists the point estimate used in the deterministic base case analysis (labelled "base case"). There is no rationale or explanation in the MS for the choice of the distributions and ranges for the PSA. The PSA contained variation in the costs, HRQoL, transition probabilities and efficacy of the treatments. The PSA did not contain variation in the input values for the demographics of the cohort, ie initial health state (F0-F4), age, gender or race; side effects; and treatment discontinuation. Beta distributions were chosen for probabilities and HRQoL, and gamma distributions chosen for costs. The distributions chosen seemed reasonable. Generally, the ranges chosen correspond to a confidence interval of +/- 10% of the mean for the quality of life parameters and +/- 30% of the mean for the cost parameters. The ranges chosen for the transition probabilities were roughly +/- 10-20% of the mean, except for parameters with small values, where the range varied up to +/- 100% of the mean. The PSA contained a couple of parameters that gave errors (pSVR_DC and pSVR_HCC) and so the ERG ran the PSA without these parameters varying.

The PSA takes about six hours to run (on a computer with 1.86 GHz dual core processor and 2 Gb memory) for 1,000 simulations. The MS reports the results of probabilistic evaluations of the base case and of the four scenario analyses (F0-F3, F4, SOC2, NR) for treatment naïve and

treatment experienced patients. Results for the probabilistic base case are presented as scatterplots and CEACs in Figure B 21 – B 24 of the MS (p277) but no aggregated results are shown in MS for total costs and total QALYs for each treatment strategy. These are shown in the electronic model in worksheet '*Menu*'. The MS presents the PSA results as the probability of boceprevir being cost-effective, compared to PEG/R, at a WTP threshold of £20,000 and £30,000 per QALY. The results show that probability of cost effectiveness for boceprevir at a WTP threshold of £30,000 is 99.5% for all patients in the treatment naïve group and 100% for all patients in the treatment experienced group. The results for the PSA results are similar to the base case results.

4.2.10 Comment on validity of results with reference to methodology used

The structure adopted for the economic model is reasonable, and consistent with previous economic evaluations developed for hepatitis C. The parameters used for the model are also generally appropriate and consistent with previous evaluations. The population used in the MS model are those from the relevant trials, but this is likely to differ from those treated in secondary care in the UK.

The transition probabilities used between fibrosis levels differs between the MS model and those used in the previous SHTAC model developed for NICE.[9] The models have used different definitions for fibrosis level which makes it difficult to compare, but the transition probabilities seem higher between fibrosis levels for the MS model than for the previous SHTAC model.

The methods of analysis are generally appropriate and conform to NICE methodological guidelines.[24] However, some errors were detected for the parameter values used in the model. These have been documented in this report along with corrected results.

4.3 Additional work undertaken by the ERG

The following deterministic sensitivity analyses have been completed by the ERG:

- vary starting fibrosis distribution of HCV patients;
- vary SVR treatment effect by the confidence intervals seen in trial;
- vary cost of boceprevir;
- model results with transition probabilities used in the previous SHTAC model;

- correct model errors.

i) Starting fibrosis distribution of HCV patients

The population fibrosis distribution was varied to one similar to that used by Hartwell et al[9], by assuming F0/F1 referred to mild, F2/F3 moderate and F4 severe. Starting distribution used by Hartwell et al[9] was 33%, 35% and 32% for existing patients and 46%, 44% and 10% for new patients for mild, moderate and cirrhosis respectively. We used the proportion with severe for F4 (cirrhosis), and split the proportion with moderate equally between F2 and F3. For mild, we assume the majority were in F1 with only a small proportion in F0. The proportions chosen for the sensitivity analysis and the base case are shown in Table 13.

Table 13: Starting distribution of fibrosis severity for MS base case analyses and ERG analyses

Fibrosis level	Treatment experienced, %		Treatment naïve, %	
	MS Base case	ERG DSA	MS Base case	ERG DSA
F0	5	3	4	6
F1	53	30	69	40
F2	21	17.5	17	22
F3	8	17.5	4	22
F4	13	32	5	10

The ICERs vary for TE from the base case of £2,744 to £1,300 per QALY gained. For TN, the ICER varies from the base case of £11,601 to £11,552 per QALY gained.

