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

Simeprevir for treating genotype 1 or 4 chronic hepatitis C

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors
Keith Cooper, Senior Research Fellow, SHTAC
Jo Picot, Senior Research Fellow, SHTAC
Jonathan Shepherd, Principal Research Fellow, SHTAC
Geoff Frampton, Senior Research Fellow, SHTAC
Jill Colquitt, Senior Research Fellow, SHTAC

Correspondence to
Jill Colquitt
Southampton Health Technology Assessments Centre (SHTAC)
University of Southampton
First Floor, Epsilon House
Enterprise Road, Southampton Science Park
Southampton SO16 7NS
www.southampton.ac.uk/shtac

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Rider on responsibility for 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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Contributions of authors

K Cooper (Senior Research Fellow) critically appraised the health economic systematic review and the economic evaluation and drafted the report; Jo Picot (Senior Research Fellow) critically appraised the clinical effectiveness review and the mixed treatment comparison and drafted the report; J Shepherd (Senior Research Fellow) critically appraised the health economic systematic review and the economic evaluation and drafted the report; Geoff Frampton (Senior Research Fellow) critically appraised the clinical effectiveness review and the mixed treatment comparison and drafted the report; J Colquitt (Senior Research Fellow) critically appraised the

clinical effectiveness review, drafted the report, project managed the review and is the project guarantor.

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[redacted].

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LIST OF ABBREVIATIONS AND GLOSSARY

BNF	British National Formulary
BOC	Boceprevir
BOC24PR28	Boceprevir therapy for 24 weeks in combination with PR for 28 weeks
BOC24PR28/48	Boceprevir therapy for 24 weeks in combination with PR for either 28 or 48 weeks (guided therapy)
BOC32PR36/48	Boceprevir therapy for 32 weeks in combination with PR for either 36 or 48 weeks (guided therapy)
BOC44PR48	Boceprevir therapy for 44 weeks in combination with PR for 48 weeks
CrI	Credibility Interval
CSR	Clinical study report
DCC	Decompensated cirrhosis
DSA	Deterministic sensitivity analyses
HAART	Highly active antiretroviral therapy
HCC	Hepatocellular carcinoma
HCHS	Hospital & Community Health Services
HCV	Hepatitis C virus
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
MAIC	Matching-adjusted indirect comparison
MTC	Mixed treatment comparison
ONS	Office for National Statistics
PBO	Placebo
PI	Protease inhibitor
PPSRU	Personal Social Services Research Unit
PR	Peginterferon + ribavirin
PR48	PR therapy delivered for 48 weeks
PROM	Patient reported outcome measure
PSA	Probabilistic sensitivity analyses
QALY	Quality Adjusted Life Year
RBV	Ribavirin
RGT	Response-guided therapy
RVR	Rapid virologic response (4 weeks after start of therapy)
SMV	Simeprevir
SMV12PR24/48	Simeprevir therapy for 12 weeks in combination with PR for either 24 or 48 weeks (guided therapy)
SMV12PR48	Simeprevir therapy for 12 weeks in combination with PR for 48 weeks
SOF	Sofosbuvir
SPC	Summary of product characteristics
STA	Single Technology Appraisal
SUCRA	Surface under the cumulative ranking
SVR4	Sustained virologic response 4 weeks after end of therapy
SVR12	Sustained virologic response 12 weeks after end of therapy
SVR24	Sustained virologic response 24 weeks after end of therapy
TVR	Telaprevir
TVR12PR24	Telaprevir therapy for 12 weeks in combination with PR for 24 weeks
TVR12PR48	Telaprevir therapy for 12 weeks in combination with PR for 48 weeks
TVR12PR24/48	Telaprevir therapy for 12 weeks in combination with PR for either 24 weeks or 48 weeks (guided therapy)

Virologic failure	Failure to achieve a virologic response
Virologic relapse	Failure to achieve a sustained virologic response after initially becoming virus undetectable
Virologic breakthrough	Reappearance of virus whilst the patient is still on therapy (implies that the emergent virus must have drug resistance mutations)

SUMMARY

Scope of the manufacturer submission

The manufacturer's submission (MS) reflects the scope of the appraisal issued by the National Institute for Health and Care Excellence (NICE). This was to consider simeprevir in combination with other medicinal products in line with its marketing authorisation for the treatment of genotype 1 or 4 chronic hepatitis C.

Summary of submitted clinical effectiveness evidence

The MS presents direct evidence of the clinical effectiveness of simeprevir in combination with peginterferon + ribavirin (PR) based on:

- Two phase 3 RCTs comparing simeprevir + PR against placebo+PR in treatment-naive patients with HCV genotype 1 (QUEST 1, QUEST 2);
- One phase 3 RCT comparing simeprevir + PR against placebo + PR in treatment-experienced patients with HCV genotype 1 (PROMISE);
- One phase 3 RCT comparing simeprevir + PR against telaprevir + PR in treatment-experienced patients with HCV genotype 1 (ATTAIN);
- One single-cohort study of simeprevir + PR in treatment-naive and treatment-experienced patients with HCV genotype 4 (RESTORE);
- One single-cohort study of simeprevir + PR in treatment-naive and treatment-experienced patients with HCV genotype 1 co-infected with HIV (C212);
- One four-arm trial of simeprevir + sofosbuvir ± ribavirin in treatment-naive and treatment-experienced patients with HCV genotype 1 (COSMOS).

Some data are pooled without conducting a formal meta-analysis.

The MS presents indirect evidence of the clinical effectiveness of simeprevir + PR compared against relevant comparators based on:

- A mixed treatment comparison (MTC) that was run separately for treatment-naive and treatment-experienced patients with HCV genotype 1; eight RCTs informed the treatment-naive analysis and seven RCTs informed the treatment-experienced analysis;
- A matching-adjusted indirect comparison (MAIC) for patients with HCV genotype 4. Due to limitations in the availability of data for matching studies, the MAIC is considered by the ERG to be not robust.

Quality of the effectiveness evidence

Overall, the searches conducted by the manufacturer were considered by the ERG to be appropriate and likely to have identified all relevant evidence. The manufacturer's methods of systematic review were also considered appropriate. The RCTs that inform the effectiveness review for simeprevir were considered to be of reasonable quality and not at high risk of bias. Inclusion of three non-randomised studies was deemed appropriate in the absence of relevant RCTs for specified subgroups (although as is common for non-randomised studies they might be subject to bias). For one RCT (ATTAIN) and the three non-randomised studies the effectiveness results are specified in the MS as being interim. The MTC of simeprevir + PR and comparator studies in HCV genotype 1 patients was judged overall to be of reasonable quality, but with caveats that: a low number of trials was available to inform the network of evidence (the majority of connections were informed by only one trial); some variations in patient characteristics were not further investigated; and the exclusion of patients with HCV genotype 1a who were Q80K positive (in line with treatment recommendations) would have broken the within-trial randomisation. The MAIC of simeprevir and comparator studies in HCV genotype 4 patients was considered by the ERG to have serious limitations, as the analytical approach is dependent upon having a reasonable range of baseline characteristics reported for the studies to be matched but in practice this was not feasible. The ERG also had concerns about a lack of clarity regarding the methods employed in the MAIC and the quality of the contributing studies, as well as a lack of any statistical analyses, including analyses of uncertainty, or processes for validating the results.

Patients with HCV genotype 1

Simeprevir + PR treatment resulted in statistically significantly higher SVR12 rates in treatment-naive patients and treatment-experienced (prior relapse) patients in comparison to PR treatment alone (treatment-naive pooled analysis simeprevir + PR 80.4% versus placebo + PR 50.0%, p<0.001; prior relapsers simeprevir + PR 79.2% versus placebo + PR 36.1%, p<0.001). Simeprevir + PR treatment resulted in similar SVR12 rates in treatment-experienced (null and partial responder) patients in comparison to telaprevir + PR (simeprevir + PR 53.6% versus telaprevir + PR 54.7%, non-inferior p<0.001). SVR24 rates in treatment-naive patients and treatment-experienced (prior relapse) patients were also statistically significantly higher in the simeprevir + PR groups compared to the placebo + PR groups whereas interim data for treatment-experienced patients (null and partial responders combined data) show [redacted]. The MTC outcomes for SVR12 and SVR24 in both the treatment-naive and treatment-experienced populations support these results.

The majority of treatment-naive patients and prior relapsers had a rapid virological response to simeprevir triple therapy (treatment-naive: simeprevir + PR 77.5% versus placebo + PR 12.1%, p<0.001; prior relapsers simeprevir + PR 77.2% versus placebo + PR 3.1% p<0.001). Response guided treatment criteria for patients receiving simeprevir + PR (which allowed PR treatment to be shortened to 24 weeks) were met by 88.2% of treatment-naive patients and 92.7% of prior relapsers. There was no response-guided therapy in the trial comparing simeprevir + PR with telaprevir + PR in null and partial responders.

Post-treatment relapse rates in treatment-naive patients with undetectable HCV RNA at end of treatment were lower with simeprevir + PR treatment compared to PR alone (pooled data simeprevir + PR 10% versus placebo + PR 15% , p-value not reported). On-treatment failure rates were also lower (pooled data simeprevir + PR 8% versus placebo + PR 33%, p-value not reported). The same pattern was observed in patients who were prior relapsers (post treatment relapse simeprevir + PR 18.5% versus placebo + PR 48.4%, p-value not reported; on-treatment failure simeprevir + PR 3.1% versus placebo + PR 27.1%, p-value not reported). Virologic failure (a composite outcome including those who did not achieve SVR12 or relapsed after SVR12), on treatment failure and post-treatment relapse occurred with similar frequency in both treatment groups (no p-values provided) among treatment-experienced patients (prior null responders and prior partial responders) receiving either simeprevir + PR or telaprevir + PR.

Health-related quality of life (HRQoL) was assessed using five patient-reported outcome measures (PROMs), including the EQ-5D. Effects of simeprevir + PR were compared against placebo + PR in three RCTs and against telaprevir + PR in one RCT. For all PROMs the effects of simeprevir + PR and placebo + PR on the scores were initially similar in magnitude, indicating an adverse impact of both regimens on patients' wellbeing, but the duration of the effect was shorter for the simeprevir + PR regimen. This pattern is consistent with HRQoL mainly being affected by the duration of the PR component of the drug regimens (24 weeks in the simeprevir regimen; 48 weeks in the placebo regimen). In the comparison of simeprevir + PR against telaprevir + PR, both regimens negatively affected fatigue severity scores and EQ-5D scores (although not other PROMs), but the initial effect was larger for telaprevir + PR, and following the end of therapy HRQoL scores in both regimens returned to baseline levels. Overall, the HRQoL assessments suggest that simeprevir + PR has a more favourable impact on patients' self-reported wellbeing than placebo + PR or telaprevir + PR. A consistent finding is that effects of the drug regimens on HRQoL were limited mainly to the period of therapy, with HRQoL scores recovering to baseline levels once treatment had stopped.

Subgroup analyses by HCV genotype show that the benefit of simeprevir is reduced in patients with the HCV genotype 1a Q80K polymorphism. Simeprevir is not licensed for this subgroup. Other pre-planned analyses for cirrhosis status or fibrosis score, European patients and type of interferon demonstrate the benefit of simeprevir + PR over placebo + PR in all subgroups. Patients with no cirrhosis achieved higher rates of SVR12 than those with cirrhosis with both simeprevir + PR and telaprevir + PR.

Evidence from non-RCTs

Evidence from one non-comparative trial each for patients with HCV genotype 4, patients co-infected with HCV genotype 1 and HIV, and patients treated with an interferon-free regimen (either with or without ribavirin) provides an early indication that the benefits of simeprevir triple therapy may extend beyond the existing RCT evidence base.

Adverse Events

A pooled analysis of adverse events for HCV genotype 1 patients (treatment-naive and treatment-experienced) identified that pruritus was the only common adverse event to occur with higher incidence in simeprevir + PR patients compared to placebo + PR patients. The

proportions with any serious adverse event were similar between the groups; there were three serious adverse events with fatal outcome (0.4%) in the simeprevir + PR group (after the 12 week simeprevir treatment phase) but none in the placebo + PR group. The incidence of some adverse events of special or clinical interest (increased bilirubin, rash, pruritus, photosensitivity conditions and dyspnoea) was [redacted] among patients treated with simeprevir + PR than those receiving placebo + PR whereas the incidence of neutropenia and anaemia was [redacted]. Treatment discontinuation of at least one drug was less frequent in patients receiving simeprevir + PR

Interim data for HCV genotype 1 patients comparing simeprevir + PR against telaprevir + PR shows that differences in adverse events between the groups were generally in favour of simeprevir + PR. Exceptions are [redacted] and [redacted].

[redacted]. Differences in adverse events of special or clinical interest were also typically in favour of simeprevir + PR with the exception of photosensitivity conditions. Treatment discontinuations were fewer in patients receiving simeprevir + PR.

Neutropenia, pruritus, rash, and anaemia rates were outcomes of the MTCs for treatment-naive and treatment-experienced patients and were inputs to the economic model. For both treatment-naive and treatment experienced MTCs these outcomes were generally in favour of simeprevir + PR. Exceptions in the treatment-naive MTC were pruritus (higher risk than both PR and boceprevir + PR), neutropenia (higher risk than telaprevir + PR and one of three boceprevir regimens), and rash (similar risk to boceprevir + PR). In the treatment-experienced MTC a similar or higher risk of neutropenia, pruritus and rash than PR was indicated.

The majority of adverse events in the three non-RCTs were grade 1 or 2. In HCV genotype 4 patients receiving simeprevir + PR (RESTORE), [redacted] experienced a serious adverse event (none fatal). In HCV genotype 1 patients co-infected with HIV (C212), grade 3 or 4 events were reported in [redacted] of patients, with neutropenia being the most frequently reported ([redacted]% by preferred term). No patient on HAART (highly active antiretroviral therapy) needed to discontinue antiviral treatment because of an adverse event. In the HCV genotype 1 patients receiving simeprevir+sofosbuvir in an interferon-free regimen (COSMOS), grade 3 or 4 events were reported in fewer than [redacted] of patients in each arm

Summary of submitted cost effectiveness evidence

The MS includes:

- a review of published economic evaluations of dual therapy with PR or of triple therapy with either simeprevir +PR, telaprevir + PR or boceprevir + PR.
- a de novo economic evaluation to estimate the cost effectiveness for simeprevir + PR in patients with HCV genotypes 1 and 4 and simeprevir and sofosbuvir in patients with genotype 1 who are ineligible for or intolerant to peginterferon alfa.

A systematic search of the literature was undertaken by the manufacturer to identify previous economic evaluations of anti-viral therapy in adults with chronic hepatitis C, published since 2004. Forty-three papers met the inclusion criteria, of which ten were conducted in a UK setting. No economic evaluations featuring simeprevir were identified; however, the ERG identified a 2014 cost effectiveness study of simeprevir and sofosbuvir combination therapy.

Separate economic models have been constructed for genotype 1 patients, for genotype 4 patients and for genotype 1 patients ineligible for or intolerant to peginterferon alfa, respectively. The models use a Markov approach and share a common structure. Separate base case analyses are reported for treatment-naive patients and for those who had previously been treated. The model adopt a lifetime horizon, with an annual cycle length, and the primary treatment outcome (SVR) assigned at the end of the first year of the model.

The modelling approach and structure adopted are based on previous models for HCV. The distribution of patients across age and stage of compensated liver disease in the models is based on the populations recruited to the simeprevir trials. Health related quality of life has been adapted from previous appraisals for NICE, with on-treatment disutility derived from the included RCTs. Resource use and costs have been adapted from previous appraisals for NICE.

Results are presented for lifetime costs, quality adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) for both treatment-naive and treatment-experienced patients. For genotype 1 patients, simeprevir + PR is slightly more effective and has lower total costs than telaprevir + PR and boceprevir + PR for both treatment-naive and treatment experienced patients. The MS reports ICERs for simeprevir + PR compared to PR of £14,206 and £9,793 per QALY in treatment-naive and treatment experienced patients respectively. For genotype 4 patients, ICERs of £11,662 and £8,896 per QALY are reported compared to PR in treatment

naive and treatment experienced patients respectively. For the simeprevir and sofosbuvir analysis, ICERs of £15,431 and £13,971 per QALY are reported for simeprevir and sofosbuvir versus no treatment for treatment naive and treatment experienced patients respectively.

The manufacturer's deterministic sensitivity analysis (DSA) reported both one-way analyses and scenario analyses. These indicated that the model results were most sensitive to changes in SVR for the various treatments, and post-treatment transition probabilities. In scenario analyses, results were robust across both the treatment naive and experienced patient groups and simeprevir dominated telaprevir and boceprevir in all scenarios explored.

The manufacturer conducted probabilistic sensitivity analyses (PSA) for each of the populations. The PSA estimates there is a 92.9% and 97.5% probability of simeprevir being cost-effective compared to all comparators at a threshold willingness to pay of £20,000 and £30,000 per QALY gained for genotype 1 treatment-naive patients. For treatment-experienced patients the corresponding probabilities were 63.9% and 68.4% respectively. For treatment-naive HCV genotype 4 patients the probability of simeprevir being cost-effective, at a threshold willingness to pay of £20,000 and £30,000 per QALY gained, compared to PR was 78.6% and 87.4% respectively, and for treatment-experienced patients was 97.2% and 99.9% respectively. For treatment-naive genotype 1 HCV patients intolerant to or ineligible for interferon the probability of simeprevir and sofosbuvir being cost-effective compared to no treatment at a threshold willingness to pay of £20,000 and £30,000 per QALY was 76.7% and 94.3% respectively. For treatment-experienced patients the corresponding probabilities were 83.2% and 96.3% respectively.

The MS concludes that simeprevir is a cost effective option for genotype 1 and genotype 4 patients and genotype 1 patients intolerant to or ineligible for interferon.

Commentary on the robustness of submitted evidence

Strengths

The assessment of clinical effectiveness is based on a well conducted systematic review. Three good quality RCTs provide evidence for the effectiveness of simeprevir + PR versus placebo + PR in HCV genotype 1, and one RCT provides interim data demonstrating non-inferiority of simeprevir + PR compared with telaprevir + PR. The MTC conducted for the comparison of simeprevir + PR against relevant comparators in HCV genotype 1 was considered to be well conducted, although few studies were available to form the network.

The economic model presented in the MS was similar to previous models and used an appropriate approach for the disease area.

The economic model used a similar structure and parameter inputs to those used in previous economic models developed for NICE.

Weaknesses and areas of uncertainty

There is a lack of head to head RCTs comparing simeprevir + PR with alternative anti-viral treatments. For clinical effectiveness data the economic evaluation therefore relies on an MTC in genotype 1 patients, on matched adjusted indirect comparisons for genotype 4 patients and on unadjusted indirect comparisons for patients ineligible for or intolerant to interferon. The cost-effectiveness estimates for the latter patient groups are therefore subject to greater uncertainty.

The MTC for patients with HCV genotype 1 is informed by a relatively small number of RCTs, meaning that the majority of MTC links are informed by single trial arms. Also, it was necessary to break the randomisation within the MTC for consistency with the licensed indication for simeprevir (patients with HCV genotype 1 who had the Q80K polymorphism were excluded). These factors could introduce some uncertainty into the MTC results.

The cost-effectiveness of simeprevir + sofosbuvir in genotype 1 patients ineligible for or intolerant to interferon is made in relation to comparators that are either not within the NICE scope (i.e. no anti-viral treatment), or comparison drug regimens that include interferon (i.e. telaprevir + PR, boceprevir + PR) and therefore do not reflect clinical practice for this patient

group. No cost-effectiveness evidence was presented for simeprevir + sofosbuvir in genotype 4 patients intolerant to or ineligible for interferon.

The base case model does not include genotype 1a patients who are positive for the Q80K polymorphism (assumed to be around 30% of genotype 1a patients). The summary of product characteristics for simeprevir recommends that alternative therapy should be considered for these patients. Alternative therapy could include telaprevir + PR or boceprevir + PR, both of which are recommended by NICE for use in genotype 1a patients. However, these would not be appropriate in Q80K positive genotype 1a patients ineligible for or intolerant to interferon alfa who would therefore lack any alternative therapy (though this is likely to be a relatively small patient group).

The cost-effectiveness of simeprevir + PR in patients co-infected with HIV and HCV has not been estimated as the manufacturer has assumed that they are equal in efficacy.

Summary of additional work undertaken by the ERG

The ERG corrected the model for minor errors identified. These had a minimal impact on the cost effectiveness results.

The ERG undertook additional analyses to investigate:

- Using ONS data for all-cause mortality in genotype 1 patients
- ITT analysis for simeprevir trials (i.e. including Q80K positive and negative patients)
- SVRs by separate baseline fibrosis grades for peginterferon alfa and ribavirin taken from the pooled QUEST 1 and 2 trials
- 1.5% discount rate for costs and outcomes
- Variations in the transition probability between SVR achieved in the F4 (compensated cirrhosis) health state and the HCC / DCC health states
- Variations in the transition probability between the F4 and DCC health states
- Changes in the treatment duration for telaprevir and boceprevir and PR
- Alternative SVRs for genotype 4 patients
- An older baseline age for patients intolerant to or ineligible for interferon alfa treated with simeprevir and sofosbuvir.

Of these changes, varying the treatment duration had the most effect on the model results. This scenario used the treatment durations as reported in the telaprevir and boceprevir clinical trials. For this change in genotype 1 patients, simeprevir + PR continued to dominate telaprevir + PR and had an ICER of £22,541 and £6,885 per QALY compared to boceprevir + PR in treatment naive and treatment experienced patients respectively.

The ERG noted several limitations to the MAIC for genotype 4 patients and conducted an analysis using SVRs for PR treatment from an alternative trial. Changing the SVR produced an ICER of £39,286 per QALY for simeprevir + PR vs. PR compared to the base analysis ICER of £11,662 per QALY for treatment naive patients.