We also varied the starting distribution by increasing the proportion with F4 and decreasing the proportion with F1 in the treatment naïve population, whilst keeping the proportions in the other categories constant. In this case, the ICER was £13,489 for F4 of 10%, and £18,344 for F4 of 20%.

ii) SVR treatment effect

The treatment effect for achieving SVR was varied for the BOC/PEG/R group using the confidence intervals from the trials as ranges for the TN group.

For the F0-F3 population the SVR was varied between 63% - 73% (compared to a base case of 68%) and the resulting ICER ranges from £16,092 - £8,751. For the F4 population the SVR was varied between 32% - 52% (base case 42%) and the resulting ICER ranges from £12,119 - £11,103.

The numbers of cirrhotic patients in the trials were small (<15) and so the probability of achieving SVR for this group is not adequately powered. Using the same SVR treatment effect for F4 as for the F0-F3 group, the ICER is £10,496 for TN patients and £3,160 for TE patients.

iii) Cost of boceprevir

The cost of boceprevir was varied from £75 to £125 per day and the resulting ICER ranges from £7,275 - £15,927 for the TN population and £463 - £5,025 for the TE population.

iv) Transition probabilities used in previous SHTAC model

The ERG found some discrepancy between the transition probabilities in the MS model and the previous SHTAC model. The MS model was run with parameter values as in the previous SHTAC model for progression between fibrosis states for mild to moderate, that is for F0_F1 and F1_F2 (p=0.025). These changes significantly affect the results, with resulting ICERs of £26,645 for the TN population and £6,902 for the TE population.

v) Correcting model results

The ERG found some minor discrepancies between the health state costs used in the MS and the model previously used for NICE guidance as shown in Table 11. The model was run with the suggested values in the last column of that table. This results in minor changes to the model results with ICERs of £11,658 for the TN population and £2,888 for the TE population.

4.4 Summary of uncertainties and issues

- It is unlikely that the trial population reflects the UK population treated in secondary care in terms of its distribution by level of fibrosis. The population treated in secondary care in the UK has a larger proportion of cirrhotic patients (F4) than the trials.
- The characteristics of the patient groups considered in the marketing authorisation (F0-3 and F4) differ from the trials' participant groups (F0-2 and F3-4) in terms of their initial fibrosis level. The cirrhotic group is not powered adequately to provide effectiveness estimates for this subgroup.
- Different definitions of early responders and stopping rules for naïve and experienced patients were used in the clinical trials SPRINT-2 and RESPOND-2, and these differ from the ones indicated in the SPC.

- The methods for deriving efficacy estimates are not clearly described in the MS. The probabilities of achieving SVR for the BOC/PEG/R arm by initial level of fibrosis seem to have been derived from the boceprevir clinical trials, whereas the probabilities of achieving SVR for the PEG/R arm seems to have been derived from a meta-analysis performed by the manufacturer.
- The transition probabilities used for progression between fibrosis levels seemed significantly higher than those used in previous models.
- The impact of the main AE of BOC/PEG/R therapy – anaemia – is uncertain as it might lead to a higher proportion of discontinuation in the UK where EPO is not routinely used for treatment of anaemia.

5 END OF LIFE

NICE end of life treatment criteria were not applicable and not included in the MS.

6 DISCUSSION

6.1 Summary of clinical effectiveness issues

The MS includes evidence on the clinical effectiveness of boceprevir in combination with peginterferon alfa and ribavirin for the treatment of genotype 1 chronic hepatitis C from three Phase III RCTs supported by two Phase II studies. Results presented in the MS suggest that triple therapy containing boceprevir is superior to peginterferon alfa and ribavirin and appear to be unbiased estimates of effectiveness.

6.2 Summary of cost effectiveness issues

The MS includes evidence on the cost effectiveness of boceprevir in combination with peginterferon alfa and ribavirin compared to peginterferon alfa and ribavirin. The model structure and methods adopted for the economic evaluation are reasonable and are generally appropriate. The model structure and model parameter inputs are consistent with previous economic evaluations developed for hepatitis C. The model results suggest that boceprevir is a cost effective option for treatment-experienced and treatment naïve patients for a willingness-to-pay threshold of £20,000 per QALY.

7 REFERENCES

(1) Kwo PY, Lawitz EJ, McCone J, Schiff ER, Vierling JM, Pound D et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *The Lancet* 2010; 376(9742):705-716.

(2) Poordad F, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS et al. Boceprevir for untreated chronic HCV genotype 1 infection. *The New England Journal of Medicine* 2011; 364(13):1195-1206.

(3) Schiff E, Poordad F, Jacobson I, Flamm S, Bacon B, Lawitz E et al. Boceprevir (B) combination therapy in null responders (NR): response dependent on interferon responsiveness. Journal of Hepatology 48, S46. 2008.

(4) Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *The New England Journal of Medicine* 2011; 364(13):1207-1217.

(5) Flamm S, Lawitz E, Jacobson I, Rubin R, Bourliere M, Hezode C et al. High sustained virologic response (SVR) among genotype 1 previous non-responders and relapsers to preginterferon/ribavirin when re-treated with boceprevir (BOC) plus peginterferon alfa-2a/ribavirin. Journal of Hepatology 54, S541-S542. 2011.

(6) Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. Third edition. 2009. York Publishing Services Ltd., CRD.

(7) MSD Data on File. Boceprevir pooled safety analysis. 2011.

(8) Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. [11], 1-205, iii. 2007. Health Technology Assessment.

(9) 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(17):i-210.

(10) Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996; 313(7052):275-283.

(11) Mann AG, Trotter CL, Balogun MA, Ramsay ME. Hepatitis C in ethnic minority populations in England. *J Viral Hepat* 2008; 15(6):421-426.

(12) electronic Medicines Compendium. Summary of Product Characteristics for Victrelis. www medicines org uk 2011

(13) Mills E, Druyts E, Cooper C. Rates of sustained viral response among hepatitis C genotype 1 patietns receiving pegylated interferon alpha 2a or 2b along with Ribavirin: a systematic review and meta-analysis. 2011.

(14) Morgan TR, Ghany MG, Kim HY, Snow KK, Shiffman ML, De Santo JL et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. *Hepatology* 2010; 52(3):833-844.

(15) Planas R, Balleste B, Alvarez MA, Rivera M, Montoliu S, Galeras JA et al. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. *J Hepatol* 2004; 40(5):823-830.

(16) 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.

(17) National Institute for Health and Clinical Excellence. TA 106 PegInterferon alfa for the treatment of mild chronic hepatitis C. www nice org uk 2007

(18) National Institute for Health and Clinical Excellence. TA 200 Peginterferon alfa and ribavirin for chronic hepatitis C (part review of NICE technology appraisal guidance 75 and 106). www nice org uk 2011

(19) Wright M, Grieve R, Roberts J, Main J, Thomas HC, UK Mild Hepatitis C Trial Investigators. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol Assess* 2006; 10(21):1-113.

(20) Dolan P, Gudex C, Kind P, Williams A. A social tariff for Euroqol: results from a UK general population survey. Centre for Health Economics Discussion Paper 138. http://www york ac uk/che/publications/in-house/archive/1990s/ 1995

(21) MIMS. Presciption drug database and drug prescribing guide. http://www mims co uk/ 2011

(22) Curtis L. Unit Costs of Health and Social Care 2009. http://www pssru ac uk/pdf/uc/uc2010/uc2010 pdf 2010

(23) Joint Formulary Committee. British National Formulary 61. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2011.

(24) National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. *NICE, London* 2008.