1 INTRODUCTION TO ERG REPORT

This report is a critique of the manufacturer's submission (MS) to NICE from Janssen on the clinical effectiveness and cost effectiveness of simeprevir for genotype 1 or 4 chronic hepatitis C. It identifies the strengths and weakness of the MS. Clinical experts were 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 9th June 2014. A response from the manufacturer via NICE was received by the ERG on 2nd July 2014 and this can be seen in the NICE Committee papers 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. MS p.24 states that simeprevir will provide an alternative treatment option to telaprevir in combination with peginterferon + ribavirin (PR) and boceprevir + PR in patients who do not achieve an extended rapid virologic response with PR alone at week 4. However, there is no lead-in period with PR specified in the licence or in the clinical trials, and a clinical expert advised that it is not known whether there will be a lead-in period with PR in clinical practice.

2.3 Critique of manufacturer's definition of decision problem

Population

The population described in the decision problem [adults with genotype 1 or 4 chronic hepatitis C who have not been previously treated or in whom previous treatment has not resulted in a sustained virological response (SVR)] is appropriate for the NHS and matches the population described in the final scope issued by NICE.

Intervention

Simeprevir was granted marketing authorisation on 15th May 2014. The description of simeprevir in the decision problem reflects its use in the UK and is appropriate for the NHS. Simeprevir is indicated in combination with other medicinal products for the treatment of chronic hepatitis C in adult patients with HCV genotype 1 or 4, including those with or without cirrhosis and those co-infected with HIV. It must not be taken as a monotherapy. Genotype 1a patients should be tested for the presence of virus with the NS3 Q80K polymorphism and alternative treatments should be considered for those with this virus polymorphism. The recommended dose is one capsule of 150 mg once daily, taken with food.

Duration of treatment

- Treatment-naive and prior relapse patients: simeprevir + PR for 12 weeks, followed by 12 weeks of PR.
- Prior non-responder patients: simeprevir + PR for 12 weeks, followed by 36 weeks of PR.
- Patients who are intolerant to or ineligible for interferon therapy, and are in urgent need of treatment (regardless of prior treatment history): simeprevir + sofosbuvir (+/- ribavirin) for 12 weeks. Treatment up to 24 weeks could be considered on an individual basis.

Treatment stopping rules

Stopping rules are based on HCV RNA levels at weeks 4, 12 and 24 for patients receiving simeprevir + PR:

- At treatment week 4, if HCV RNA ≥ 25 IU/ml: discontinue simeprevir + PR
- At treatment week 12, if HCV RNA detectable: discontinue PR (treatment with simeprevir is complete at week 12)
- At treatment at week 24, if HCV RNA detectable: discontinue PR.

Comparators

The comparators described in the decision problem for simeprevir triple therapy (PR for genotype 1 or 4; telaprevir in combination PR for genotype 1; and boceprevir in combination with PR for genotype 1) are appropriate for the NHS.

The decision problem states that the same comparators apply for the simeprevir + sofosbuvir combination as there are currently no other recommended treatment options for these patients in the UK.

Sofosbuvir, if approved by NICE, could have been considered as a comparator, however this was not approved by NICE at the time of the simeprevir appraisal.

Outcomes

The outcomes stated in the MS are appropriate and clinically meaningful. All the outcomes specified in the NICE scope are included with some additions. The ERG notes that other patient reported outcome measures (PROMs) not specified in the decision problem (including activity, productivity, depression) are reported in the clinical results section (see MS p. 57-62).

Economic analysis

The economic analysis described in the decision problem appears to be appropriate for the NHS. A model with a lifetime horizon for costs and outcomes is used to calculate the incremental cost per quality adjusted life year (QALY) gained. The perspective is that of the NHS and Personal Social Services.

Other relevant factors

The decision problem appropriately notes the following subgroups:

- Response in treatment-experienced patients who are prior relapsers, partial responders and null responders;
- Response in HCV/HIV co-infected patients.

Other subgroup analyses reported in the MS are:

- Genotype
- Cirrhosis status
- Fibrosis score
- European patients
- Type of interferon

These subgroup analyses were pre-planned within study protocols (MS Table 15 p.46).

There are no special considerations related to equity or equality.

3 CLINICAL EFFECTIVENESS

3.1 Critique of manufacturer's approach to systematic review

3.1.1 Description of manufacturer's search strategy

There is one overarching search strategy representing clinical effectiveness, cost effectiveness, quality of life and resource use. It is good practice to conduct separate searches; however the search is overall fit for purpose. The sets and their combined results are all clearly labelled for appraisal or replication of the search; however, the PRISMA diagram of included and excluded studies is harder to analyse with total results being reported, rather than split into the separate entities. On request from the ERG, the manufacturer supplied separate PRISMA diagrams for each of the systematic reviews (clarification A1).

The minimum range of databases specified by NICE have been employed.

The searching of key conferences, company databases and in-house research reports has been undertaken by the manufacturer to identify unpublished and ongoing trials. There is no separate adverse drug reaction search as the information was extrapolated from key clinical trials. The term sofosbuvir is missing from the search strategy; the ERG assumes this is because sofosbuvir was not in the original NICE scope, due to simeprevir/sofosbuvir gaining EU licence approval subsequent to the searches being conducted. As sofosbuvir is a potential comparator, the ERG conducted a search for sofosbuvir and identified no additional relevant trials.

There are minor inconsistencies in the search; for example, trade names have been used for comparator products, but not for the manufacturer's own product. The ERG ran searches on the following known simeprevir trade names: Olysio, Sovriad and Galexos, and no additional references were identified.

The manufacturer had conducted the searches six months before the submission. The ERG conducted a six months update search, replicating the clinical part of the searches on all databases. The results were screened by two ERG researchers and no additional relevant references were identified. The ERG also undertook an ongoing trials search on clinicaltrials.gov, controlled-trials.com and UKCRN and no additional relevant references were identified.

Overall the search strategy was fit for purpose and appears to have identified all the relevant evidence.

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

Inclusion and exclusion criteria are specified for systematic reviews of:

- clinical studies of interventions (MS Table 3, p. 30) – also duplicated in MS Appendix 2, Table 173 (p. 260) which gives an additional criterion 'Geographical location [Not applied]';
- clinical studies of comparators used in a mixed treatment comparison (MTC) for HCV genotype 1 (MS Table 19, p. 64) – also duplicated in MS Appendix 4, Table 175 (p. 263);
- clinical studies of comparators used in a matching-adjusted indirect comparison (MAIC) for HCV genotype 4 (MS Table 46, p. 92);
- economic evaluations (MS Table 76, p. 129);
- HRQoL (MS Table 88, p. 153);
- resource use (MS Table 93, p. 164).

The inclusion/exclusion criteria are consistent with the licensed indication and the decision problem. Quality of the RCTs and the nature of the healthcare setting were not specified as inclusion/exclusion criteria.

A flow chart is provided in MS Figure 4 (p. 31). However, the flow chart is for a combined systematic review of clinical efficacy, HRQoL, resources, and economic evaluations. As such it is not possible to determine which of the reported exclusion criteria and numbers of excluded references shown in the chart relate specifically to the clinical efficacy studies. On request from the ERG the manufacturer provided separate PRISMA flow charts for each of the systematic reviews (clarification A1) and provided a list of the excluded references with the reasons for

exclusion (clarification A2). The ERG has checked and agrees that the flow chart and list of exclusions for the clinical effectiveness review are transparently reported and concordant. The MS states (p. 30) that among the identified studies, a phase 2 study 'OPERA' was excluded as it had only a short duration of simeprevir + PR treatment. Details of OPERA are provided in MS Table 182 (p. 292) and the ERG agrees that the study does not meet the licensed indication for simeprevir.

The flow chart (MS p. 31) appears to omit four phase 3 simeprevir RCTs which are mentioned in the text (CONCERTO-1, CONCERTO-2, CONCERTO-3, DRAGON) (MS p. 30). The source of these trials is not specified (they were published after the manufacturer's searches were conducted). These four RCTs were excluded by the manufacturer due to their simeprevir dosing regimens (50 mg or 100 mg/day) being different to the UK licensed indication (150 mg/day) (MS p. 30 and p. 291-292). The ERG agrees with the manufacturer's decision to exclude these RCTs from the systematic review, however these trials could potentially have been used to help build the evidence network for the MTC. A further RCT, CONCERTO-4, which is unpublished, is mentioned only on MS p. 291, and was also excluded from consideration in the MS since it employed a 100 mg/day dose of simeprevir; again the ERG concurs with its exclusion from the systematic review, but this trial could also potentially have been used to help build the evidence network for the MTC.

Note that the flow chart in MS Figure 4 (p. 31) refers to interventions but not comparators; results of comparator selection are reported separately for MTC analyses later in the MS. A flow chart for the selection of comparator studies is provided in MS Fig 24 (p. 66) (the original version was unreadable; a corrected version was provided by the manufacturer on request from the ERG).

The MS does not explicitly consider bias in study selection.

3.1.3 Identified studies

Study designs

The ERG re-ran the manufacturer's search for simeprevir RCTs and did not identify any in addition to those included in the MS.

For simeprevir interventions the MS identified two phase 2 RCTs (ASPIRE, PILLAR) and four phase 3 RCTs (QUEST 1, QUEST 2, PROMISE, ATTAIN) (MS p. 31). Note that in section 6.2.6 the MS states that there are six large phase III studies, but there are in fact only four. The MS states that the phase 2 RCTs 'have not been included in the main body of the evidence submission for brevity' as PILLAR and ASPIRE were primarily dose-finding trials (as stated on MS p. 34 and 292) and the phase II trials were not powered for superiority, but are included in the MTC of comparators. Three of five arms in the PILLAR RCT and five of seven arms in the ASPIRE RCT are not relevant as they did not employ the licensed dose and/or duration of simeprevir therapy. However, both PILLAR and ASPIRE included one relevant simeprevir + PR intervention arm (150 mg/day simeprevir for 12 weeks, with PR for 48 weeks) and one relevant comparator arm (placebo + PR for 48 weeks), in treatment-naive and treatment-experienced patients respectively. Therefore the ERG does not agree with their exclusion. As these phase 2 trials provide supporting information for the phase 3 trials the ERG has summarised their results in Appendix 1.

Details of the phase 3 RCTs (QUEST 1, QUEST 2, PROMISE, ATTAIN) are reported as study design characteristics (MS Tables 7-9, p. 37-39), eligibility criteria (MS Table 10, p. 40-41), patient baseline characteristics (MS Tables 11-12, p. 42-43), outcome descriptions (MS Table 13, p. 44), statistical analysis approaches (MS Table 14, p. 45-46), planned subgroup analyses (MS Table 15, p. 46), patient flow charts (MS Figures 5 and 6, p. 47-48), and results (MS p. 50-61).

Details of the phase 2 RCTs (ASPIRE, PILLAR) are reported less extensively in the MS than for the phase 3 RCTs and only in Appendices. Summaries of the phase 2 RCT designs and results are given on MS p. 293-298. Patient flow charts for the phase 2 RCTs are given in MS Figures 69-72 (p. 301-302).

For comparators in patients with HCV genotype 1, the MS (MTC section) identified a total of 15 trials: 8 RCTs on treatment-naive patients, which included QUEST 1, QUEST 2 and PILLAR (MS Table 20, p. 68) and 7 RCTs on treatment-experienced patients, which included ASPIRE, PROMISE and ATTAIN (MS Table 21, p. 70). The MS states (p. 65) that 15 trials were included in the base case and 4 were included in sensitivity analyses, giving a total of 19 trials in the MTC. There is an error in the MTC PRISMA flow chart provided on request by the manufacturer

(02/07/14), but the identity of studies included/excluded in the MTC is deducible. For comparators in patients with HCV genotype 4, the MS identified 12 RCTs (MS Table 47, p. 93).

The MS reports three non-randomised studies (RESTORE, C212, COSMOS) which are summarised briefly in MS Table 6 (p. 35) and in more detail later in the MS (p. 97-111). Note that although COSMOS is an RCT, the MS refers to it as non-randomised, presumably because none of the comparators are relevant to the scope and no comparative results are presented. Therefore the ERG report also refers to COSMOS in this way. These studies investigated efficacy of simeprevir:

- in HCV genotype 4 patients (RESTORE);
- in HCV patients co-infected with HIV (C212);
- in combination with sofosbuvir ± ribavirin (COSMOS).

The four phase 3 RCTs, two phase 2 RCTs and three non-randomised studies on simeprevir were all sponsored by Janssen.

Relevance of included studies to the decision problem

All included RCTs meet the inclusion criteria and are relevant to the decision problem. The PILLAR and ASPIRE phase 2 RCTs meet the inclusion criteria for some but not all of their arms. They are excluded from the main clinical effectiveness section of the MS but are included in the MTC.

Characteristics of the studies

Baseline characteristics of the four phase 3 RCTs are provided in MS Table 11 (p. 42) (QUEST 1, QUEST 2) and Table 12 (p. 43) (ATTAIN, PROMISE).

Eligibility criteria for the four RCTs are given in MS Table 10 (p. 40-41). The four RCTs required that participants had HCV genotype 1 infection and plasma HCV RNA > 10,000 IU/mL at screening. Two RCTs (QUEST 1, QUEST 2) were on treatment-naive patients and two (ATTAIN, PROMISE) were on treatment-experienced patients. Patients with non-HCV liver disease, co-infection with HIV, or hepatic decompensation were excluded.

The ERG noted some discrepancies in the participant characteristics reported in the MS in Tables 11 and 12 (p. 42-43). These discrepancies are mostly minor and do not affect the ERG's summary of patient characteristics given below.

Overall, across the four RCTs, the participant characteristics were: male 54.5% to 68.8%; mean age 45.2 to 50.3 years; mean body weight 76.25 to 82.52 kg; median BMI 25.8 to 27.2 kgm^{-2}; white race 86.6% to 96.2%; genotype 1a 40.3% to 56.9%; genotype 1b 43.1% to 59.4%; Q80K positive 7.4% to 23.3%; Q80K negative 76.7% to 92.6%; Metavir score F4 6.9 to 18.3. The MS implies (on p. 20) that Metavir score F4 indicates compensated cirrhosis. The clinical study reports (CSRs) for QUEST 1,[1] QUEST 2,[2] and PROMISE[3] also define cirrhosis as Metavir score F4. For the ATTAIN RCT the proportion of patients with cirrhosis is reported (MS Table 12, p. 43), but this does not agree with the proportion who had Metavir F4 (in the simeprevir and telaprevir groups of ATTAIN the respective numbers of patients with an F4 score were 57 and 51 whereas the numbers classed as having cirrhosis were 88 and 75).

The baseline characteristics of the four RCTs were broadly similar, apart from treatment history. The main differences in baseline characteristics between the RCTs were that the treatment-naive patients in QUEST 1 and QUEST 2 were slightly younger (mean age 45.2 to 46.3 years) than the treatment-experienced patients in ATTAIN and PROMISE (mean age 49.3 to 50.3 years); and the proportion of patients with HCV genotype 1a was slightly higher in QUEST 1 (55.7% to 56.9%) than in the three other RCTs (40.3% to 43.0%). As noted in the MS (p. 42), Metavir scores were slightly higher in the treatment-experienced patients.

Within each RCT the patients in each study arm were generally well matched on potential prognostic baseline characteristics.

For ATTAIN, the MS states that the RCT involved 14 countries, not including the UK (MS Table 9, p. 39) but the presentation[4] (and also the trial record at controlled-trials.com) lists 24 countries, including the UK. It is not clear whether the interim results presented in the MS for ATTAIN include any UK data. The ERG notes that the geographical composition of trials may be important. The MS reports that within QUEST 1, QUEST 2 (MS p. 52) and PROMISE (MS p. 54), the subgroups of patients from European countries had higher SVR12 rates than those of the overall trial populations. Clinical advice suggests the different SVR12 rates may be due to

different proportions of genotype 1a and 1b, lower frequencies of the Q80K polymorphism and a different prevalence of IL28B genotypes in European patients compared with the USA.

Ongoing trials

The ERG searches for ongoing trials did not identify any additional to those reported in the MS.

As noted above, the MS reports interim results for the ATTAIN RCT and RESTORE non-randomised study which are currently ongoing (the ATTAIN full CSR is expected to be available in September 2014).

The MS also lists the following further ongoing trials, which are relevant to the NICE scope, in section 1.6 (MS p. 15-16):

- OPTIMIST-1: phase 3 RCT, evaluating efficacy and safety of simeprevir+sofosbuvir without ribavirin in HCV genotype 1 patients without cirrhosis (treatment-naive or experienced).
- OPTIMIST-2: single-arm study of simeprevir+sofosbuvir without ribavirin in HCV genotype 1 with cirrhosis (treatment-naive or experienced).

Three other ongoing trials noted in the MS (HELIX-1, HELIX-2 and TMC435HPC3014) are outside of the NICE scope (unlicensed drug combination and/or unlicensed duration of simeprevir + PR therapy).

3.1.4 Description and critique of the approach to validity assessment

Critical appraisal is reported for the four phase 3 RCTs (MS Table 16, p. 49, repeated in Tables 174/176 for the MTC), the two phase 2 RCTs (MS Table 185, p. 299) and the three non-RCTs (MS Table 177, p. 271-272). The quality of the phase 2 and phase 3 RCTs was assessed using NICE criteria. There are some inconsistencies between the tables in the appraisal of the phase 3 RCTs, as noted below.

The ERG mostly concurs with the manufacturer's assessment of quality for the phase 3 RCTs (see Table 1). However there are some uncertainties around the numbers of drop-outs, and hence the numbers analysed, due to minor inconsistencies between the MS, CSRs and publications:

- For QUEST 1 the MS and CSR[5] state there were 2 more drop-outs in the placebo + PR arm and 4 more in the simeprevir + PR arm than are reported in the main publication.[6]
- For QUEST 2 The MS states there were 4 more drop-outs in each study arm than are reported in the CSR[2] and main publication.[7]
- For PROMISE the MS flow chart (p. 48) mentions there were no adverse events but the CSR[3] and main publication[8] state there was one adverse event in the simeprevir + PR arm. Also for PROMISE there is a discrepancy between the MS and CSR[3] in the numbers unblinded (Table 1) and these do not appear explicitly in the list of dropouts in the flow chart (MS p. 48).
- For ATTAIN, although the MS and related presentation[4] agree in the total numbers of drop-outs, there are some differences in the numbers assigned to the reasons 'withdrawal by subject', 'non-compliance' and 'other'.

On balance the ERG considers the phase 3 RCTs as being of reasonable quality, with the study groups in each trial well balanced in terms of: population characteristics; adequate blinding of patients and investigators; and adequate reporting of relevant outcomes. Although there are some discrepancies in drop-outs in three of the RCTs as noted above, the analyses for primary outcomes (SVR12) include all the randomised patients and sensitivity analyses indicated a relatively minor influence of missing data imputation on SVR12 rates (reported in the CSRs but not the MS or related publications). When interpreting non-inferiority in ATTAIN it should be borne in mind that an ITT analysis may not be conservative and the per-protocol results may assist interpretation.

The ERG also mostly concurs with the manufacturer's assessment of quality for relevant arms of the two phase 2 RCTs (see Table 2).

The MS provides quality assessment of the three non-randomised studies (RESTORE, C212, COSMOS) using a checklist of unspecified origin (MS Appendix 7, p. 271-272). The ERG notes that the checklist primarily assesses the quality of reporting of the studies rather than providing a critical appraisal of their methods. The MS rates the three non-randomised studies as having no significant potential for bias, with the justification being that clear inclusion and exclusion criteria are stated in the studies (MS Table 177, p. 271). The ERG disagrees that there is no potential for bias as these are all open label observational studies.

Table 1: Manufacturer and ERG assessments of trial quality for phase 3 RCTs

		ATTAIN	PROMISE	QUEST 1	QUEST 2
1. Was randomisation carried out appropriately?	MS:	Yes	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes	Yes
Comment: Stated that randomisation codes were generated centrally by computer. For ATTAIN, ERG assessment is based only on information provided in the MS (Table 9, p. 39) since not reported in the available presentation[4] or interim CSR.[9]					
2. Was concealment of treatment allocation adequate?	MS:	Yes	Yes	Yes / Unclear §	Yes / Unclear §
	ERG:	Yes	Yes	Yes	Yes
Comment: § MS states 'Yes' in Table 16 (p. 49) and 'Unclear' in Tables 174/176 (p. 261/266). MS reports use of central allocation with interactive web-based/voice response system in all four trials (Tables 7-9, p. 37-39). Confirmed by CSRs for QUEST 1[5] & QUEST 2.[2] Allocation concealment not reported in CSRs/publications/presentations for ATTAIN[9] or PROMISE.[3]					
3. Were groups similar at outset in terms of prognostic factors?	MS:	Yes / Unclear §	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes	Yes
Comment: § MS states 'Yes' in Table 16 (p. 49) and 'Unclear' in Tables 174/176 (p. 261/268); no explanation is given in the MS for the 'Unclear' classification. ERG assessment is based on information provided in the MS (Tables 11-12, p. 42-43) which generally agrees with the CSRs/publications/presentations.					
4. Were care providers, participants and outcome assessors blind to treatment allocation?	MS:	Yes	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes	Yes
Comment: MS states (Tables 7-9, p. 37-39) for all four RCTs that patients, investigators & the sponsor were blinded. Methods of blinding are not reported but rules for unblinding are specified, i.e. a reasonable attempt appears to have been made to prevent the blinding being broken unnecessarily.					
5. Were there any unexpected imbalances in drop-outs between groups?	MS:	No / Unclear §	No / Yes †	No	No
	ERG:	Yes	Yes	No	Yes
Comment: ATTAIN: § MS states 'No' in Table 16 (p. 49) and 'Unclear' in Tables 174/176 (p. 261/268); no explanation is given in the MS for the 'Unclear' classification. Higher discontinuations occurred with telaprevir (20% vs 13%), especially for adverse events (8% vs 2%). PROMISE: † MS states 'No' in Table 16 (p. 49) and 'Yes' in Tables 174/176 (p. 261/267-268); the explanation in the MS for the 'Yes' classification is based on unblinding (5 vs 10) patients 'prematurely' (timing not stated). However the PROMISE CSR[3] states the number of patients unblinded prematurely was eight. Overall, withdrawals in PROMISE were unbalanced (simeprevir + PR 3.8% vs placebo + PR 10.5%). QUEST 2: judged to be 'Yes' due to higher discontinuations in PR arm (16% vs 6%).					
6. Is there any evidence that authors measured more outcomes than reported?	MS:	No	No	No	No
	ERG:	No	No	No	No
Comment: All key clinical outcomes are specified in the MS methods section (Table 13, p. 44) and reported later in the MS.					
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	Yes
	ERG:	Yes – modified ITT*	Yes – modified ITT	Yes – modified ITT	Yes – modified ITT
Comment: Not strict ITT analysis according to Cochrane Collaboration definition (required to include all randomised patients) but in practice almost all randomised participants were included (see text) * ATTAIN tested for non-inferiority, for which ITT analysis may not be a conservative approach – this is acknowledged in the MS and the per protocol population is also presented for ATTAIN to assist interpretation.					

Table 2: Manufacturer and ERG assessments of trial quality for phase 2 RCTs

(assessed for simeprevir (150 µg/day for 12 weeks) + PR and placebo + PR arms only)

		ASPIRE	PILLAR
1. Was randomisation carried out appropriately?	MS:	Yes	Yes
	ERG:	Yes	Yes
Comment: Central randomisation system – ASPIRE,[10] PILLAR[11]			
2. Was concealment of treatment allocation adequate?	MS:	Yes	No
	ERG:	Yes	Yes
Comment: ASPIRE CSR[12] and PILLAR CSR:[13] both state that a central interactive web response system/interactive voice response system was employed.			
3. Were groups similar at outset in terms of prognostic factors?	MS:	Yes	Yes
	ERG:	Yes	Yes
Comment: ERG consulted ASPIRE[10] and PILLAR[11] publications for data on patients' age, sex, race, BMI, baseline HCV RNA and Metavir score			
4. Were care providers, participants and outcome assessors blind to treatment allocation?	MS:	Yes	No
	ERG:	Yes	Yes
Comment: ASPIRE CSR[12] and PILLAR CSR:[13] both stated that an external HCV RNA monitor who was unblinded to treatment informed the investigator of the required treatment action while the investigator and subjects remained blinded to treatment and HCV RNA values. The MS (Table 185, p. 299) incorrectly reports PILLAR was open-label whereas the main publication[11] and CSR[13] state PILLAR was double blind.			
5. Were there any unexpected imbalances in drop-outs between groups?	MS:	No	Unclear
	ERG:	No	No
Comment: Numbers and reasons for drop-out appear balanced between the relevant arms, according to flow charts in the main ASPIRE publication[10] and the PILLAR CSR[13]			
6. Is there any evidence that authors measured more outcomes than reported?	MS:	No	No
	ERG:	No	No
Comment: The MS reports limited details for adverse events (which are pooled across trials arms not relevant to the licensed indication) - the study publications and/or CSRs provide relevant arm-specific supporting data on adverse events data that could have been used (the relevant arms in both RCTs being simeprevir at 150 µg/day for 12 weeks and placebo (each with PR).			
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
	ERG:	Yes (modified ITT)	Yes (modified ITT)
Comment: Not strict ITT analyses as the main publication for ASPIRE [10] and the CSR for PILLAR[13] defined their ITT analyses to include all randomised patients who received at least one dose of study medication. In practice, however, nearly all randomised patients did receive study medication: only one patient in ASPIRE and 2 patients in PILLAR did not. These numbers would equate to ≤1.7% of the randomised patients per relevant arm in ASPIRE (deduced from supplementary Figure 2 in the publication[10]) and ≤2.6% of the randomised patients per relevant arm in PILLAR (deduced from Figure on p. 104 of the CSR[13]).			

3.1.5 Description and critique of manufacturer's outcome selection

Outcomes for the four phase 3 RCTs are reported in the methods section of the MS (MS Table 13, p. 44). The primary outcome in all RCTs was SVR12. Secondary outcomes in QUEST 1,

QUEST 2 and PROMISE were SVR24, on-treatment relapse rates, fatigue, work productivity and activity, depression, HRQoL (EQ-5D), proportion with an early response (definition not provided), and proportion eligible for shortened simeprevir + PR treatment. These outcomes are relevant to the NICE scope.

The list of outcomes in MS Table 13 does not specify mortality and adverse events which are listed in the NICE scope, but the ERG notes that adverse events reported in the four phase 3 RCTs and two phase 2 trials are included in the MTC analysis (section 3.3.4 *MTC results for adverse events HCV genotype 1 patients*).

For the ATTAIN RCT, the only secondary outcome specified in the methods section (MS Table 13, p. 44) is SVR4 (as stated on MS p. 56 this is a sustained virologic response 4 weeks after end of treatment). Although not listed in the methods section, the same secondary outcomes are reported for ATTAIN in the results section of the MS (p.55-59) as for the other three phase 3 RCTs. Exceptions are that, for ATTAIN, SVR4 is reported instead of rapid virologic response, and the Skindex-16 questionnaire for skin condition was employed only in the ATTAIN RCT.

QoL was assessed using the generic EQ-5D (visual analogue scale and 'valuation index'). No disease-specific HRQoL measure was used in the included RCTs [although relevant measures are available, e.g. the Chronic Liver Disease Questionnaire (CLDQ-HCV)[14]]. The measures of fatigue (Fatigue Severity Scale - FSS), work productivity and impairment (Work Productivity and Activity Impairment – WPAI), and depression (Center for Epidemiologic Studies Depression Scale – CES-D) are appropriate for patients with chronic hepatitis C since fatigue, activity impairment and depression may be associated with the use of pharmacologic therapies for chronic hepatitis C. The ERG assumes that the role of the Skindex-16 instrument (employed only in the ATTAIN RCT), which specifically assesses severity of skin symptoms, was to assess skin-related manifestations of chronic hepatitis C therapy such as pruritus, although this is not explained in the MS. The ERG notes that the PROMs reported in the MS reflect mainly the on-therapy period, with no longer-term follow up of post-therapy PROMs being reported after week 72.

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

The clinical effectiveness results for the four phase 3 RCTs are presented for all relevant effectiveness outcomes. However, the results are generally superficial and given in summary form:

- SVR12 (primary outcome) data and secondary virologic outcomes, including SVR24, are given as percentages only (apart for some subgroups), without indication of the sample size (denominator) (MS Figures 7, 9, 10, 12, 13, 16 on p. 51-56). Sample sizes and confidence intervals for between-arm differences in outcomes are not reported in the MS but are available in some of the supporting publications (where available the ERG has sourced and summarised these).
- For QUEST 1 and QUEST 2 (treatment-naive) SVR12, is reported as a percentage value obtained by simple pooling (rather than meta-analysis) of the SVR12 in both RCTs, without indication of heterogeneity or uncertainty (MS Fig. 7, p. 51).
- Pre-planned subgroups of SVR12 outcomes are reported (by presence/absence of Q80K polymorphism and fibrosis score but are presented inconsistently: SVR12 by fibrosis score subgroups are pooled across QUEST 1 and QUEST 2 whilst SVR12 by Q80K subgroups are reported separately for these RCTs).
- Subgroup analysis for SVR12 by presence/absence of cirrhosis is reported in the MS only for the ATTAIN RCT (MS Figure 15, p. 56). SVR12 by cirrhosis subgroups are available in the CSRs for QUEST 1,[1] QUEST 2,[2] and PROMISE[3] but are not reported in the clinical effectiveness section of the MS. Cirrhosis is not listed as a planned subgroup analysis (MS Table 15, p. 46), although Metavir score is.
- The subgroup data for SVR12 by presence/absence of cirrhosis reported in MS Figure 15 is further broken down by prior treatment response – this would result in relatively small subgroups but sample sizes are not specified.
- Depression (CES-D) scores are reported only narratively for ATTAIN but quantitatively for the other three RCTs
- The results section reporting PROMs (MS p. 57-62) refers to clinically important changes in outcomes but apart from the FSS does not define what is meant by clinically important. A 1-point change in FSS is deemed clinically important (MS p. 60) but no justification for this assertion is given. The cited reference by Scott and colleagues[15] defines clinically important changes in the CES-D (≥ 6 point increase), WPAI (≥ 10 point

increase) and EQ-5D VAS (≥ 10 point decrease) but it is unclear whether these are arbitrary or evidence-based thresholds.

- For the ATTAIN RCT the worst Skindex-16 score per patient during the first 12 weeks is presented as an outcome measure, but actual data are not reported in the MS. It would have been more informative to present actual scores at different time points.

The MS (Table 14, p. 45) defines the ITT population as excluding patients who did not receive at least one dose of study drug. In practice, nearly all patients randomised did receive at least one dose (MS flow charts, p. 47-48). The MS reports the numbers per trial, rather than per trial arm, who did not receive ≥ 1 dose. These numbers (n=1 in QUEST 1 and PROMISE; n=2 in QUEST 2; n=8 in ATTAIN), would equate to <1% of the randomised population per arm in QUEST 1 and PROMISE; <1.5% of the randomised population per arm in QUEST 2; and <2.1% of the randomised population per arm in ATTAIN (data deduced from flow chart, MS p. 47-48). On balance the ERG considers that the analysis populations can be considered to reasonably approximate an ITT analysis. For ATTAIN, the ERG concurs with the MS (Table 14, p. 45-46) that ITT analysis may not be conservative for a test of non-inferiority and as such both ITT and per protocol analyses are appropriate in this RCT.

Interim data are presented for ATTAIN and RESTORE (stated on MS p. 15). Data for C212 and COSMOS are yet to be published and are based on conference presentations.

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

A narrative review of the evidence is presented in the MS. Many of the data reported are only available in the trial CSRs. Where possible, the ERG has checked key data presented in the MS against those in the publications, posters and/or oral presentations provided by the manufacturer and if necessary the CSRs. A number of (mostly minor) discrepancies in the data were identified and we have indicated these where applicable in the relevant sections of the ERG report.

The manufacturer has not reported a meta-analysis of direct evidence within the MS; however, an MTC is reported for HCV genotype 1 which includes elements of meta-analysis and indirect comparison (see section on MTC below). Another type of indirect comparison, matching-

adjusted indirect comparison (MAIC), was conducted for HCV genotype 4 (see below). Additionally, data from QUEST 1 and QUEST 2 (treatment-naive patients receiving simeprevir + PR versus placebo + PR) are presented separately for each trial and as a pooled analysis. Methods for the pooled analysis are not described in the MS; however, a poster referenced by the MS (Jacobson 2013[16]) states that data from these trials were pooled according to the International Conference on Harmonisation (ICH) guideline on statistical principles for clinical studies (ICHE9) (the ERG notes that the ICHE9 guideline does not provide explicit guidance on pooling data across trials other than that analyses should be pre-specified and clearly reported). The poster[16] states that pooling was pre-specified and appropriate because of the similarity in study designs and populations, but it provides no further information. Results from pooled analyses are presented for SVR12 rates (MS Figure 7, p.50), SVR24 and RVR at week 4 (MS Figure 9, p. 51), response guided treatment (MS p. 52), virologic failure (MS p. 52) and the above outcomes in a subgroup of European patients (MS p. 52).

A pooled analysis of QUEST 1, QUEST 2 (both trials included treatment-naive patients) together with PROMISE (patients who had relapsed after previous interferon based therapy) is presented for fatigue, functioning, QoL and depressive symptoms (MS p. 59-62). The rationale/appropriateness of this pooled analysis of three trials is not described in the MS but the PROMISE CSR[3] mentions the possibility of a pooled analysis and states this would have a separate analysis plan however it is not clear whether this was prespecified (PROMISE CSR[3] page 85).

ERG appraisal of MTC approach

The MS reports an MTC conducted for HCV genotype 1 patients with separate evidence networks for treatment-naive and treatment-experienced patients (MS Figure 25 p. 82). No explicit rationale for conducting the MTC is provided but the outcomes inform the economic model. The three key methodological assumptions of an MTC, homogeneity, similarity and consistency, appear to have been considered[17] although this is not always clearly documented [the separate MTC report[17] (p. 13) mentions that 'any trial considered as a potential source of heterogeneity or inconsistency was excluded to further explore the validity of the similarity assumption between trials'].

A literature search was conducted to identify relevant studies and inclusion and exclusion criteria are described. These differ slightly from the NICE scope in that:

- only HCV genotype 1 patients were included
- HIV co-infected patients (a subgroup of interest) were not included
- comparators were limited to:
  - Boceprevir + PR
  - Telaprevir + PR
  - PR

The NICE scope is less restrictive stating "Established clinical management without simeprevir including, but not limited to" the three comparators listed above.

The outcomes are SVR12 (with SVR24 considered in sensitivity analysis), overall discontinuations, discontinuations due to adverse events and incidence of the individual adverse events neutropenia, pruritus, rash and anaemia. These outcomes were selected to provide clinically relevant endpoints, to inform the cost-effectiveness analyses, and ensure consistency with the outcomes assessed in previous indirect comparisons comparing boceprevir and telaprevir. Only drug doses licensed for use in Europe were included therefore this excluded some trials (CONCERTO 1, 2, 3 and 4; DRAGON) and the arms of trials (PILLAR and ASPIRE) that used other doses of simeprevir (50mg, 75mg, 100mg).

Although search strategies and inclusion criteria are reported the methods for identifying relevant studies (e.g. process for screening references) are not described. Nineteen trials met all the inclusion criteria, 15 of which were included in the base case. The four trials that met the inclusion criteria but which were excluded from the base case were all trials that compared peginterferon alfa-2a and peginterferon alfa-2b in treatment-naive patients. They were excluded because peginterferon alfa-2a and peginterferon alfa-2b were considered as the same comparator in the MTC. These four trials were included in a sensitivity analysis. An assessment of study quality for all 19 trials meeting the inclusion criteria is reported (MS Appendix 5, p. 264). As indicated in Table 1 there were a few minor differences between the manufacturer's and ERG's judgements on the quality of the four RCTs that were also presented in the clinical effectiveness section. The 15 trials included in the base case are divided between the treatment-naive (8 trials) and treatment-experienced (7 trials) populations so there are few trials to inform the evidence network with the majority of comparisons informed by only one trial. For the treatment-naive network all closed loops consisted of three arms from the same trial so there was no opportunity to assess consistency between direct and indirect evidence.

The MTC for treatment-experienced patients considered all treatment-experienced participants together: prior relapsers, null and partial responders. However the proportions of different types of treatment-experienced participants across the trials included in the MTC varies (MS Table 21, p. 70). For the simeprevir trials, PROMISE enrolled prior relapsers whereas ATTAIN enrolled partial responders and null responders and ASPIRE enrolled all three types of treatment-experienced patients. The telaprevir trials also included all three types of treatment-experienced patients and the boceprevir trials did not include any null responders. For the three trials that enrolled all three types of treatment-experienced patients the proportions of the different types varied between the studies. The ERG believes that the effect of simeprevir in the three subgroups of treatment-experienced participants could potentially differ and these variations may be important. The ERG view is supported by the separate MTC report[17] which included subgroup analyses of SVR based on prior treatment response which differ for prior relapsers, null and partial responders. However these data are not robust because of the absence of the required information in some trials (leading to fewer trials in the analyses) together with the lower sample sizes for each treatment arm which results in wide credibility intervals in comparison to the base case.

Some differences in baseline characteristics of the included trials (MS Table 20 p. 68-69 and MS Table 21 p. 70) can be observed. In particular for both the treatment-naive patient trials and the treatment-experienced trials variability was observed in the proportion of HCV genotype 1a patients (range 38% to 67% and 35% to 62% respectively), Black patients (range 1% to 27% and 2% to 15% respectively) and Metavir 4 score (range 0 to 13% and 10% to 27%). For some trials there were missing data for certain characteristics (e.g. Metavir score 0-2, 3 and 4; IL-28B genotype). Overall however the MS states that heterogeneity was not a big concern and a scenario analysis was conducted which excluded the PILLAR study as this was the only study to exclude cirrhotic patients. Meta-regression could have been undertaken to determine what effect the variations in the baseline characteristics noted above would have on the results.

Data for patients with HCV genotype 1a who were Q80K positive were excluded from the simeprevir arms in the analysis of SVR because this is in line with the simeprevir Summary of Product Characteristics (SPC). The exclusion of these data breaks randomisation which is a limitation highlighted in the separate MTC report (p. 76).[17] Furthermore the exclusion of these data may have an impact on the comparison with telaprevir in the ATTAIN trial in the MTC, as subgroup analysis (MS Figure 14 p55) shows that Q80K positive patients in both the simeprevir

+ PR and telaprevir + PR groups have similar and poorer outcomes in comparison to patients without Q80K (HCV genotype 1a with the Q80K mutation: simeprevir + PR 27.0%,telaprevir + PR 25.9%; HCV genotype 1a without the Q80K polymorphism simeprevir + PR 43.5%,telaprevir + PR 39.8%). Retaining Q80K positive patients in the telaprevir arm included in the MTC could potentially disadvantage telaprevir in comparison to simeprevir. However, the ERG notes that ATTAIN was not stratified to examine the impact of this polymorphism, and there is no evidence from other telaprevir trials that the Q80K mutation confers resistance to telaprevir.

Meta-analyses of direct evidence (two or more trials for the same comparison) were conducted when possible using the inverse variance method. For some direct comparisons heterogeneity was identified but other than providing potential reasons for this it was not discussed further. The MTC was based on a Bayesian hierarchical model and code for this (which comes from the Decision Support Unit Technical Support Document) was supplied. Meta-analysis and MTC outcomes were reported as odds ratios. The separate MTC report[17] presents results of the direct evidence meta analyses and those of the MTC differently (event and non-event switched for meta-analysis) which does not aid comparison. The analysis of inconsistency was only applicable to the treatment-experienced network (as noted in the treatment-naive network all closed loops consisted of arms from the same trial) and the MS reports that no inconsistency was detected. The ERG has checked a very limited set of data and found results of direct and indirect analyses to be similar. Sensitivity analyses were conducted but these are not presented in detail in the MS (the results are available in the separate MTC report[17]). The sensitivity analyses involved exclusion of open-label trials; use of SVR24 instead of SVR12 for all studies; pooling of studies of different PR treatment duration (24+48 weeks); excluding trials that assumed the same efficacy of peginterferon 2a and peginterferon 2b; and excluding one trial (PILLAR) that excluded cirrhotic patients. These analyses appear reasonable and did not appreciably change the conclusions.

In summary the ERG judges the MTC to be of reasonable quality. The key caveats to the MTC are:

- The low number of trials available to inform the network of evidence with the majority of connections informed by only one trial;
- The MTC for treatment-experienced patients considered all treatment-experienced participants together: prior relapsers, null and partial responders, and SVR is likely to differ in these subgroups;

- Variations in some patient characteristics that were not further investigated e.g. by meta-regression;
- The exclusion of patients with HCV genotype 1a who were Q80K positive from the simeprevir arms for the analysis of SVR breaks randomisation but this is in line with treatment recommendations in the SPC.

HCV genotype 4 patients: matching-adjusted indirect comparison (MAIC)

The MS reports one non-randomised single arm study of simeprevir in genotype 4 patients (RESTORE). The trial is not yet complete and data are taken from the week 60 analysis, the point at which all patients had reached the time-point for the primary endpoint (SVR12).

In the absence of a PR comparator arm in RESTORE, the MS states that an MAIC[1;18] was conducted. However, although the MS uses the approach to match data to other trials, a statistical analysis of the comparisons was not undertaken. The MAIC approach uses individual patient data (IPD) from RESTORE and compares the outcomes from a cohort of patients which are matched to the baseline aggregate statistics of other studies of interest. Matching is accomplished by re-weighting patients in RESTORE by their inverse odds of having enrolled in that trial versus having enrolled in the other trials. After matching, the weighted mean baseline characteristics match those of the other study and treatment outcomes can be compared across study populations. The MS uses this approach to calculate the relative efficacy of simeprevir in genotype 4 patients. However, the tolerability data for the genotype 4 population were drawn from the MTC carried out for the HCV genotype 1 model.

MS section 7.8 (Validation, p. 230) refers to an unpublished report which gives details of the MAIC analysis,[19] which is not referred to in MS section 6.7 (Indirect and mixed treatment comparisons, p. 62). However, there are a number of inconsistencies between the MS and the MAIC report,[19] such as the reported methods of searching and screening, and the studies identified and included.

The MS states that the search for PR trials was the same as that for MTC of genotype 1. Inclusion and exclusion criteria are reported in MS Table 46 and indicate that RCTs of PR in adult treatment-naive and relapsed or refractory genotype 4 patients were eligible for inclusion. Although not explicitly stated, it appears that trials of HCV patients where outcomes were presented for genotype 4 patients separately (i.e. as a subgroup) were also eligible. The number of studies identified by searches and a PRISMA flow chart of study inclusion were not

reported. Twelve studies were identified. Trials with less than 15 genotype 4 patients were excluded to allow credible matching, although the value used for the cut-off was not justified. The MS states that five of the 12 identified studies were excluded on this basis (MS p. 93) and seven studies remained for potential consideration in the MAIC. The ERG notes that the seven studies were not all controlled trials, in contrast to the criteria specified in MS Table 46.

The MS reports that a further three (of seven) trials were excluded due to insufficient data to match baseline characteristics (MS Table 48, p.94). One of these was an abstract with insufficient baseline data. The ERG considers that it may not have been appropriate to exclude the two other studies from consideration in the MAIC. One reported all baseline data except mean BMI (Derbala 2006); the ERG note that not all six baseline variables were included in the final algorithm and that BMI is considered to be a 'parameter of limited or inconsistent relevance' by the MAIC report.[19] One study was excluded as the reference was unavailable (Varghese 2009), however the manufacturer notes in their clarification that this paper has since become available (see below).

Four trials were therefore included in the matching process. For three of the trials, matching on all variables resulted in small pseudo populations and baseline characteristics still differed from aggregated data. The match with Rumi and colleagues 2010[20] resulted in a sample size of 15, which the MS states was considered acceptable and that baseline characteristics matched well. Therefore the MS presents the matched comparison between RESTORE and Rumi 2010 [20] (Table 3; MS Table 55, p. 97), which is used in the base case for the HCV genotype 4 economic model. This comparison is matched on five parameters: fibrosis score, baseline viral load, BMI, age and gender.

The 18 patients from Rumi and colleagues[20] are a subgroup from the peginterferon alfa-2a arm of a larger RCT. The ERG notes that Rumi and colleagues' study[20] includes only treatment-naive people, whereas RESTORE also includes treatment-experienced people, although this is not mentioned in MS section 6.7.14. The matched data comprise a very small proportion (only 15 of 107) of RESTORE, and the ERG assumes these are all treatment-naive (the MAIC informs the economic model for treatment naive patients, but not for treatment experienced patients – see section 4.2.4). Baseline characteristics and SVR12 rates from RESTORE are summarised in Table 4 according to prior HCV treatment response (baseline data from Moreno and colleagues,[21] SVR12 data from MS p. 101). A visual comparison of the matched data from RESTORE in Table 3 with baseline trial data in Table 4 suggests that the 15 matched patients

may not be representative of the RESTORE population. The SVR rate for RESTORE matched data appears incorrect (12/15 = 80% not 77%). An important limitation in this MAIC is the absence of a common comparator to allow for detection of residual confounding, as no validation of the matching or use of relative effect measures is possible.[1] None of the eligible PR trials reported SVR12, therefore MS Table 55 compares SRV24 data from Rumi and colleagues[20] with SVR12 data from RESTORE, which the ERG considers appropriate. As stated, the MS does not undertake a statistical indirect comparison of the matched data. The ERG notes that the SVR12 for the RESTORE matched data [12 (77%)] is higher than that for the overall RESTORE population (65.4%), but slightly less than that for the treatment-naive subgroup (82.9%). The comparator SVR24 data from Rumi and colleagues,[20] on the other hand, is lower than that from the three other studies selected for consideration in the MAIC, which ranges from 50.0% to 70.6%. It is the opinion of the ERG that the data in MS Table 55 are viewed with caution. The ERG explores alternative SVR24 data in a scenario analysis (see section 4.3).

Table 3 RESTORE population characteristics and SVR after matching (MS Table 55, p. 97)

Matching parameters	Patients (N)	Effective n* (n)	Fibrosis (% S5-6 / F4)	Viral load (% HCV RNA < 600,000 IU/ml)	BMI (mean baseline)	Age (mean)	Sex (% female)	SVR N (%)
Rumi (2010)[20]	18		28%	72%	26.4	43,00	17%	8 (44%)
RESTORE matched	35	15	28%	72%	26.4	43,01	17%	12 (77%)

* effective population size after matching algorithm applied.

Table 4 RESTORE baseline characteristics[21] and SVR12 (MS p. 101)

RESTORE	Patients (N)	Fibrosis Metavir (% F4)	Viral load (% HCV RNA < 600,000 IU/ml)	BMI (mean baseline)	Age (mean)	Sex (% female)	SVR12 N (%)
Overall	107	28.8	Not reported	26.5	49.6	21.5	70 (65.4)
Treat-naive	35	5.7	Not reported	26.2	47.6	25.7	29 (82.9)
Prior relapsers	22	40.9	Not reported	26.7	52.0	13.6	19 (86.4)
Prior partial responders	10	50.0	Not reported	26.1	49.1	0	6 (60)
Prior null responders	40	37.8	Not reported	26.1	50.3	27.5	16 (40)

In their clarification letter the manufacturer notes that the Varghese 2009 paper is now available, and is assessed as having a good fit to the RESTORE study based on some relevant matching parameters. The manufacturer considers the Varghese 2009 study to be a less relevant population from a decision making perspective than that of Rumi 2010, but presents scenario analysis for genotype 4 using MAIC with Varghese 2009 for completeness (clarification point A1).

On balance, the ERG cautions that the results of the MAIC may not be reliable, for the following reasons:

- Unclear eligibility criteria and selection process for study inclusion, and inconsistencies between the MS and MAIC report;[19]
- The minimum sample size permissible for studies to be included appears arbitrary and the effect of varying this cut-off was not explored;
- The MS and MAIC report[19] are not explicit about the quality of the trials that were included in the matching process;
- The MAIC approach is dependent upon having a reasonable range of baseline characteristics reported for the studies to be matched[1;18] but in practice limited baseline details were available; the selection process was therefore driven by availability of baseline variables rather than by an objective consideration of which variables might have most prognostic relevance;

- A key limitation of the MAIC approach, noted in the MAIC report,[19] is that unobserved differences in baseline characteristics across studies may result in residual confounding and bias;
- Where MAIC is applied across single-arm trials validation of the matching is not possible;[1]
- No statistical analyses, including analyses of uncertainty, were undertaken.

3.2 Summary statement of manufacturer's approach

Overall the ERG believes that the submitted evidence does reflect the decision problem. Furthermore the chance of systematic error in the systematic review is likely to be low based on the methods employed.

Two reviewers screened titles and abstracts but it is not clear whether this was done independently - MS p. 29 states "A second reviewer quality checked the assessment" which suggests they were not blind to the first reviewer's assessment. The MS does not indicate whether the same process was used for screening full texts (the detailed systematic review report by Amaris[22] does not provide any further information on the screening process). Data extraction was undertaken by one reviewer and tabular summaries of 20% of the publications were checked by a second reviewer. For those data included in the meta-analysis data were checked by a second analyst. The ERG assumes that the data checked may have been those contributing to the MTC and/or MAIC as no separate meta-analysis of direct evidence is reported in the MS (MS section 6.6, p.62).

Table 5 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 - eligibility criteria are reported (MS p. 30). Separate criteria are reported for the MTC (MS p. 64).
2. Is there evidence of a substantial effort to search for all relevant research? Ie all studies identified	Yes - A single search strategy is reported in MS Appendix 2 (MS p. 254-259) which aimed to identify all studies required for clinical effectiveness, cost-effectiveness, costs, resource use, and HRQoL. Selected conference proceedings were also searched and the manufacturer provided clinical study reports where these were available. The search strategy also identified literature on comparators to inform the G1 MTC and the G4 MAIC.
3. Is the validity of included studies adequately assessed?	Yes - Each RCT included in the clinical effectiveness section was quality assessed using appropriate criteria (MS Table 16, p. 49 and Appendix 3, MS p. 261). The same criteria were used to assess the quality of the phase II RCTs (MS Table 185, p. 299) and comparator studies included in the MTC (MS Appendix 5, p. 264-269). Quality assessment of the non-RCT studies is reported in MS Table 177, p. 271-272 (based on a checklist of criteria from an unspecified source).
4. Is sufficient detail of the individual studies presented?	Yes - individual study information for RCT characteristics (MS Table 5, p. 33) with further detail on trial methodology (MS Tables 7-9, p. 37-39), eligibility criteria (MS Table 10, p. 40-41), participant characteristics (MS Tables 11 & 12, p. 42-43), trial outcome measures & statistical analyses (MS Tables 13 & 14, p. 44-46). Summary baseline characteristics are presented for studies contributing to the HCV genotype 1 MTC (MS Tables 20 & 21, p. 68-70) and the HCV genotype 4 MAIC (MS Table 48, p. 94) and the data used in these analyses are also tabulated (MTC: MS Tables 24-29, p. 74-79; and MAIC: Tables 51-55, p. 96-97).
5. Are the primary studies summarised appropriately?	Yes - Results are summarised and presented in narrative form with accompanying charts and tables. The results for clinical effectiveness (which appear on MS p. 50-62) do not include confidence intervals for SVR12 comparisons between trial arms, but these are available in the supporting publications for QUEST 1,[6] QUEST 2[7] and PROMISE.[8] For the HCV genotype 1 MTC and HCV genotype 4 MAIC results are presented in tables with accompanying text (MS Tables 30-45, p. 83-89 and Table 55, p. 97).

3.3 Summary of submitted evidence

Results are presented from the four phase three RCTs that report evidence for three groups of patients with HCV genotype 1 [treatment-naive (QUEST 1 and QUEST 2), treatment-experienced: prior relapsers (PROMISE), treatment-experienced: null and partial responders (interim data from ATTAIN)]. Not all outcomes are reported for each group of patients in the MS.

The results of the manufacturer's MTC are also presented by outcome measure. Patients who were Q80K-positive were excluded from the simeprevir + PR arms in the MTC analyses of SVR12. MTC data from the comparisons of simeprevir, telaprevir and boceprevir versus PR for the outcomes of SVR12, and adverse events of neutropenia, pruritus, rash and anaemia are used in the manufacturer's economic model base case. For some economic model inputs [e.g. odds ratios (ORs) for boceprevir + PR versus PR and for simeprevir + PR versus PR in treatment-experienced patients] data outputs from the MTC for different treatment regimens have been combined (section 4.2.4). MTC data for SVR24 (which are not reported in the MS) are used in sensitivity analysis.

Data have been reproduced here from the MS, trial journal publications and supplemented with data from CSRs or other documents referenced in the MS where necessary. Data from the arms of the phase two dose finding studies PILLAR and ASPIRE that contribute to the MTC are also briefly summarised in Appendix 1. Finally, results are presented from the three non-randomised studies for the efficacy of simeprevir in HCV genotype 4 patients (RESTORE), simeprevir in HCV patients co-infected with HIV (C212), and simeprevir in combination with sofosbuvir ± ribavirin (COSMOS).

3.3.1 Patients with HCV genotype 1

Summary of SVR12 results

Treatment-naive patients (QUEST 1 and QUEST 2; PILLAR included in the MTC only)

Data are presented separately for each RCT and from a pre-specified pooled analysis of data from the two trials (Table 6). SVR12 rates were similar in both trials and statistically significantly higher in the simeprevir + PR groups compared to the placebo + PR groups (pooled analysis simeprevir + PR 80.4% versus placebo + PR 50.0%, $p<0.001$).

Table 6 SVR12 following treatment with simeprevir + PR or placebo + PR in treatment-naive patients

Primary end-point (ITT analysis) % of subjects with SVR12 (n/N)	Simeprevir + PR	Placebo + PR	Mean difference (95% CI); p-value
QUEST 1 From MS and paper[6]	79.5 (210/264)	50.0 (65/130)	29.3 (20.1 to 38.6)[a]; p<0.001
QUEST 2 From MS and paper[7]	81.3 (209/257)	50.0 (67/134)	32.2 (23.3 to 41.2)[a]; p<0.001
Pooled data QUEST 1 and QUEST 2 From MS and poster[16]	80.4 (419/521)	50.0 (132/264)	Not reported; p<0.001

[a] Mean difference and 95% CI were obtained from a logistic regression model including baseline HCV RNA as a continuous variable with stratification factors of HCV genotype 1 subtype and IL28B genotype.[6;7] PR: peginterferon + ribavirin.

In the economic model the fixed effect MTC median OR plus 95% credibility interval (CrI) for each triple therapy versus PR was used. For this analysis of SVR12, patients who were Q80K-positive were excluded from the simeprevir arms in line with the simeprevir SPC. For simeprevir + PR versus PR alone the OR used in the model was 4.83 (95% CrI 3.50 to 6.70), data for telaprevir + PR versus PR came from TVR12PR24/48 OR 3.79 (95% CrI 2.78 to 5.20), whereas the boceprevir + PR versus PR economic model input (OR 3.483) was derived from more than one boceprevir +PR treatment regimen. The base case results for each intervention versus PR are displayed in MS Table 30 p.83.

Table 7 reports the fixed effect MTC ORs for simeprevir +PR against the telaprevir + PR and boceprevir + PR regimens. Median odds ratios for simeprevir + PR versus telaprevir +PR ranged from 1.27 (95% CrI 0.81 to 2.00) to 2.00 (95% CrI 1.14 to 3.49) and for simeprevir + PR versus boceprevir + PR from 1.36 (95% CrI 0.89 to 2.09) to 2.61 (95% CrI 1.44 to 4.74).

Table 7 MTC results SVR12/24[a] in treatment-naive population (Simeprevir + PR versus telaprevir + PR or boceprevir + PR) reproduced from MS Table 31, p. 83

	Median OR	sd	CrI95%	Probability	SUCRA
SMV12PR24/48_150mg[b]					[redacted]
TVR12PR24/48	1.27	[redacted]	[0.81 ; 2.00]	[redacted]	[redacted]
BOC44PR48	1.36	[redacted]	[0.89 ; 2.09]	[redacted]	[redacted]
TVR12PR48	1.58	[redacted]	[0.78 ; 3.16]	[redacted]	[redacted]
BOC24PR28/48	1.62	[redacted]	[1.04 ; 2.50]	[redacted]	[redacted]
TVR12PR24	2.00	[redacted]	[1.14 ; 3.49]	[redacted]	[redacted]
BOC24PR28	2.61	[redacted]	[1.44 ; 4.74]	[redacted]	[redacted]

[a] SVR at 12 weeks or 24 weeks (primary efficacy endpoint in each clinical trial)
BOC24PR28 - Boceprevir therapy for 24 weeks in combination with PR for 28 weeks; BOC24PR28/48 - Boceprevir therapy for 24 weeks in combination with PR for either 28 or 48 weeks (guided therapy); BOC44PR48 - Boceprevir therapy for 44 weeks in combination with PR for 48 weeks; SMV12PR24/48 - Simeprevir therapy for 12 weeks in combination with PR for either 24 or 48 weeks (guided therapy); TVR12PR24 - Telaprevir therapy for 12 weeks in combination with PR for 24 weeks; TVR12PR48 - Telaprevir therapy for 12 weeks in combination with PR for 48 weeks; TVR12PR24/48 - Telaprevir therapy for 12 weeks in combination with PR for either 24 weeks or 48 weeks (guided therapy).
[b] data excluded from the simeprevir arm for patients who were Q80K-positive

Treatment-experienced patients: prior relapsers (PROMISE)

The proportion of trial participants with SVR12 was statistically significantly higher in the simeprevir + PR group compared to the placebo + PR group (simeprevir + PR 79.2% versus placebo + PR 36.1%, p<0.001) (Table 8).

Table 8 SVR12 following treatment with simeprevir + PR or placebo + PR in prior relapsers

Primary end-point (ITT analysis)	Simeprevir + PR	Placebo + PR	Mean difference (95% CI); p-value
% (n/N) of subjects with SVR12 From MS and paper[8]	79.2 (206/260)	36.1[a] (48/133)	43.8 (34.6 to 53.0)[b]; p<0.001

[a] value given in CSR[3] is [redacted]; [b] Mean difference and 95% CI controlling for stratification factors of HCV genotype 1 subtype and IL28B genotype.[8] PR: peginterferon + ribavirin.

Treatment-experienced patients: null and partial responders (interim data from ATTAIN)

The proportion of trial participants with SVR12 was reported for the overall population and separately for the subgroups that were prior null responders and those who were prior partial responders (Table 9). For the overall trial population and both subgroups of participants simeprevir + PR treatment resulted in similar proportions of participants achieving SVR12 in

comparison to telaprevir + PR treatment indicating that simeprevir + PR treatment is non-inferior to telaprevir + PR treatment (overall population simeprevir + PR 53.6% versus telaprevir + PR 54.7%, non-inferior p<0.001).

Table 9 SVR12 following treatment with simeprevir + PR or telaprevir + PR in null and partial responders

Primary end-point (from MS, poster[4] and interim CSR[9])	**Simeprevir + PR**	**Telaprevir + PR**	**Mean difference weighted by stratification factors (95% CI); p-value**
% of subjects with SVR12 Overall population (ITT analysis)	53.6 (203/379)	54.7 (210/384)	-1.1 (-7.8 to 5.5); p<0.001 non-inferior
% of subjects with SVR12 Overall population (per protocol analysis)	[redacted]	[redacted]	[redacted]
- prior null responders (ITT analysis)	43.6 (102/234)	46.2 (110/238)	-2.8 (-11.3 to 5.8); p<0.001 non-inferior
- prior partial responders (ITT analysis)	69.7 (101/145)	68.5 (100/146)	1.5 (-9.0 to 12.0); p<0.001 non-inferior

PR: peginterferon + ribavirin.

The fixed effect MTC considered all treatment-experienced participants together (prior relapsers, null and partial responders). Two simeprevir treatment regimens were considered separately [simeprevir + 24 or 48 weeks PR (PROMISE) and simeprevir + 48 weeks PR (ASPIRE & ATTAIN)]. The fixed effect MTC median ORs (95% CrI) that were used in the economic model were 9.02 (95% CrI 5.54-15.01) for simeprevir 24 or + 48 weeks PR vs PR, and 8.73 (95% CrI 5.42-14.19) for simeprevir + 48 weeks PR vs PR. Data for telaprevir + PR versus PR came from TVR12PR48 median OR 8.38 (95% CrI 5.41 to 13.15), whereas the boceprevir + PR versus PR economic model input (OR 6.948) was derived from more than one boceprevir +PR treatment regimen. The base case results for each intervention versus PR are displayed in MS Table 38 p.86.

Table 10 shows that for both simeprevir treatment regimens the OR is close to 1 for the comparisons with TVR12PR48, ranging to OR 1.32 (95% CrI 0.58 to 2.92) for SMV12PR48_150mg and 1.37 (95% CrI 0.60 to 3.09) for SMV12PR24/48_150mg in comparison with TVR12PR24. For the comparisons with boceprevir triple therapy regimens ORs range from 1.21 (95% CrI 0.62 to 2.37) to 1.74 (95% CrI 0.84 to 3.61).

Table 10 MTC results SVR12/24[a] in treatment-experienced population (Simeprevir + PR versus telaprevir + PR or boceprevir + PR) reproduced from MS Table 39, p. 86

	SMV12PR48_150mg				SMV12PR24/48_150mg				SUCRA
	median	sd	CrI95%	Prob	median	sd	CrI95%	Prob	
SMV12PR24/48[b]	0.97	[redacted]	[0.48 ; 1.93]	[redacted]					[redacted]
SMV12PR48[b]					1.04	[redacted]	[0.52 ; 2.07]	[redacted]	[redacted]
TVR12PR48	1.04	[redacted]	[0.78 ; 1.38]	[redacted]	1.08	[redacted]	[0.55 ; 2.10]	[redacted]	[redacted]
BOC44PR48	1.21	[redacted]	[0.62 ; 2.37]	[redacted]	1.26	[redacted]	[0.64 ; 2.48]	[redacted]	[redacted]
TVR12PR24	1.32	[redacted]	[0.58 ; 2.92]	[redacted]	1.37	[redacted]	[0.60 ; 3.09]	[redacted]	[redacted]
BOC32PR36/48	1.68	[redacted]	[0.81 ; 3.44]	[redacted]	1.74	[redacted]	[0.84 ; 3.61]	[redacted]	[redacted]

[a] SVR at 12 weeks or 24 weeks (primary efficacy endpoint in each clinical trial)
BOC32PR36/48 - Boceprevir therapy for 32 weeks in combination with PR for either 36 or 48 weeks (guided therapy); BOC44PR48 - Boceprevir therapy for 44 weeks in combination with PR for 48 weeks; SMV12PR24/48 - Simeprevir therapy for 12 weeks in combination with PR for either 24 or 48 weeks (guided therapy); SMV12PR48 - Simeprevir therapy for 12 weeks in combination with PR for 48 weeks; TVR12PR24 - Telaprevir therapy for 12 weeks in combination with PR for 24 weeks ;TVR12PR48 - Telaprevir therapy for 12 weeks in combination with PR for 48 weeks
[b] data excluded from the simeprevir arm for patients who were Q80K-positive

Summary of SVR24 results

Treatment-naive patients (QUEST 1 and QUEST 2)

Data are presented separately for each trial (Table 11). SVR24 rates were statistically significantly higher in the simeprevir + PR groups compared to the placebo + PR groups in both trials (p<0.001).

Table 11 SVR24 following treatment with simeprevir + PR or placebo + PR in treatment-naive patients

Secondary end-point % of subjects with SVR24	**Simeprevir + PR**	**Placebo + PR**	**Mean difference (95% CI); p-value**
QUEST 1 (data from MS)	79.5	49.2	Not reported; p<0.001
QUEST 1 (data from paper[6])[a]	83 (205/247)	60 (18/30)	18.1 (-0.4 to 36.6); p=0.0253[b]
QUEST 2 (data from MS)	80.5	50	Not reported; p<0.001
Pooled data QUEST 1 and QUEST 2	not reported	not reported	not reported

[a] based on data available at the time of the primary analysis. [b] weighted difference. PR: peginterferon + ribavirin.

Treatment-experienced patients: prior relapsers (PROMISE)

The majority of participants who achieved SVR12 went on to achieve SVR24 (simeprevir + PR 97.6% versus placebo + PR 93.8%) (Table 11). SVR24 rate was statistically significantly higher in the simeprevir + PR group compared to the placebo + PR group (simeprevir + PR 77.3% versus placebo + PR 33.8% p<0.001).

Table 12 SVR24 following treatment with simeprevir + PR or placebo + PR in prior relapsers

Secondary end-point	**Simeprevir + PR**	**Placebo + PR**	**Mean difference (95% CI); p-value**
% of subjects with SVR 12 who also achieved SVR24 (n/N) (from MS)	97.6 (201/206)	93.8 (n/N not reported)	not reported
% of subjects with SVR24 (n/N)	77.3	33.8	not reported; p<0.001

PR: peginterferon + ribavirin.

Treatment-experienced patients: null and partial responders (interim data from ATTAIN)

Data are from an interim analysis and therefore SVR24 data were only reported for the subset of participants who had completed a week 72 visit (Table 13). Overall a slightly lower proportion of participants receiving simeprevir + PR achieved SVR24 than those receiving telaprevir + PR (simeprevir + PR 53.7% versus telaprevir + PR 58.1%). In the subgroup of prior null responders a similar pattern was observed (simeprevir + PR 40.5% versus telaprevir + PR 49.4%). For the subgroup of prior partial responders, similar proportions in each treatment arm achieved SVR24 (simeprevir + PR 70.8% versus telaprevir + PR 69.1%). As SVR24 data are from an interim analysis and not available for all participants, the MS also presents data for SVR4 which are available for all patients. The MS comments that for the subgroups of prior null and prior partial responders the complete SVR4 data were very similar to the interim SVR24 data.

Table 13 SVR24 following treatment with simeprevir + PR or telaprevir + PR in prior relapsers

Secondary end-point (from MS and interim CSR[9])	**Simeprevir + PR**	**Telaprevir + PR**	**p-value**
% of subjects with SVR24	n=149	n=155	
- overall population	53.7 (80/149)	58.1 (90/155)	not reported
- prior null responders	40.5 (34/84)	49.4 (43/87)	not reported
- prior partial responders	70.8 (46/65)	69.1 (47/68)	not reported
% of subjects with SVR4 (available for all patients)	n=379	n=384	
- overall population	56.5 (214/379)	58.9 (226/384)	not reported
- prior null responders	46.6 (109/234)	50.0 (119/238)	not reported
- prior partial responders	72.4 (105/145)	73.3 (107/146)	not reported

PR: peginterferon + ribavirin.

Summary of rapid virological response results

Treatment-naive patients (QUEST 1 and QUEST 2)

Data were consistent between the two trials with the majority of patients receiving simeprevir + PR achieving a rapid virological response (RVR) (HCV RNA <25 IU/ml undetectable at week 4) (Table 14). In the pooled data set 77.5% of the simeprevir + PR group had an RVR in comparison to 12.1% of the placebo + PR group (p<0.001).

Table 14 RVR following treatment with simeprevir + PR or placebo + PR in treatment-naive patients

Secondary end-point % of subjects with RVR (n/N)	**Simeprevir + PR**	**Placebo + PR**	**Mean difference (95% CI); p-value**
QUEST 1 (MS and paper[6])	79.5 (202/254)	11.8 (15/127)	68.0 (60.5 to 75.4)[a]; p<0.001
QUEST 2 (MS and paper[7])	79.2 (202/255)	12.8 (17/133)	Not reported; p<0.001
Pooled data QUEST 1 and QUEST 2 (MS and poster[16])	77.5 (404/521)	12.1 (32/264)	Not reported; p<0.001
In the pooled data set the majority of simeprevir + PR patients (77.5%) had HCV RNA <25 IU/ml undetectable at week 4, and in these patients, the SVR12 rate was 90%.			

[a] Mean difference and 95% CI were obtained from a logistic regression model including baseline HCV RNA as a continuous variable with stratification factors of HCV genotype 1 subtype and IL28B genotype.[6]
[b] Note that the denominators for the pooled analyses are greater than the sum of the denominators for the individual studies. The poster[16] states 12 participants in the pooled simeprevir + PR groups and four in the pooled placebo + PR groups had no assessment at week 4. This would be consistent with the discrepancy (i.e. 254+255+12 = 521 and 127+133+4 = 264). PR: peginterferon + ribavirin.

Treatment-experienced patients: prior relapsers (PROMISE)

The majority of patients receiving simeprevir + PR achieved RVR whereas in comparison very few of the placebo + PR group had an RVR (simeprevir + PR 77.2% versus placebo + PR 3.1% p<0.001) (Table 15).

Table 15 RVR following treatment with simeprevir + PR or placebo + PR in prior relapsers

Secondary end-point	Simeprevir + PR	Placebo + PR	Mean difference (95% CI); p-value
% of subjects with RVR (from MS and paper[8])	77.2 (200/259)	3.1 (4/129)	not reported; p<0.001
The majority of simeprevir + PR patients (77.2%) had HCV RNA <25 IU/ml undetectable at week 4, and of these patients 86.5% (173/200) subsequently achieved SVR12			

PR: peginterferon + ribavirin.

Summary of results on proportions meeting response guided treatment criteria

Treatment-naive patients (QUEST 1 and QUEST 2)

The majority (88.2% in the pooled analysis) of simeprevir + PR treated patients met the criteria for response guided treatment (RGT) and therefore could receive PR treatment shortened to 24 weeks (Table 16).

Table 16 Response guided treatment with simeprevir + PR or placebo + PR in treatment-naive patients

Secondary end-point % (n/N) meeting RGT - protocol defined criteria (PR treatment shortened to 24 weeks)	Simeprevir + PR	Placebo + PR
QUEST 1 (MS and paper[6])	85.0 (224/264) [90.6% (203/224) achieved SVR12]	not reported
QUEST 2 (MS and paper[7])	91.4 (235/257) [86% (202/235) achieved SVR12]	not reported
Pooled data QUEST 1 and QUEST 2	88.2 (459/521) [88.2% (405/459) achieved SVR12)	not reported

PR: peginterferon + ribavirin.

Treatment-experienced patients: prior relapsers (PROMISE)

The majority (92.7%) of simeprevir + PR treated patients met the criteria for RGT and therefore could receive PR treatment shortened to 24 weeks (Table 17). The majority of these patients (83%) then went on to achieve SVR12.

Table 17 Response guided treatment with simeprevir + PR or placebo + PR in prior relapsers

Secondary end-point (from MS and paper[8])	**Simeprevir + PR**	**Placebo + PR**
% (n/N) meeting RGT - protocol defined criteria (PR treatment shortened to 24 weeks)	92.7 (241/260) [83% (200/241) achieved SVR12]	not applicable
The majority of patients (75.8%) had HCV RNA levels of <25 IU/ml undetectable at week 4, and in these, the SVR12 rate was 87.3%. A total of 44 patients (16.9%) who met the protocol-defined RGT criteria had HCV RNA <25 IU/ml detectable at week 4, with an SVR12 rate of 63.6%.		

PR: peginterferon + ribavirin.

Treatment-experienced patients: null and partial responders (interim data from ATTAIN)

There was no response-guided therapy in the ATTAIN trial

Summary of virologic relapse and failure results

The terms ‘virologic relapse’ and ‘virologic failure’ were not always clearly defined within the MS and supporting references. The ERG has included a definition for each outcome if this was provided in the MS or supporting references.

Treatment-naive patients (QUEST 1 and QUEST 2)

The failure rate (=viral relapse) after the end of treatment in the pooled analysis among patients with undetectable HCV RNA and who had available follow-up data (numbers not reported) was lower in the simeprevir + PR group than in the placebo + PR group (pooled data 10% simeprevir + PR versus 15% placebo + PR, p-value not reported) (Table 18). On-treatment failure rates were also lower in the simeprevir + PR group in both trials (pooled data 8% simeprevir + PR versus 33% placebo + PR, p-value not reported).

Table 18 Post-treatment relapse and on-treatment failure with simeprevir + PR or placebo + PR in treatment-naive patients

Secondary end-point	Simeprevir + PR	Placebo + PR
Post-treatment relapse (patients with undetectable HCV RNA at end of treatment), % (n/N)		
QUEST 1 (paper[6])	9 (21/234)	21 (18/84)
QUEST 2 (paper[7])	13 (30/236)	24 (21/88)
Pooled data QUEST 1 and QUEST 2 (MS and poster[16])	10[a]	15[a]
On-treatment failure (HCV RNA confirmed detectable at end of treatment) rates % (n/N)		
QUEST 1	9 (24/264)	34 (44/130)
QUEST 2	7 (18/257)	32 (43/134)
Pooled data QUEST 1 and QUEST 2 (MS and poster[16])	8%	33%
The MS states that data from QUEST 1 and QUEST 2 suggest that approximately 7% of patients would stop treatment with simeprevir + PR at week 4 (9.4% in QUEST 1 and 4.3% in QUEST 2), according to the stopping rules in the product licence.		

[a] There is a discrepancy between these percentages and those that can be obtained by simple pooling of the n/N data for QUEST 1 and QUEST 2 (QUEST 1: 21/234 + 30/236 = 51/470 = 10.9%; QUEST 2: 18/84 + 21/88 = 39/172 = 22.7%). PR: peginterferon + ribavirin.

Treatment-experienced patients: prior relapsers (PROMISE)

The relapse rate after the end of treatment among patients with undetectable HCV RNA and who had available follow-up data was lower in the simeprevir + PR group than in the placebo + PR group (18.5% simeprevir + PR versus 48.4% placebo + PR, p-value not reported) (Table 19). On treatment failure rates were also lower in the simeprevir + PR group (3.1% simeprevir + PR versus 27.1% placebo + PR, p-value not reported).

Table 19 Post-treatment relapse and on-treatment failure with simeprevir + PR or placebo + PR in prior relapsers

Secondary end-point (from MS and paper[8])	**Simeprevir + PR**	**Placebo + PR**
Post-treatment relapse (%) among patients with undetectable HCV RNA at end of treatment	18.5 (46/249)	48.4 (45/93)
On treatment failure rate (%) among patients with confirmed detectable HCV-RNA levels at end of treatment	3.1 (8/260)	27.1 (36/133)
Five patients in the simeprevir + PR group with viral relapse achieved SVR12 but subsequently had viral relapse at the SVR24 assessment time point. The MS states that data from PROMISE suggest that in clinical practice, 4.6% of patients would stop treatment with simeprevir + PR at week 4, according to the stopping rules in the simeprevir licence.		

PR: peginterferon + ribavirin.

Treatment-experienced patients: null and partial responders (interim data from ATTAIN)

Data are not presented separately for the two patient subgroups (prior null responders and prior partial responders) (Table 20). Virologic failure (a composite outcome including those who did not achieve SVR12 or relapsed after SVR12), on treatment failure and post-treatment relapse occurred with similar frequency in both treatment groups (no p-values provided).

Table 20 Failure and relapse with simeprevir + PR or telaprevir + PR in null and partial responders

Secondary end-point	**Simeprevir + PR**	**Telaprevir + PR**
Virologic failure (not achieved SVR12 or relapsed after SVR12), % (n/N) (from MS and interim CSR[9])	46.4 (176/379)	45.8 (176/384)
On treatment failure (confirmed detectable HCV RNA levels at actual end of treatment), % (n/N) (from presentation[4])	34.3 (130/379)	32.3 (124/384)
Post-treatment relapse (%) (not explicitly defined but ERG believes this is relapsed after SVR12) (from MS and interim CSR[9])	12.1 (46/379)	13.5 (52/384)
Viral relapse (Among all patients with undetectable HCV RNA at end of treatment), % (n/N) (from presentation[4] and interim CSR[9])	17.5 (43/246)	16.8 (43/256)
Data from ATTAIN suggests that in clinical practice, 19.6% of patients overall (23.5% null responders and 13.3% partial responders) would stop treatment with simeprevir + PR at week 4, according to the stopping rules in the simeprevir licence.		

PR: peginterferon + ribavirin.

Summary of Health related quality of life

The MS (p. 57-62) presents results from each of the four phase 3 RCTs for the following PROMs: EuroQol 5-Dimension Questionnaire (EQ-5D) measured by the visual analogue scale and the descriptive system; Fatigue Severity Score (FSS); Work Productivity and Activity Impairment Index (WPAI) (productivity and activity scales); and Center for Epidemiologic Studies Depression Scale (CES-D). Clinically meaningful changes for the FSS, WPAI and CES-D scores were defined in a separate referenced PROM summary report.[23]

PROMs were assessed in all the phase 3 RCTs at 0, 4, 12, 24, 36, 48, 60 and 72 weeks, with the 72-week results stated as being interim. The MS does not discuss response rates and attrition for these outcomes, although Figures presented in the MS (p. 57-61) for some of the PROMs do provide numbers of subjects for each time point, indicating that there were missing data. Reasons for missing data are not given but the numbers of participants are generally balanced across the study groups at each time point. Overall, the ERG considers that the results presented for the PROMs appear reliable.

Results of these PROMs are not used in the manufacturer's economic model base case. As such, a brief summary of the key HRQoL results is provided here. This is based on information presented graphically in the MS (Figs 18-23, p. 58-61) and the PROM summary report.[23]

HRQoL results: simeprevir + PR compared against placebo + PR

The MS summarises HRQoL results pooled from the QUEST 1, QUEST 2 and PROMISE RCTs. Further detail is given in a supporting PROM summary report on the pooled HRQoL analyses.[23] The MS and supporting PROM summary report[23] do not present separate results for treatment-naive and experienced patients. However, standard errors for the pooled results are relatively small (MS Figs 20-23) suggesting that responses were similar for treatment-experienced and naive patients.

Scores for the EQ-5D Valuation Index, FSS, WPAI productivity scale, WPAI activity scale and CES-D showed similar patterns (MS Figs 20-23, p. 60-61). In the simeprevir + PR group the scores indicated that a negative effect (i.e. a decrease in EQ-5D, or an increase in FSS, WPAI, or CES-D) occurred for all measures during weeks 4 to 24, with scores thereafter returning to baseline values (weeks 36 to 72). In the placebo + PR group the scores indicated a negative effect on all measures from weeks 4 to 48, with scores thereafter returning to baseline values

(weeks 60 to 72). The difference between study groups was clinically meaningful for the three instruments where a clinically meaningful difference had been defined (FSS, WPAI, CES-D).

The pattern of results for the five PROs indicates that negative effects on patients' wellbeing were initially of similar magnitude in both the simeprevir + PR and placebo + PR groups, but the duration of effects was consistently shorter in the simeprevir + PR group. The PROM summary report on the pooled outcomes[23] concluded that the duration of worsening in symptoms and functional limitations corresponded with the duration of PR therapy received by most of the patients in each treatment group (i.e. 24 weeks for simeprevir + PR and 48 weeks for placebo + PR). Negative effects of simeprevir + PR on PROMs therefore reflect the PR component of the simeprevir or placebo regimen and did not persist once the regimen was stopped.

HRQoL results: simeprevir + PR compared against telaprevir + PR

The MS presents interim data on PROMs from the ATTAIN RCT. In both groups EQ-5D VAS scores (MS Fig. 18, p. 58) declined from baseline and remained below baseline levels to week 48 but had recovered to be at or slightly above baseline scores by week 60. The MS suggests narratively (p. 58) that scores on the EQ-5D Valuation Index showed a similar pattern to the VAS scores (no quantitative data are reported in the MS).

Fatigue (FSS scores) (MS Fig. 19, p. 59) in both groups increased (worsened) after baseline and remained higher than baseline values up to week 48, then at week 60 declined below baseline and remained below baseline up to week 72.

WPAI daily activity and work impairment scores did not differ between the treatment groups at any point during the study (narrative on MS, p. 59; no quantitative data are reported in the MS).

CES-D depression scores in weeks 4-12 were worse for telaprevir than simeprevir, but from week 16 onwards were the same in both groups (narrative on MS, p. 59; no quantitative data are reported in the MS).

Overall, the results for the EQ-5D and FSS suggest that during the first 12 to 16 weeks of therapy effects of telaprevir on patients' wellbeing are worse than those of simeprevir but both regimens have similar effects on these PROMs during the dual (PR) phase of the therapy up to 48 weeks; once patients were no longer receiving treatment the scores returned to baseline

values. According to the MS (p. 58) this pattern reflects negative effects of the regimens on haemoglobin levels and anaemia.

HRQoL results: key points

- Negative effects of simeprevir + PR on patients' PROMs including HRQoL appear to be driven by the duration of the PR component of the therapy (shorter duration of the PR component led to shorter duration of negative effects).
- Compared to simeprevir + PR, telaprevir + PR had stronger negative effects on PROMs although these did not persist once the telaprevir component of the therapy ended.
- The clinical trials do not provide any long-term HRQoL or other PROM results beyond end of therapy (i.e. after 72 weeks from baseline).
- The ERG notes that EQ-5D results from all six RCTs, including the phase 2 trials PILLAR and ASPIRE, informed a scenario analysis of on-treatment utility decrements in the manufacturer's economic model (see section 4.2.5). Data used in the scenario analysis are given in the health economics section of the MS in Table 92 (MS p. 161). However, the MS does not present any further HRQoL results for the phase 2 RCTs.

3.3.2 Sub-group analyses results for HCV genotype 1

The MS reports subgroup analyses for SRV12 by:

- HCV genotype (QUEST 1, QUEST 2, PROMISE, ATTAIN)
- Fibrosis score (QUEST 1, QUEST 2, PROMISE)
- Cirrhosis status (ATTAIN)
- European patients (QUEST 1, QUEST 2, PROMISE)
- Interferon type (QUEST 2)

Additional subgroup analyses were reported in published papers but not in the MS (e.g. by IL28B genotype, baseline HCV RNA concentration, sex).

HCV genotype

Simeprevir + PR is not licensed for the subgroup of patients with the Q80K polymorphism. Data were presented according to genotype 1a with Q80K, genotype 1a without Q80K, and genotype 1b. SVR12 rates were reduced in patients treated with simeprevir + PR with the HCV genotype 1a Q80K polymorphism for both treatment-naive patients (MS Figure 8, p.51) and prior

relapsers (MS Figure 11, p.53). The benefit of both simeprevir + PR and telaprevir + PR was lower for treatment-experienced patients with the Q80K polymorphism (MS Figure 14, p.55).

Fibrosis score or cirrhosis status

The benefit of simeprevir + PR treatment over placebo + PR treatment was observed for each of the subgroups by fibrosis score (F0-1, F3 or F4):

- Treatment-naive patients (QUEST 1 and QUEST 2), MS Table 17, p. 51.
- Prior-relapsers (PROMISE), MS Table 18, p.53.

The proportion of patients achieving SVR12 was similar between simeprevir + PR and telaprevir + PR for both those with and without cirrhosis. Patients with no cirrhosis achieved higher rates of SVR12 than those with cirrhosis (MS Figure 15, p.56). The highest SVR12 rates were in the subgroup of non-cirrhotic prior partial responders (simeprevir + PR 72.9%; telaprevir + PR 72.3%), with the lowest SVR12 rates being in the group of cirrhotic prior null responders (simeprevir + PR 24.6%; telaprevir + PR 31.3%).

European patients

Patients enrolled into the trials from European countries represented just over half of the patients enrolled in either QUEST1 or QUEST2 and over two thirds of patients included in the PROMISE trial. The proportions of European patients achieving SVR12 in these studies was slightly higher (up to 8.3% higher for the simeprevir + PR arms) than in the trial populations overall (MS p.52 and p.54).

Interferon type

The benefit of simeprevir + PR over placebo + PR was observed for regimens with both peginterferon alpha-2a and peginterferon alpha-2b in treatment-naive patients (QUEST 2,[7] MS p.50). SVR12 rates were higher in patients treated with peginterferon alpha-2a versus peginterferon alpha-2b in both arms (88.3% versus 77.5% for simeprevir + PR; 62.2% versus 41.9% for placebo +PR).

3.3.3 Summary of non-RCT results

Evidence for simeprevir in patients with HCV genotype 4, patients co-infected with HCV genotype 1 and HIV, and patients treated with an interferon-free regimen (either with or without ribavirin) comes from non-comparative trials because there are no comparative trials in these patient populations:

- HCV genotype 4 patients (RESTORE);
- HCV patients co-infected with HIV (C212);
- Simeprevir in combination with sofosbuvir ± ribavirin (COSMOS).

In view of the non-comparative nature of these studies a summary of SVR12 results is presented for each study. Other outcomes (e.g. SVR 24, RVR, RGT, virologic relapse and failure) including some subgroup analyses are presented in the MS (MS section 6.8: RESTORE results p.101-102, C212 results p.106-107, COSMOS results p.110-111).

HCV genotype 4 patients (RESTORE)

Overall 65.4% of patients with HCV genotype 4 achieved SVR12 (Table 21). Individual patient data for SVR12 were used in the MAIC critiqued in section 3.1.7.

Table 21 SVR12 following treatment with simeprevir + PR in patients with HCV genotype 4

Primary end-point	Simeprevir + PR
SVR12, % (n/N) (from MS & paper[21])	
Overall	65.4 (70/107)
- treatment-naive	82.9 (29/35)
- prior relapsers	86.4 (19/22)
- partial responders	60.0 (6/10)
- null responders	40 (16/40)

PR: peginterferon + ribavirin.

HCV genotype 1 patients co-infected with HIV (C212)

Overall 73.6% of HCV genotype 1 patients co-infected with HIV achieved SVR12 (Table 22).

Table 22 SVR12 following treatment with simeprevir + PR in patients with HCV genotype 1 and coinfected with HIV

Primary end-point	Simeprevir + PR
% of subjects with SVR12	
Overall (n=106)	73.6 (78/106)
- treatment-naive (n=53)	79.2 (42/53)
- prior relapsers (n=15)	86.7 (13/15)
- partial responders (n=10)	70.0 (7/10)
- null responders (n=28)	57.1 (16/28)

PR: peginterferon + ribavirin.

Simeprevir in combination with sofosbuvir ± ribavirin in an interferon-free regimen (COSMOS)

Data in the MS were taken from an interim analysis. There are two cohorts of patients with HCV genotype 1:

- prior null responders without advanced liver fibrosis (n=80 enrolled at database lock & all had completed)
- prior null responders or treatment-naive patients with advanced liver fibrosis (n=87 enrolled at database lock 84 of whom still participating).

The study had four arms, two of which received simeprevir for 24 weeks which is not in line with the product licence of 12 weeks of therapy.

Overall over 90% of patients with HCV genotype 1 treated with simeprevir in combination with sofosbuvir ± ribavirin in an interferon-free regimen achieved SVR12 (Table 23).

Table 23 SVR12 in patients with HCV genotype 1 following treatment with simeprevir + sofosbuvir ± ribavirin in an interferon-free regimen

Primary end-point % of patients with SVR12	COHORT 1	COHORT 2
Overall	90.0 (n=80)	94.3 (n=87)
- SMV + SOF + RBV (24 weeks)	79.2 (n=24)	93.3 (n=30)
- SMV + SOF (24 weeks)	93.9 (n=15)	100.0 (n=16)
- SMV + SOF + RBV (12 weeks)	96.3 (n=27)	92.6 (n=27)
- SMV + SOF (12 weeks)	92.9 (n=14)	92.9 (n=14)

RBV: ribavirin; SOF: sofosbuvir; SMV: simeprevir

3.3.4 Summary of adverse events

Trial data

The MS summarises data on adverse events in genotype 1 patients from four studies (QUEST 1, QUEST 2, PROMISE, and ATTAIN). Three of these trials (QUEST 1, QUEST 2 and PROMISE) assessed simeprevir + PR versus placebo + PR with safety a secondary objective. The MS indicates (Appendix 14, p. 305) that it was appropriate to pool adverse event data from these three trials because

i. study designs were identical apart from that in QUEST 2 either peginterferon alfa-2a or peginterferon alfa-2b was used (the other two studies used peginterferon alfa-2a) and prior treatment status differed [treatment-naive in QUEST 1 and QUEST 2, treatment-experienced (prior relapsers) in PROMISE]
ii. Phase IIb study results suggested that treatment history would not affect the safety profile

A rationale for pooling the studies is not provided in the MS however the supporting reference[24] cited in the MS states the rationale for pooling was "to increase the likelihood of detecting infrequent events by increasing the number of subjects per pooled treatment group and to increase the sample size for subgroup analyses." Because of the stated similarity between the trials that have been pooled, a meta-analysis of adverse events data might also have been appropriate. The fourth RCT (ATTAIN) assessed simeprevir + PR versus telaprevir + PR in a non-inferiority trial, where safety was a secondary outcome.

Some adverse event data tables in the MS do not appear to be consistent with one another for example MS Table 72 and MS Table 73 (MS pages 120-121) which both report on pruritus, rash, neutropenia and anaemia with differing values presented in each table. The ERG believes that whereas MS Table 72 is reporting by preferred term (as stated in the column heading) MS Table 73 is reporting by type (where adverse event type can included more than one preferred term, hence values in MS Table 73 are slightly higher than those in Table 72). Data contributing to the MTC appear to be based on adverse events reported by preferred term.

The included non-randomised evidence provided additional adverse event data. Adverse events reported in HCV genotype 4 patients are available from one study (RESTORE). Similarly one study provides information on adverse events in HCV genotype 1 patients co-infected with HIV (C212) and another study provides adverse event data for HCV genotype 1

patients treated with simeprevir in combination with sofosbuvir (COSMOS) (See '*Summary of Non-RCTs adverse event data*' below).

No adverse event data from the PILLAR and ASPIRE studies are included in the MS section on Adverse events (MS section 6.9, p. 112) however data from both of these studies contributes to the MTC outcomes for adverse events (MS p. 74-75). A brief summary of adverse events for these studies is reported in the MS Appendix 10.14 section 10.14.2.1 p. 294 for ASPIRE and section 10.14.2.2 p. 296 for PILLAR.

Simeprevir + PR vs placebo + PR in HCV genotype 1

The most common adverse events among the simeprevir + PR treated patients were known adverse events associated with PR treatment. Of these, only pruritus occurred with a higher incidence in simeprevir + PR patients (20.6% versus 13.6% in placebo + PR patients) (MS Table 72 p.120). The proportion of patients with any serious adverse event was similar during the first 12 weeks of treatment (simeprevir + PR 2.0%, placebo + PR 2.5%) and over the whole treatment phase (simeprevir + PR 5.1% vs placebo + PR 7.1%). There were three serious adverse events with fatal outcome (0.4%) in the simeprevir + PR group (after the 12 week simeprevir treatment phase) but none in the placebo + PR group. The incidence of some adverse events of special or clinical interest (MS Table 73 p.121) was higher among patients treated with simeprevir + PR (increased bilirubin, rash, pruritus, photosensitivity conditions, dyspnoea) whereas the incidence of neutropenia and anaemia was similar to patients treated with placebo + PR. Treatment discontinuation of at least one drug was lower in patients receiving simeprevir + PR.

Simeprevir + PR versus telaprevir + PR in HCV genotype 1

Types of adverse events were similar in both groups, most were grade 1 or 2 (MS Table 67, p. 113) and all were known adverse events associated with PR treatment. Differences in adverse events between simeprevir + PR and telaprevir + PR were typically in favour of simeprevir + PR, the biggest exceptions being cough ([redacted]) and neutropenia ([redacted]) (MS Table 68, p. 115). During the entire treatment phase the proportion of patients with any serious adverse event was lower in the simeprevir + PR group ([redacted]. Differences in adverse events of special or clinical interest (MS Table 69,

p. 116) were also typically in favour of simeprevir + PR with the exception of photosensitivity conditions (entire treatment phase simeprevir + PR [redacted] versus [redacted] telaprevir + PR). Treatment discontinuations were lower in patients receiving simeprevir + PR.

MTC results for adverse events in HCV genotype 1 patients

The adverse event data reported in the systematic review of clinical effectiveness and summarised above were pooled for those trials which investigated simeprevir + PR versus placebo + PR [ie. QUEST 1 and 2 (in treatment-naive patients), and PROMISE (in treatment-experienced patients)]. Consequently these data are not directly comparable with the MTC results where treatment-naive and treatment-experienced patients are considered in separate analyses. All these MTC results are from a fixed effect model. It should be noted that MS Table 36 (MS p.85) and Table 44 (MS p.88) report *mean* ORs for the comparisons of key adverse events versus PR48. However *median* ORs are used in the economic model (for adverse events of neutropenia, pruritus, rash and anaemia) therefore the ERG reports the median odds ratios for these outcomes which are available from the separate MTC report.[17] As the MTC includes more than one regimen for each intervention, the ERG clarifies below the values that are selected for the base case in the manufacturer's economic model. The boceprevir + PR versus PR ORs used in the economic model were derived from more than one boceprevir +PR treatment regimen (section 4.2.4).

MTC results for overall treatment discontinuations and treatment discontinuations due to adverse events can be found in MS tables 32 to 35 (MS p. 83-84) and MS tables 40 to 43 (MS p. 87). In general simeprevir + PR was associated with lower risks of treatment discontinuation than either PR or the telaprevir or boceprevir containing triple therapies (the exception being overall treatment discontinuations in treatment-experienced patients in comparison to other triple therapies MS Table 41, p. 87). These data are not used in the economic model and therefore are not summarised further here.

MTC results for neutropenia

Treatment-naive patients

Simeprevir + PR was associated with a similar risk of neutropenia compared to PR alone which is included in the economic model as a median OR 1.24 (95%CrI 0.88 to 1.78). Data in the economic model for telaprevir + PR versus PR came from TVR12PR24/48 median OR 0.70

(95% CrI 0.47 to 1.04), whereas the boceprevir + PR versus PR (OR 1.53) was derived from more than one boceprevir +PR treatment regimen.

The comparisons of simeprevir + PR versus telaprevir + PR or boceprevir + PR are presented in MS Table 37, p. 85. This shows that with simeprevir triple therapy (SMV12PR24/48) there was a higher risk of neutropenia compared to telaprevir but a lower risk when compared to boceprevir (except for the BOC24PR28 regimen).

Treatment-experienced patients

Neutropenia data were not available for all trials therefore there are no results for T12PR24 and B32PR36/48. In comparison to PR results for simeprevir + PR differed with SMV12PR48 being associated with a higher or similar risk of neutropenia (median OR 1.77 [redacted]) and SMV12PR24/48 associated with a lower risk: 0.71 [redacted]. In the economic model these values are combined (section 4.2.4) and the OR used is [redacted]. Data in the economic model for telaprevir + PR versus PR came from TVR12PR48 median OR 1.51 (95% CrI [redacted]), and for boceprevir + PR versus PR (BOC44PR48 OR 2.14, 95% CrI [redacted]).

The comparisons of simeprevir + PR versus telaprevir + PR or boceprevir + PR are presented in MS Table 45, p. 88. Simeprevir (SMV12PR24/48) was associated with a lower risk of neutropenia compared to telaprevir and boceprevir.

MTC results for pruritus

Treatment-naive patients

Simeprevir + PR was associated with a higher risk of pruritus compared to PR48 alone incorporated in the economic model as a median OR 1.18 95% CrI 0.87 to 1.61). Data in the economic model for telaprevir + PR versus PR came from TVR12PR24/48 median OR 1.75 (95% CrI 1.30 to 2.35), data used in the economic model for boceprevir + PR versus PR (OR 0.923) were derived from more than one boceprevir +PR treatment regimen.

The comparisons of simeprevir + PR versus telaprevir + PR or boceprevir + PR are presented in MS Table 37, p. 85. Simeprevir + PR was associated with a higher risk of pruritus than boceprevir + PR but a lower risk than with telaprevir + PR.

Treatment-experienced patients

Simeprevir + PR was associated with a similar or higher risk of pruritus compared to PR48 alone (SMV12PR24/48 median OR 1.03 [redacted]; SMV12PR48 median OR 2.09.[redacted]). In the economic model these values are combined (section 4.2.4) to provide the value used (OR [redacted]). Data for telaprevir + PR versus PR came from TVR12PR48 median OR 2.94 (95% CrI [redacted]), and for boceprevir + PR versus PR from BOC44PR48 OR 1.14, 95% CrI [redacted]).

In comparison to the other triple therapies, simeprevir + PR was associated with probabilities of a lower risk of pruritus compared to telaprevir (MS Table 45, p. 88). The outcome for the comparison with boceprevir was different for SMV12PR24/48 and SMV12PR48 with the former being associated with odds ratios of 0.92 (95% CrI [redacted]) and 0.87 (95% CrI [redacted]) for lowering the risk of pruritus compared to boceprevir but this was not the case [OR 1.88 (95% CrI [redacted]) and OR 1.78 (95% CrI [redacted]) with SMV12PR48.

MTC results for rash

Treatment-naive patients

Simeprevir + PR was associated with a similar risk of rash compared to PR48 alone which is included in the economic model as a median OR 1.16;[redacted]). Data for telaprevir + PR versus PR came from TVR12PR24/48 median OR 1.80[redacted], data used in the economic model for boceprevir + PR versus PR ([redacted]) were derived from more than one boceprevir +PR treatment regimen.

In comparison to the other triple therapies simeprevir + PR was associated with a similar risk of rash compared to boceprevir (median ORs of 1.08 and 1.01 versus B44PR48 and B24PR28/48 respectively) and a lower risk compared to telaprevir triple therapy (MS Table 37, p. 85).

Treatment-experienced patients

Simeprevir + PR was associated with a similar or higher risk of rash compared to PR48 alone (SMV12PR24/48 median OR 0.92,[redacted]; SMV12PR48 median OR 1.46[redacted]). In the economic model the OR for simeprevir + PR is [redacted] is obtained by combining these data (section 4.2.4). Data for telaprevir + PR versus PR came from TVR12PR48 median OR 2.49 (95% CrI [redacted]), data used in the economic model for

boceprevir + PR versus PR (OR [redacted]) were derived from more than one boceprevir +PR treatment regimen.

The comparisons of simeprevir + PR versus telaprevir + PR or boceprevir + PR are presented in MS Table 45, p. 88. Simeprevir + PR was associated with a lower risk of rash compared to both boceprevir and telaprevir triple therapies.

MTC results for anaemia

Treatment-naive patients

Simeprevir + PR was associated with a lower risk of anaemia compared to PR48 alone which is reflected in the model as a median OR 0.80[redacted]. Data for telaprevir + PR versus PR for the economic model came from TVR12PR24/48 median OR 2.47[redacted], data used in the economic model for boceprevir + PR versus PR ([redacted]) were derived from more than one boceprevir +PR treatment regimen.

The comparisons of simeprevir + PR versus telaprevir + PR or boceprevir + PR are presented in MS Table 37, p. 86. Simeprevir triple therapy is associated with a lower risk of anaemia than both telaprevir and boceprevir triple therapies.

Treatment-experienced patients

Simeprevir + PR was associated with a lower or similar risk of anaemia compared to PR48 alone (SMV12PR24/48 median OR 0.86,[redacted]; SMV12PR48 median OR 1.01,[redacted]). In the economic model the values are combined (section 4.2.4) to generate an OR for simeprevir + PR of [redacted]. Data for telaprevir + PR versus PR for the economic model came from TVR12PR48 median OR 2.12 [redacted], whereas data for boceprevir + PR versus PR ([redacted]) were derived from more than one boceprevir +PR treatment regimen.

In comparison to the other triple therapies simeprevir + PR was associated with a lower risk of anaemia (MS Table 45, p. 89).

Summary of Non-RCTs adverse event data

RESTORE: HCV genotype 4 patients

The overall incidence of adverse events in the RESTORE study was 98.1%. The majority of adverse events (98/107) were grade 1 or 2 in severity although adverse events of Grade 3 (5.6% of patients) and Grade 4 (0.9% of patients) were also reported. During the entire study treatment period 7.5% of patients experienced a serious adverse event and none were fatal. One patient (0.9%) discontinued simeprevir because of adverse events. The MS states that the tolerability profile of simeprevir +PR, in HCV genotype 4 infected patients, is consistent with that observed in HCV genotype 1 infected patients.

C212: HCV genotype 1 patients co-infected with HIV

The overall incidence of adverse events during the 12-week simeprevir plus PR phase was [redacted] and most were grade 1 or 2. Each grade 3 or 4 adverse event typically occurred in [redacted] of patients except for neutropenia which was reported in [redacted]% of patients. Overall [redacted]% of patients experienced a grade 3 or 4 adverse event and [redacted] (six patients) had serious adverse events during 12-week simeprevir plus PR treatment. [redacted] discontinued treatment due to anaemia which was considered to be related to ribavirin treatment.

Comparison of patients on HAART and not on HAART found no clinically relevant differences in the incidence of AEs in these two groups. No patient on HAART needed to discontinue antiviral treatment because of an adverse event. The MS states that the data suggest simeprevir has a similar safety profile in HIV co-infected patients as seen in chronic HCV mono-infected patients (data not presented in the MS).

COSMOS: HCV genotype 1 receiving simeprevir+sofosbuvir in an interferon-free regimen

For participants receiving 12-weeks of treatment the incidence of adverse events was 85.2% (study arm with ribavirin) and 71.4% (study arm without ribavirin). The majority of adverse events were grade 1 or 2 in severity with grade 3/4 adverse events reported in fewer than [redacted] of patients in each arm (MS Table 74, p. 122). Adverse events reported in more than 15% of patients did not lead to treatment discontinuation or ribavirin dose reduction and most were grade 1 or 2 in severity.

3.4 Summary

The ERG considers that the MS presents a generally unbiased estimate of the treatment effect for HCV genotype 1 patients within the stated scope of the decision problem. The MS is based on a systematic review of effectiveness which includes four phase three RCTs, judged to be of reasonable quality, conducted in HCV genotype 1 patients. Three of these RCTs compare simeprevir + PR against placebo + PR (two in treatment-naive patients, one in treatment-experienced patients) and one compares simeprevir + PR against telaprevir + PR in treatment-experienced patients. An MTC provides supporting evidence for patients with HCV genotype 1 treated with simeprevir + PR. For patients with HCV genotype 4, HCV genotype 1 patients co-infected with HIV and patients with HCV genotype 1 treated with an interferon-free regimen the only evidence available comes from a single uncontrolled study for each of the three populations. The ERG believes there is the potential for bias in these three open label observational studies.

The MS states that in comparison to the most efficacious treatment for HCV genotype 1 patients in current clinical practice (telaprevir + PR or boceprevir + PR), simeprevir + PR improves the proportion of patients with HCV genotype 1 achieving SVR providing they are Q80K negative. The MS states that the MTC supports the trial data indicating that simeprevir + PR is likely to be the most efficacious treatment in comparison to telaprevir + PR or boceprevir + PR for both treatment-naive and treatment-experienced patients. The MS highlights the reduced pill burden (achieved because simeprevir is given as a once daily capsule and because treatment-naive and prior-relapse patients have shortened duration of PR treatment) and the better adverse event profile with simeprevir +PR from the single head-to-head RCT with telaprevir + PR in null and partial responders (ATTAIN study) for rash, pruritus and anaemia.

For HCV genotype 4 patients the MS states that simeprevir has good efficacy and tolerability. The MS indicates that the evidence base also supports the use of simeprevir + PR in HIV-co-infected patients and in an interferon-free regimen.

The manufacturer's interpretation of the evidence presented in the MS is on the whole appropriate and justified. However, the ERG has some concerns and has identified some uncertainties. These are presented below:

- The ATTAIN trial is ongoing and interim data, based on ITT analyses, were presented in the MS. These interim ITT data may not be conservative for a test of non-inferiority so

both ITT and per protocol analyses would be appropriate as indicated by the MS (Table 14, p. 45-46).

- The manufacturer's MTC for treatment experienced patients considered all treatment-experienced participants together: prior relapsers, null and partial responders. However the effect of simeprevir in the three subgroups of treatment-experienced participants potentially differs. The ERG's view is supported by the separate MTC report[17] which included subgroup analyses of SVR based on prior treatment response. However the absence of the required information in some trials together with the lower sample sizes for each treatment arm meant the analysis was not robust.
- There were a low number of trials available to inform the network of evidence for the MTC with the majority of connections informed by only one trial. RCTs with simeprevir dosing regimens that were different to the UK licensed indication were excluded.
- Evidence for the treatment effect in HCV genotype 4 patients comes from a single ongoing uncontrolled trial that enrolled 107 patients (75 patients completed). Participants included treatment-naive and treatment-experienced (prior relapsers, prior null and partial responders) patients. Analysis by treatment experience shows the effect of simeprevir differs among the groups but sample sizes are small. Data for treatment-naive patients were used in an MAIC conduced to inform the economic model but the ERG cautions that the results of the matching exercise may not be reliable.
- Evidence for the treatment effect in HCV genotype 1 patients co-infected with HIV comes from a single uncontrolled trial that enrolled 109 patients. Participants included treatment-naive and treatment-experienced (prior relapsers, prior null and partial responders) patients. Analysis by treatment experience shows the effect of simeprevir differs among the groups but sample sizes are small. No data are available for HCV genotype 4 patients co-infected with HIV.
- Evidence for treatment effect in patients with HCV genotype 1 treated with simeprevir in an interferon-free regimen (simeprevir + sofosbuvir either with or without ribavirin) comes from a single ongoing uncontrolled study that enrolled 54 (12 weeks SMV + SOF + ribavirin) and 28 (12 weeks SMV + SOF) participants in the arms of the study relevant to this STA. Participants were either treatment-naive or prior null responders. SVR rates were high (over 92%) but not presented by treatment experience. No data are available for HCV genotype 1 patients who were prior relapsers or prior partial responders and no data are available for HCV genotype 4 patients.

- At the time of this STA sofosbuvir was not approved by NICE but if approved, could be considered as a comparator. The ERG conducted a search for sofosbuvir and identified no additional trials that could be included in the MTC.

4 ECONOMIC EVALUATION

4.1 Overview of manufacturer's economic evaluation

The manufacturer's submission to NICE includes:

- a review of published economic evaluations of dual therapy with PR, or triple therapy with either simeprevir, telaprevir or boceprevir with PR.
- a report of an economic evaluation undertaken for the NICE STA process. The cost effectiveness of simeprevir + PR is compared with telaprevir + PR and boceprevir + PR, and also with PR dual therapy, for patients with genotype 1 HCV (for genotype 4 HCV simeprevir + PR is compared to just PR). A comparison is also made of the cost effectiveness of simeprevir in combination with sofosbuvir and ribavirin (SMV + SOF) to simeprevir, telaprevir, or boceprevir triple therapy with PR, and to no antiviral treatment, in genotype 1 patients ineligible for or intolerant to interferon.

Manufacturer's review of published economic evaluations

A systematic search of the literature was conducted by the manufacturer to identify economic evaluations of treatments for patients with genotype 1 or genotype 4 chronic hepatitis C. The review included economic evaluation studies of dual therapy (PR); and triple therapy (either simeprevir, telaprevir or boceprevir with PR) in patients with genotype 1 or genotype 4 chronic hepatitis C.

A total of 43 economic evaluations were included in the systematic review. Of these, ten were conducted in a UK setting, and nine of these explored cost-effectiveness. Only limited discussion of the results of the studies is presented. The MS concluded on the basis of this review that all but one of the dual therapy studies were cost-effective compared to no treatment and to peginterferon alfa and ribavirin at the £20,000 threshold. Triple therapy regimens with boceprevir or with telaprevir in combination with PR were concluded to be generally cost-

effective across most patient sub-groups. No economic evaluations featuring simeprevir were identified in the MS. However, the ERG has identified a 2014 cost effectiveness study of simeprevir and sofosbuvir combination therapy by Hagan and colleagues[25] (summarised below in section 4.2).

CEA Methods

The cost effectiveness analysis (CEA) uses a state-transition Markov model to estimate the cost-effectiveness of simeprevir compared with licensed comparators in genotype 1 or 4 treatment-naive or treatment-experienced patients with chronic hepatitis C. The model uses a lifetime horizon with a one year cycle length (and half cycle correction).

The interventions and comparators are:

- Simeprevir in combination with PR, versus telaprevir or boceprevir in combination with PR, or PR alone for genotype 1 patients;
- Simeprevir in combination with PR versus PR alone for genotype 4 patients;
- Simeprevir in combination with sofosbuvir (SMV + SOF) (with ribavirin) versus licensed comparators (simeprevir, telaprevir or boceprevir in combination with PR), and versus no anti-viral treatment, for genotype 1 patients only.

A separate model has been constructed for each of the three different patient groups: genotype 1, genotype 4 and genotype 1 patients ineligible for or intolerant to peginterferon alfa receiving simeprevir and sofosbuvir combination therapy. The models share a common structure but differ in certain input parameters and assumptions (as described in MS Section 7.6.4 and 7.6.5, and see below). The genotype 1 model base case only includes simeprevir patients who are Q80K polymorphism negative.

Patients enter the model and commence treatment at Metavir grades F0-2 (no or mild fibrosis), F3 (moderate fibrosis) or F4 (compensated cirrhosis). Patients receiving simeprevir and sofosbuvir commence treatment at F3 or F4. Other key assumptions are: that SVR is considered a cure for patients initially in health states F0 to F3 and assumed to be at no risk of HCV reactivation or re-infection; patients cannot spontaneously clear HCV; progression to more severe health states cannot occur during the treatment phase of the model; patients who achieve an SVR experience an improvement over their baseline HRQoL; patients are assumed

to experience a decrement in HRQoL during treatment resulting from treatment-related adverse events. A full list of assumptions is provided in MS Tables 86 and 87 (pages 150-151).

The MS presents sub-group analyses by treatment experience (treatment-naive; prior relapsers, partial responders and null responders) in MS Section 7.9.1. Sub-group analysis for HCV+HIV co-infected patients is not provided, but the MS suggests that cost-effectiveness in this population is expected to be very similar to that observed in the genotype 1 population based on results of the clinical trials.

The model is based on the model assessed in previous NICE technology appraisals (TA252 telaprevir;[26] TA253 boceprevir;[27] TA200 peginterferon alfa and ribavirin for the treatment of chronic hepatitis C;[28] TA106 peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C[29]). The model comprises a 'treatment phase' [0-72 weeks whereby patients receive anti-viral treatment for up to 48 weeks (with separate health states for initial level of fibrosis)], and a post-treatment Markov phase comprising 5 health states covering their remaining lifetime. Annual transition probabilities are used to progress patients through the health states. These are based on treatment effectiveness estimates (treatment phase), or estimates of the natural history of HCV from the literature (post treatment phase).

SVR is the principle measure of clinical effectiveness used in the model. For genotype 1 patients SVR estimates are derived from the manufacturer's MTC (MS section 6.7.6) which uses results of the simeprevir clinical trials (QUEST 1, QUEST 2, PILLAR, ATTAIN, ASPIRE, PROMISE). The OR of achieving an SVR or experiencing an adverse event with protease inhibitor (PI) + PR treatment was derived from the MTC and applied to the baseline probability of achieving an SVR with PR treatment. For genotype 4 treatment naive patients SVRs were taken from the MAIC which matched the single arm RESTORE study of simeprevir[30] with the PR arm of a separate RCT in genotype 4 patients. In genotype 4 treatment experienced patients it was not possible to conduct a MAIC. For the simeprevir and sofosbuvir analysis SVRs from the COSMOS trial[31] were compared indirectly with SVRs from trials of boceprevir and telaprevir.

The model estimates the reduction in HRQoL associated with progressive liver disease, the reduction in HRQoL due to treatment-related adverse events, and the improvement in HRQoL following successful antiviral treatment (MS section 7.4.7). The decline in HRQoL over time is influenced by symptoms of hepatic and extra-hepatic liver disease, such as cirrhosis and

decompensated cirrhosis (DCC), and hepatocellular carcinoma (HCC). Although EQ-5D data were collected in the simeprevir clinical trials, the MS base case uses treatment utility decrements and increments adopted in previous economic models (citing Hartwell and colleagues, 2011[32], NICE TA200[28]). The same utility decrement is used for all treatment comparisons (irrespective of treatment experience), with treatment-specific decrements (derived from clinical trials and varying according to treatment experience) used in scenario analyses.

A systematic review was conducted to identify studies of costs and resource use (MS Section 7.5.3). Twenty one articles were identified but none related to the UK. Quantification of resource use, such as pre- and on-treatment monitoring costs, was based on previously published economic evaluations for NICE hepatitis C appraisals (citing Shepherd and colleagues 2007[33] NICE TA106[29] and Hartwell and colleagues 2011,[32] NICE TA200[28]). On-going annual HCV resource use and costs were also taken from these sources and the UK Mild HCV trial.[34] Clinician advice was sought for estimating market share of the two peginterferon alfa formulations. The cost of the Q80K polymorphism testing was assumed. Drug dosing was based on licensed dosages for each regimen, costed using the British National Formulary (BNF) (March-September 2014)[35] and applied to treatment-specific therapy durations from the clinical trials (MS Section 7.5.5). Costs of treating adverse events were estimated by contacting pharmacies and practising hepatologists (reported in a publication by Thorlund and colleagues, 2012[36]). Where necessary, costs were inflated to 2012 prices using the Hospital & Community Health Services (HCHS) Index from the Personal Social Services Research Unit (PPSRU).[37]

Deterministic sensitivity analyses (DSA) were conducted, varying input parameters within the limits of their 95% confidence intervals (Table 100, MS Section 7.6.2, for genotype 1 patients; Table 103, MS Section 7.6.4.8 for genotype 4 patients; Table 110, Section 7.6.5.5 for simeprevir and sofosbuvir treated patients). Probabilistic sensitivity analyses (PSA) included all of the input parameters in the DSA (MS Section 7.6.3). The PSA also included distribution of Metavir fibrosis class and response to prior treatment which were not included in the DSA as they are inter-dependent (MS Table 101 for genotype 1 patients; MS Table 104 for genotype 4 patients).

The MS includes 17 scenario analyses to explore the impact of varying structural assumptions on the results of the model (MS Section 7.6.1, page 99). Some scenarios were omitted from the genotype 4 patient analyses (see MS page 178-9), and from the simeprevir and sofosbuvir analyses (see MS page 184) as these were not relevant to these patient groups.

The model underwent validation by the model developer, and by a second consultancy (MS Section 7.8.1).

CEA Results

The results from the economic evaluation are presented for the base case assumptions for genotype 1 (MS Section 7.7.6, page 184), genotype 4 (MS Section 7.7.17, page 206), as incremental cost per QALY gained for simeprevir versus comparators and for all treatments versus PR. For the simeprevir and sofosbuvir analysis (MS Section 7.7.28, page 217) incremental cost per QALY gained is given for no anti-viral treatment versus comparators, and for simeprevir and sofosbuvir versus comparators. All model results are given for treatment-naive and treatment-experienced patients (the latter an amalgamation of prior relapser, partial responder and null responder sub-groups). The results of sub-group analyses by previous treatment experience are presented in MS section 7.9.4.

The base case incremental cost per QALYs gained are reported in Table 24 (NB. these are presented slightly differently to how they appear in the MS). As the table shows, simeprevir + PR is slightly more effective and has lower total costs than telaprevir + PR and boceprevir + PR in genotype 1 patients (i.e. simeprevir + PR dominates telaprevir + PR and boceprevir + PR). The ICER for simeprevir + PR versus PR was around £14,000. In genotype 4 patients the ICERs were under £12,000 for simeprevir + PR compared to PR. Simeprevir and sofosbuvir had higher costs than its comparators but also produced more QALYs. Comparing simeprevir and sofosbuvir to PI and PR dual therapy, simeprevir and sofosbuvir dominated boceprevir + PR and telaprevir + PR, and for the comparison with simeprevir + PR the ICERs ranged from £5,367 to £64,310. The comparison of simeprevir and sofosbuvir with no anti-viral treatment, which most likely reflects current clinical practice, produced ICERs of £15,431 and £13,917 for treatment naive and treatment experienced patients respectively (ICERs not shown in Table 24).

Table 24 Base case cost effectiveness results

	Total		Incremental		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICER (£/QALY)**
	Genotype 1 treatment-naive patients				
PR	£26,316	11.653			
Simeprevir + PR	£36,778	12.390	10,463	0.736	£14,206
Boceprevir + PR	£38,898	12.242	£2,119	-0.147	Dominated
Telaprevir + PR	£40,945	12.275	£2,047	-0.114	Dominated
	Genotype 1 treatment-experienced patients				
PR	£34,424	10.327			
Simeprevir + PR	£43,544	11.258	£9,120	0.931	£9,793
Telaprevir + PR	£44,502	11.226	£958	-0.032	Dominated
Boceprevir + PR	£49,582	11.128	£5,080	-0.130	Dominated
	Genotype 4 treatment-naive patients				
PR	£26,836	12.274			
Simeprevir + PR	£35,638	13.029	£8,802	0.755	£11,662
	Genotype 4 treatment-experienced patients				
PR	£36,781	10.732			
Simeprevir + PR	£45,591	11.722	£8,811	0.990	£8,896
	SMV + SOF analysis treatment naive patients				
No treatment	£32,465	9.369			
Simeprevir + PR	£42,976	11.341	£10,511	1.972	£5,367
Telaprevir + PR	£48,786	11.002	£5,810	-0.339	Dominated
Boceprevir + PR	£57,518	10.478	£14,542	-0.863	Dominated
SMV + SOF	£69,081	11.747	£26,105	0.406	£64,310
	SMV + SOF analysis treatment-experienced patients				
No treatment	£33,045	9.239			
Simeprevir + PR	£52,906	10.307	£19,861	1.068	£18,597
Telaprevir + PR	£60,075	10.182	£7,169	-0.124	Dominated
Boceprevir + PR	£67,673	10.257	£7,598	-0.050	Dominated
SMV + SOF	£68,147	11.761	£15,241	1.454	£10,480

Incremental analysis. Treatments are compared to the preceding cheaper treatment that has not been dominated. Dominated treatments are more expensive and less effective than an alternative treatment.
PR: peginterferon + ribavirin; SOF: sofosbuvir; SMV: simeprevir

Results of the sensitivity analysis showed that the model was generally robust to changes in input parameters. The most sensitive parameters were changes in SVR for the various treatments, and post-treatment transition probabilities. In scenario analyses, results were robust across both patient groups and simeprevir dominated telaprevir and boceprevir in all scenarios explored.

The MS summarises the results of the PSA stating that, for genotype 1 treatment-naive patients, there is a 92.9% and 97.5% probability of simeprevir being cost-effective, at a threshold willingness to pay of £20,000 and £30,000 per QALY gained. For treatment-experienced patients the corresponding probabilities were 63.9% and 68.4% respectively. For treatment-naive genotype 4 HCV patients the probability of simeprevir being cost-effective, at a threshold willingness to pay of £20,000 and £30,000 per QALY gained, compared to PR was 78.6% and 87.4% respectively, and for treatment-experienced patients was 97.2% and 99.9% respectively. For treatment-naive genotype 1 HCV patients the probability of simeprevir and sofosbuvir being cost-effective, at a threshold willingness to pay of £20,000 and £30,000 per QALY was 76.7% and 94.3% respectively. For treatment-experienced patients the corresponding probabilities were 83.2% and 96.3% respectively.

The manufacturer concluded that simeprevir is a cost-effective option compared to dual therapy with PR and - for genotype 1 patients – also cost-effective compared to telaprevir and boceprevir, which it dominated. The manufacturer also concluded that simeprevir and sofosbuvir is a cost-effective treatment option for patients intolerant or ineligible for peginterferon alfa.

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 treatments for patients with genotype 1 or genotype 4 chronic hepatitis C. This was part of a combined search undertaken for studies of clinical effectiveness, cost effectiveness, health related quality of life and costs. See section 3.1.1 of this report for the ERG critique of the search strategy.

The inclusion and exclusion criteria for the systematic review are listed in section 7.1.1 of the MS, page 129. The inclusion criteria state that economic evaluation studies of dual therapy (PR); and triple therapy (either simeprevir, telaprevir or boceprevir with PR) in patients with genotype 1 or genotype 4 chronic hepatitis C would be included. The exclusion criteria were: non-economic evaluations; interventions other than those stated above; studies not focussing on genotypes 1 or 4; studies published prior to 2004, or published as conference abstracts or posters; non-English language studies

A total of 4938 titles and abstracts were screened, and a total of 334 full text papers were assessed for inclusion (from the combined search, see the PRISMA flowchart in MS Figure 4). A total of 43 economic evaluations were included in the systematic review. Of these, ten were conducted in a UK setting, and nine of these explored cost-effectiveness. Details of these nine are tabulated (MS Table 77).

The checklist suggested by NICE[38] was applied to all of the 43 included references. No interpretation or conclusions of this quality assessment were provided in the MS. The review provides details of study methods and results, with most detail given for the nine UK studies that reported cost-effectiveness. MS Table 77 reports methods and results for the nine UK studies that report cost-effectiveness. There was only a brief narrative discussion of the studies.

The MS concluded on the basis of this review that all but one of the PR dual therapy economic evaluations were cost-effective compared to no treatment and interferon alfa and ribavirin at the £20,000 cost per QALY threshold. Triple therapy with boceprevir + PR or telaprevir + PR was concluded to be generally cost-effective across most patient sub-groups (NB. both of these were economic evaluations conducted for NICE STAs).

No economic evaluations featuring simeprevir were identified in the MS. However, the ERG identified a 2014 US cost effectiveness study of simeprevir and sofosbuvir compared to sofosbuvir + ribavirin by Hagan and colleagues[25] Although this comparison is not within the scope of the current appraisal the ERG has provided a brief summary of the methods and findings, to compare with the current MS. The authors constructed a decision tree with a Markov model to estimate the cost-effectiveness of 12 weeks of simeprevir and sofosbuvir (without ribavirin) compared to 24 weeks of sofosbuvir + ribavirin in genotype 1 patients ineligible for or intolerant to interferon alfa. The Markov model shares similarities with the current MS model and

previous published HCV models used in NICE appraisals, with commencement of treatment from fibrosis health states F0-F4; transitions from F4 to DCC and to HCC; and from those two states to liver transplant. Death is possible from any health state. The model includes testing for the Q80K polymorphism in genotype 1a patients and, unlike the base case model submitted in the current MS, all patients appear to be treated irrespective of whether Q80K positive or negative. However, lower SVRs were estimated for Q80K positive patients to reflect the reduced efficacy of simeprevir in this patient group, and a sensitivity analysis restricted to this patient group was provided. The model did not estimate cost-effectiveness of treating patients in the DCC health state, in common with the MS model. Costs and utility values were estimated from a range of published sources, and SVRs were taken from the COSMOS trial (though based on SVR4 as reported in a 2013 conference abstract, whereas the MS reports SVR12). In the base case simeprevir and sofosbuvir dominated SOF+RBV, with lower costs and more QALYs ($165,336 and 14.69 QALYs vs. $243,586 and 14.45 QALYs, respectively). Simeprevir and sofosbuvir remained dominant in all scenario analyses.

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 25 below, drawn from common checklists for economic evaluation methods (e.g. Drummond and colleagues[38]). Overall the manufacturer has followed recommended methodological guidance.

Table 25 Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	
Is there a clear description of alternatives?	Yes	
Has the correct patient group / population of interest been clearly stated?	Yes	
Is the correct comparator used?	Yes	All comparators in the NICE scope are included. The simeprevir + sofosbuvir combination is compared to protease inhibitor treatments which are not currently recommended by NICE for that particular patient group (patients intolerant to or ineligible for treatment with interferon). Simeprevir + sofosbuvir is also compared against no treatment.
Is the study type reasonable?	Yes	
Is the perspective of the analysis clearly stated?	Yes	
Is the perspective employed appropriate?	Yes	
Is effectiveness of the intervention established?	Yes	Limited effectiveness data for simeprevir in genotype 4 patients, and patients ineligible for or intolerant to interferon alfa
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	Yes	
Are the costs and consequences consistent with the perspective employed?	Yes	
Is differential timing considered?	Yes	3.5% for costs and health benefits as per NICE recommendations.
Is incremental analysis performed?	Yes	
Is sensitivity analysis undertaken and presented clearly?	Yes	

NICE reference case

The NICE reference case requirements have also been considered for critical appraisal of the submitted economic evaluation in Table 26.

Table 26 NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Yes	
Comparator: Alternative therapies routinely used in the UK NHS	Yes	
Perspective on costs: NHS and PSS	Yes	
Perspective on outcomes: All health effects on individuals	Yes	
Type of economic evaluation: Cost effectiveness analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	Yes	
Measure of health benefits: QALYs	Yes	
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	Yes	
Method of preference elicitation for health state values: Choice based method (e.g. TTO, SG, not rating scale)	Yes	EQ-5D (TTO) for health states, taken from Wright et al (as used in Hartwell et al, 2011[32])
Source of preference data: Representative sample of the public	Yes	As above
Discount rate: 3.5% pa for costs and health effects	Yes	

In general the methods of assessing cost-effectiveness are reasonable and conform to NICE's methodological guidance and the NICE scope.

4.2.1 Modelling approach / Model Structure

The manufacturer states that the model is based upon published models that have been considered in previous NICE appraisals for HCV anti-viral treatments (TA252 telaprevir, TA253 boceprevir; TA200 Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C, TA106 Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C). The underlying Markov structure dates back to a publication from 1995. The MS discusses how recent iterations of the model submitted (NICE TA253 boceprevir) have incorporated increased levels of sophistication such as separate SVRs according to different starting levels of fibrosis (MS Section 7.2.3). A schematic of the model is provided in Figure 1.

The model comprises two phases: (i) the treatment phase (0-72 weeks) which incorporates the maximum length of anti-viral treatment (48 weeks) and follow-up (up to 24 weeks) to assess SVR and (ii) the post-treatment phase (72 weeks – lifetime) which follows patients as they progress through the respective Markov health states. MS Table 78 provides a description of the health states within the model. To summarise:

- SVR after F0-F4. These health states include patients at varying levels of baseline liver disease (from mild fibrosis to compensated cirrhosis) who have an SVR and are therefore successfully treated. Patients in SVR F0-F2 and F3 do not experience long-term disease progression or excess mortality, but patients in SVR F4 have an increased chance of developing DCC or HCC, but in the absence of progression no excess mortality.
- Mild HCV (F0-F2) - patients who have not experienced an SVR following treatment, and who are at risk of progression.
- Moderate HCV (F3), and compensated cirrhosis (F4) – patients who have not experienced an SVR following treatment, or who have progressed from mild/moderate health states, respectively. Patients in F4 have an on-going risk of progression to DCC or HCC.
- Decompensated cirrhosis (DCC) – characterised by complications such as ascities, hepatic encephalopathy and hepatorenal syndrome (clustered into a single health state in common with previous models). Patients can progress to HCC, liver transplant or liver related death.
- Hepatocellular carcinoma (HCC) – patients can progress to this state from compensated or decompensated cirrhosis, and may progress to liver transplant or liver-related death.
- Liver transplant – this state assesses the costs, disutility and high early mortality associated with transplantation, over 12 month period.
- Post-liver transplant – patients surviving liver transplant progress to this state and experience lower excess mortality than the previous state.
- Liver-related death – patients with DCC or HCC who die from liver disease, either directly or following liver transplant
- Death – an absorbing state based on age-sex specific all-cause mortality rates to patients in all health states (and in excess to liver-related mortality).

The model uses a lifetime time horizon and this is appropriate to capture all benefits and costs given the slow progressive nature of chronic HCV. The model assumes that SVR results in a cure of HCV and that there is no further disease progression (except where an SVR is achieved in the compensated cirrhosis F4 health state, where progression can occur albeit at a reduced rate). This is consistent with clinical opinion and previous economic evaluations.

A one year cycle length was used, to reflect the slow progressive nature of chronic HCV (MS Table 79. Page 139). This is consistent with previous economic evaluations. A half-cycle correction was used, and it is stated that this was applied because drug costs are accrued over a longer cycle length (a year) and because of patient movement between states. Again, this is consistent with previous published economic evaluations. During the treatment phase of the model, the total costs and QALYs are calculated for each treatment, taking account of the treatment duration and efficacy. The effect of successful treatment, in terms of SVR, appears to happen at the end of the treatment period although the MS is not clear on this.

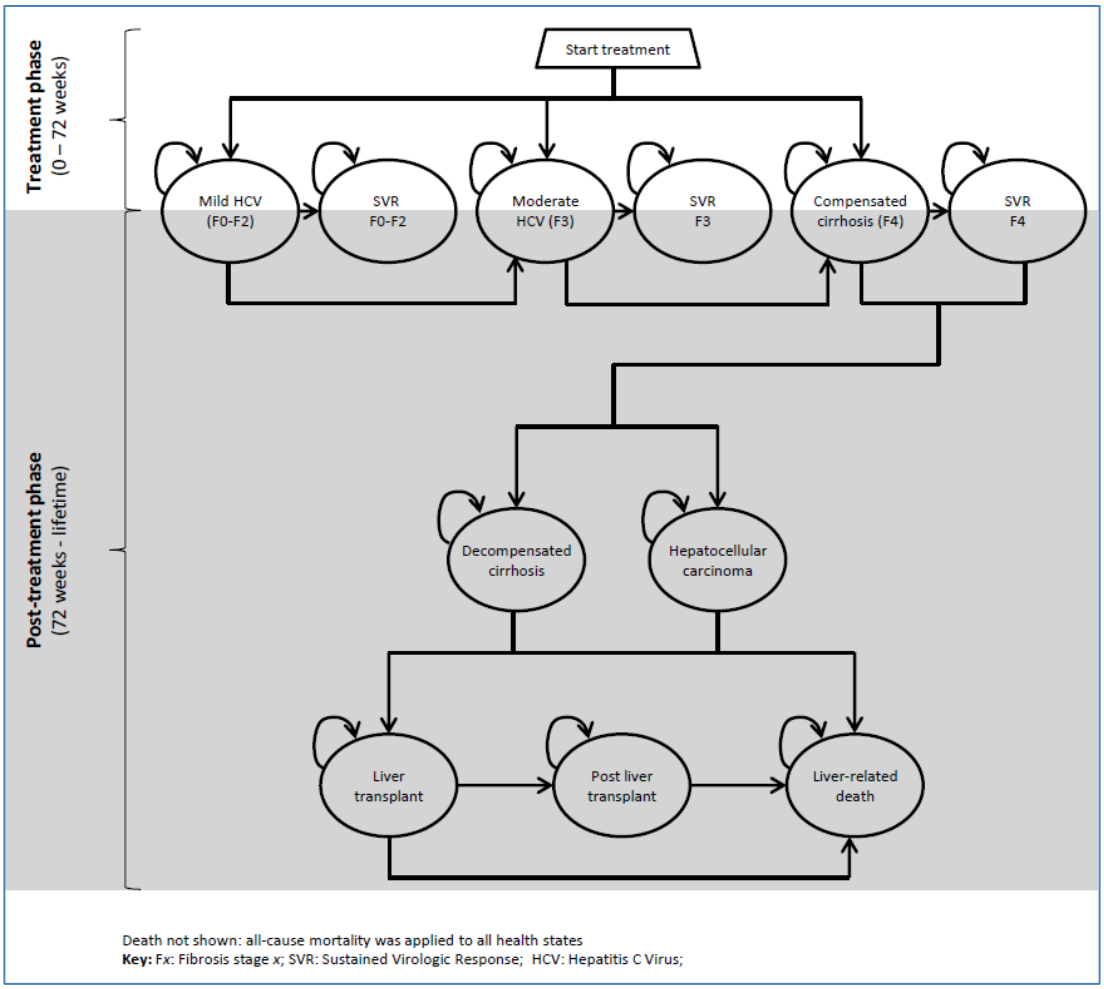

Figure 1 - Schematic of manufacturer's model for chronic hepatitis C (reproduced from MS Figure 39, MS p. 135)

MS Table 86 lists the structural assumptions, with reference to published sources where available. For many of the assumptions the justification is that they are consistent with previous published economic models included in NICE HCV appraisals. An exception is the SVR F4 (compensated cirrhosis) to HCC transition probability which is informed by a study by Cardoso and colleagues (2010),[39] and which is also used to extrapolate to the SVR F4 to DCC transition. Not all of the existing economic models have included the transition from SVR F4 to DCC. The ERG notes that the transition probability in the study by Cardoso and colleagues[39] is 0.0123, rather than the value used in the model (0.005). The ERG investigates the effect of changing this parameter value in a scenario analysis in section 4.3.2.

It is stated that patients who have an SVR are at no risk of re-infection and cites Hartwell and colleagues (2011)[32] (amongst other economic evaluations). However, Hartwell and colleagues (2011)[32] states that patients are not immune from re-infection (though does not model this). The model assumes that patients with SVR F4 have follow-up costs for 5 years which is consistent with Hartwell and colleagues (2011)[32]

The MS states that an advisory board was held in December 2013, comprising five experts in medicine and health economics. At the meeting, a draft write up of the model was presented and the experts gave advice and feedback on the model structure and inputs. The model design and structure was validated at an advisory board in March 2013 (The ERG presumes it to be the same advisory board convened in December 2013). It is stated on MS page 144 that during the finalisation of the economic model expert clinical opinion was obtained from two leading key clinical leaders in April 2014. The model underwent validation by the model developer, and a second consultancy provided a further quality assessment of the structure and functionality of the model. This revealed some minor functionality errors, and the model was adapted to include more detailed descriptions of the inputs. (MS Section 7.8.1)

In general, the ERG considers that the modelling approach adopted in the submission is reasonable for assessing the cost-effectiveness of anti-viral treatment for chronic HCV. The model design and structure appears to be well validated and in-keeping with previous models in this area.

4.2.2 Patient Group

Details of the patient baseline characteristics and their sources are given in MS Table 82 (page 143), MS Table 85 (MS page 145) and MS Table 99 (MS page 170). The starting age is 50 years, with a 71%/29% male/female gender split (NB. MS Table 99 lists this as 50/50 but this appears to be a typographical error), and an average patient weight of 79kg. Baseline Metavir fibrosis score varied according to treatment experience: for treatment naive patients the distribution of patients was F0-2: 45%; F3: 35%; F4: 20%, whilst a greater percentage of treatment-experienced patients had moderate to severe fibrosis F0-2: 25%; F3: 45%; F4: 30%. It is stated that these characteristics are identical for genotype 1 and genotype 4 patients. The

simeprevir + sofosbuvir model is reported to be based on patient characteristics from the COSMOS trial,[31] only including patients with baseline Metavir fibrosis F3-F4 (MS page 179). The MS states that this better reflects the product label and that these patients are in urgent need of treatment. Expert clinical advice to the ERG suggests many patients who are ineligible for or intolerant to interferon will have waited for new treatments to become available, and therefore are likely to have more advanced fibrosis/cirrhosis.

It is implied that the population in each model is HCV mono-infected (no formal sub-group analysis is provided for HIV+HCV co-infected patients – see below for a discussion of this).

MS page 142 states that patient age and weight at baseline and the proportion of males/females were derived from a recent analysis of patients by HCV Research UK, and baseline Metavir fibrosis score distribution and prior treatment response distribution was taken from key English opinion leaders (MS reference 106). No further information is given on the HCV Research UK dataset, how it was compiled and how representative it is of the UK patient population, though the ERG notes that it appears to be a comprehensive consortium of around 30 specialist hepatology centres across the UK. The ERG clinical advisors agree that the use of the HCV UK database is appropriate.

The manufacturer's base case population contrasts with the values used in previous published economic evaluations of HCV treatments. In Hartwell and colleagues (2011)[33] the mean starting age was around 40 years (treatment naive patients) and 45 years (treatment-experienced patients); and fewer of the treatment-naive patients had mild-moderate fibrosis, and more of the treatment-experienced patients had mild-moderate fibrosis. However, the manufacturer uses the Hartwell and colleagues characteristics in a scenario analysis (scenario 3), and this does not have much impact on the ICERs. The manufacturer also uses the ERG's estimates of the distribution of baseline Metavir scores from the boceprevir NICE appraisal in a scenario analysis,[27] along with Welsh key opinion leaders estimates (scenario 4). These estimates increase the percentage of patients in the F0-F2 Metavir category, but again, this also did not significantly alter the ICERs.

The baseline patient population was generally consistent with the patient groups in the clinical evidence reviewed in section 3.1 of this report. The mean age in the simeprevir RCTs (excluding COSMOS – see below) varied from 45-46 years (treatment naive patients), and 49-

50 years (treatment-experienced patients). However, the manufacturer might have considered a lower starting age for treatment naive patients (this would be a conservative assumption). Mean body weight across the simeprevir RCTs was 76-81 kg. The percentage of male patients in the simeprevir RCTs varied from 54% to 57% (treatment naive patients) and 58% to 68% (treatment-experienced patients).

For the simeprevir + sofosbuvir treated patients the manufacturer based the model patient population on the COSMOS trial.[31] It is stated that the base case only explores treating patients with Metavir F3-F4 (reflecting cohort 2 of the COSMOS study which included patients with advanced fibrosis, rather than cohort 1 which included patients without advanced fibrosis). The simeprevir + sofosbuvir model uses a stating age of 50.1 years. However, age in the COSMOS study of simeprevir + sofosbuvir was higher: median [redacted] (cohort 1); and median [redacted] (cohort 2 – advanced fibrosis). The manufacturer could have considered a higher starting age in this model in their base case, or in a scenario analysis. The ERG has therefore conducted a scenario analysis accordingly (see section 4.3.2).

The MS presents sub-group analysis/analyses by treatment experience (treatment-naive; prior relapsers; partial responders and null responders) in MS Section 7.9.1. A sub-group analysis for HCV+HIV co-infected patients is not provided, but the MS suggests that cost-effectiveness in this population is expected to be very similar to that observed in the genotype 1 (mono-infected) population based on results of clinical trials. Clinical advice to the ERG suggested that this was reasonable.

In general the ERG considers that the patient group in the model is representative of the clinical HCV population. It is noted that some of the patient characteristic values used are different from those used in previous economic evaluations, though variation in these values in scenario analysis does not significantly change the ICERs.

4.2.3 Interventions and comparators

The NICE scope specifies that the comparator is established clinical management without simeprevir including, but not limited to telaprevir in combination with PR, boceprevir in combination with PR, and PR dual therapy. The cost effectiveness analysis for genotype 1 includes these three comparisons. For genotype 4 patients a comparison is only made with PR due to lack of available evidence for telaprevir or boceprevir in these patients. The ERG also

notes that NICE's guidance for telaprevir or boceprevir does not include genotype 4 patients. A comparison is also made for each of the three PIs in combination with PR versus PR dual therapy. No other comparisons are made, though the ERG notes that sofosbuvir is currently being appraised by NICE and could potentially become a comparator if recommended for use in the NHS.

The simeprevir + sofosbuvir and ribavirin combination treatment is compared with simeprevir, boceprevir and telaprevir each in combination with PR. A no antiviral treatment comparison is also included against which all of the above treatments are compared. A comparison with PR dual therapy is not included. The manufacturer notes that use of simeprevir + sofosbuvir is only indicated in patients who are ineligible for or intolerant of interferon-containing regimens, and that PR is therefore not an appropriate comparator. Furthermore, none of the PIs are currently recommended by NICE for treatment in a regimen without interferon alfa. The manufacturer has included these comparisons for consistency with the scope. The ERG agrees with the manufacturer that, given the lack of available treatments, the no anti-viral treatment option is likely to be the most clinically appropriate comparator, though this is not listed as a comparator within the NICE scope. Again, if NICE recommend sofosbuvir for use in the NHS this could potentially be a comparator as it can be used without interferon alfa.

4.2.4 Clinical Effectiveness

The key clinical effectiveness parameters used in the model are SVR and adverse events. In the base case analysis SVR was estimated at 12 weeks after treatment cessation in accordance with the simeprevir clinical trials where this was the primary outcome. SVR at 24 weeks was a secondary outcome measure in the simeprevir trials and is included in a scenario analysis (scenario 13) as this was the primary measure used in the telaprevir and boceprevir clinical trials. The MS suggests that SVR12 and SVR24 are closely correlated based on the results of phase II clinical trials of simeprevir, and expert clinical advice provided to the ERG says that this is generally accepted.

MS Table 85 lists the SVRs and adverse events values used in the model for genotype 1 patients, and MS Table 102 lists the SVRs used for genotype 4 patients. Genotype 4 patients are assumed to experience the same level of adverse events as genotype 1 patients. SVRs used in the SMV+SOF model are given in MS Table 106, and adverse events are given in MS

Table 107. Table Table 27 - Summary of clinical effectiveness sources used in the economic evaluation. Table 27 summarises the key sources of clinical effectiveness data for the three models, which will be described in further detail throughout this sub-section.

Table 27 - Summary of clinical effectiveness sources used in the economic evaluation

	Simeprevir effectiveness (SVRs)		**Simeprevir adverse events**	
	TN	TE	TN	TE
Genotype 1	MTC	MTC	MTC	MTC
Genotype 4	MAIC	RESTORE study	QUEST 1 & 2[a]	ASPIRE, PROMISE[a]
SMV+SOF (G1)	COSMOS study[b]	COSMOS study[b]	COSMOS study[c]	COSMOS study[c]

[a] A MAIC was not possible for adverse events so it was assumed that genotype 4 patients would experience similar level of adverse events as genotype 1
[b] Appears to be Cohort 2, Arm 3 of the study (refer to MS Table 62, page 108 for the study design)
[c] Assumed treatment naive and null responders equivalent
TN= treatment naive; TE= treatment experienced

The model includes percentage SVRs for PR, stratified by Metavir fibrosis grade. The ORs of achieving SVR for each PI+PR treatment (as derived from the MTC for genotype 1 patients - see below) are applied to the baseline SVR probability for PR treatment. SVRs for PR are given separately for F0-F2, F3 and F4 to enable the model to generate estimates of treatment effect from each of the initial fibrosis health states (i.e. SVR from F0-F2, SVR from F3 etc). The PR SVR is highest for F0-F2, and lower for F3 and F4 (which have been combined). Whilst using PR as the baseline probability for assessing cost-effectiveness of simeprevir and its comparators seems logical, the ERG considers applying an OR to it that has been estimated irrespective of baseline fibrosis level to be a limitation. The implicit assumption is that the relationship between initial fibrosis grade and SVR (i.e. that effectiveness declines with increasing fibrosis) is the same across all of the comparators. It is also not clear why the same SVR for F3 patients has also been used for F4 patients in the genotype 1 model, when patients with compensated cirrhosis (F4) might be expected to have a lower SVR. The ERG has therefore conducted a scenario analysis using different SVRs for F3 and F4 patients (see section 4.3).

For genotype 1 patients an MTC was conducted (described in MS section 6.6 and in further detail in a supplemental report[17]) (see section 3.1.7 of this report for the ERG critique of this). The MTC includes the pivotal RCTs of simeprevir from the manufacturer's systematic review (PILLAR, ASPIRE, QUEST 1 and 2, PROMISE and ATTAIN). The ATTAIN RCT is the only one of these that compares simeprevir directly with another PI (telaprevir). The MTC therefore

includes direct and indirect evidence for this comparison. The MS states that SVRs for PR were taken from the QUEST 1 and 2 RCTs for treatment-naive patients (stratified by fibrosis level). The SVRs for PR in the treatment naive population in the economic model (51.9% (F0-F2), 35.4% (F3), 35.4% (F4) – reported in MS Section 7.3.6; Table 85; Page 146) differ slightly from SVRs from the pooled QUEST I and II RCTs [55.2% (F0-F2), 37.5% (F3), 34.4% (F4)]. It is assumed that this is because the SVRs in the model have been estimated via the MTC and therefore may be expected to vary slightly. In the treatment-experienced population SVRs from the PR arm of the phase III REALIZE trial of telaprevir assessed in NICE TA252[26] were used. PR SVRs were not stratified by baseline fibrosis due to the small numbers of patients available in that trial. It is not clear why SVRs were chosen from this trial in preference to any of the other available trials. For example, the PROMISE trial of simeprevir + PR versus PR reported an SVR in PR treated prior relapsers of 36.1% (MS page 52), which is higher than the SVR of 26.5% for relapsers reported in the REALIZE trial. However, this is unlikely to substantially change the results of the model.

The ERG notes that the MTC estimates ORs for multiple regimens of some treatments (namely telaprevir and boceprevir), though not all of them are used as inputs to the economic model. For example, for treatment naive genotype 1 patients median ORs range from 2.42 to 3.79 across the three regimens included in the MTC. Some of the regimens are for fixed treatment duration and some appear to be for RGT. It is not explicit why only some regimens are modelled. MS Table 81 shows the treatment regimens evaluated in the economic evaluation incorporating RGT rules, though it is not explicit how all of these regimens match the regimens used in the MTC. However, the ERG notes that of the ORs available for the comparators, in each case, the MS has tended to use the highest one which provides conservative results.

As stated earlier (see section 3.1.7) for genotype 4 treatment-naive patients a MAIC was conducted. The single arm RESTORE study was the only simeprevir study identified that included patients with this genotype.[30] It was therefore not possible to construct an MTC or perform a pairwise adjusted indirect comparison. Instead an RCT of PR by Rumi and colleagues (2010)[20] was matched to the RESTORE study to create a comparison between simeprevir and PR treatment. The ERG considers there to be a number of limitations to the MAIC and urges caution in the interpretation of the results of the cost-effectiveness analysis for genotype 4 patients. For genotype 4 treatment-experienced patients a MAIC was not possible. Instead, the SVR for these patients was estimated assuming the same decline in SVR of PR between

treatment-experienced and treatment naive as seen for genotype 1 patients from the MTC. The SVR for simeprevir was taken from the RESTORE study.[30]

For patients treated with SMV+SOF an MTC was not possible as the only study evaluating this combination that was identified in the MS was the COSMOS trial. This trial did not include a comparison with any other PI or PR regimens and therefore the MS performed an unadjusted indirect comparison (not adjusted to preserve randomisation) with selected trials. SVRs from separate trial arms were entered directly into the economic model (MS Table 105). No rationale is given for the selection of these comparator trials. The ERG therefore urges caution in the interpretation of the comparisons with the other PIs from this model (notwithstanding the clinical inappropriateness of these comparisons, as discussed in section 4.2.3).

The MS does not explicitly report which of the four COSMOS trial arms the SVRs are taken from. As the MS models 12 weeks of SMV+SOF treatment with ribavirin in patients with F3-F4 fibrosis, it appears that arm 3 (cohort 2) of the trial was used to provide SVRs for the model (refer to MS page 108, Table 62, for information on the study design). The total number of patients allocated to arm 3 was 27 (87 patients enrolled in the cohort in total). This would seem to be a relatively small number of patients to support clinical effectiveness estimates in the model.

The base case analysis for the genotype 1 model and for the SMV+SOF model (which is restricted to genotype 1 patients) is based upon clinical effectiveness estimates for the genotype 1a Q80K negative patient sub-group and for genotype 1b patients combined. This is reflected in the default model setting labelled ‘treatment regimens as outlined in the label (screen for Q80K in simeprevir)’. The alternative model setting is ‘treatment regimens as outlined in the clinical trials’ which uses clinical effectiveness estimates for genotype 1a patients, irrespective of presence of the Q80K polymorphism, and for genotype 1b patients. The ERG noted that selecting this setting generated a different set of ICERs not reported in the MS. The manufacturer clarified that these analyses were developed at model exploration stage, prior to final marketing authorisation, and were retained in the submitted model in the interest of transparency. They are not intended to be alternative/scenario analyses (manufacturer’s response to ERG clarification questions, question A3).

Adverse events (anaemia, neutropenia, rash, pruritus) and treatment discontinuation due to adverse events were estimated from the MTC (genotype 1 patients, with same values used for genotype 4 patients by assumption, MS page 176). The ORs of experiencing each adverse event whilst on a PI and PR treatment regimen versus PR for the four adverse events were then calculated and applied to the baseline adverse event rates observed for PR alone (using the same approach as described for estimating treatment effectiveness discussed earlier in this section). A scenario analysis for genotype 4 patients used adverse event rates from the RESTORE study.[30] For the SMV+SOF model adverse events are taken from the COSMOS trial. The same values are used for treatment naive and treatment-experienced patients, however, the ERG notes that the manufacturer assumes different on-treatment utility estimates for treatment naive and treatment-experienced patients, with utility decrements related to treatment adverse events. Adverse events for telaprevir and boceprevir are taken from individual trials of those treatments (see MS Table 107). As was the case with sourcing SVRs for the simeprevir + sofosbuvir model, no explicit rationale is given for why particular trials were chosen as the source of adverse events.

MS Table 83 (reproduced below in Table 28) gives the annual transition probabilities for disease progression with source references. The majority of these are informed by data values used in previous economic evaluations for NICE TAs, particularly Hartwell and colleagues (2011)[32] which, in turn, are based on data from published epidemiological literature. The exception is the transition from SVR F4 to DCC and to HCC which was informed by the study by Cardoso and colleagues 2010[39] (this transition was not included in Hartwell and colleagues 2011 - mentioned above). The ERG notes that previous economic models have assumed that the transition probability from SVR F4 to DCC was 0. In addition the ERG notes that the parameter value used for SVR F4 to HCC is 0.005, whilst the actual value in the Cardoso and colleagues study[39] is 0.0123. The ERG analyses the effect of the changes on the model results in a scenario analysis (section 4.3.2). The MS uses different all-cause mortality probabilities across the economic models. The genotype 1 model uses mortality rates from the Government's Actuary Department, whilst the genotype 4 and SMV+SOF models use mortality rates from the Office for National Statistics (ONS). It is not clear whether there was a rationale for using different rates for the genotype 1 model so the ERG has conducted a scenario analysis using ONS rates (see section 4.3).

Table 28 Annual transition probabilities used in the economic model (post-treatment phase)

From	To	Value	Source
F0-F2	F3	0.025	Wright 2006,[34] Hartwell 2011[32]
F3	F4	0.037	Wright 2006,[34] Hartwell 2011[32]
F4	DCC	0.039	Fattovitch 1997,[40] Hartwell 2011[32]
	HCC	0.014	Fattovitch 1997,[40] Hartwell 2011[32]
SVR F4	DCC	0.014	Proportionate reduction applied to the F4=>DCC rate (see MS section 7.3.8)
	HCC	0.005	Cardoso 2010,[39]
DCC	HCC	0.014	Fattovitch 1997,[40] Hartwell 2011[32]
	Liver transplant	0.020	Siebert 2003,[41] Hartwell 2011[32]
	Liver related death	0.130	Fattovitch 1997,[40] Hartwell 2011[32]
HCC	Liver transplant	0.020	Siebert 2003,[41] Wright 2006[32]
	Liver related death	0.430	Fattovitch 1997,[40] Hartwell 2011[32]
Liver transplant	Liver related death	0.150	RCS audit 2003, Hartwell 2011[32]
Post liver Transplant	Liver related death	0.057	RCS audit 2003, Hartwell 2011[32]
All-cause mortality		age/gender specific	Interim Life Tables, UK

In general the ERG considers the manufacturer's approach to estimating clinical effectiveness and other transition probabilities in the model to be reasonable. However, there is limited available RCT evidence for the effectiveness of simeprevir in patients with genotype 4 and in patients ineligible for or intolerant to interferon. This has necessitated a matched adjusted / unadjusted indirect comparisons based on studies with relatively small numbers of patients. There are also uncertainties in the approach taken to estimate SVRs according to baseline fibrosis levels in the model.

4.2.5 Patient outcomes

The MS conducted a systematic review of the literature for quality of life studies. The MS reports the strategy and results of searches conducted specifically for HRQoL estimates (page 153 of the MS) and found six studies that reported EQ-5D. Within, these six studies there are several trial based analyses of the quality of life of patient on boceprevir and telaprevir. The MS concluded that the Mild Hep C trial[34] was considered the most appropriate to use in the evaluation as it was conducted in UK patients, and the data can be grouped by varying degrees

of severity, which are aligned with the health states in the model. More detail on the quality of life from the simeprevir trials is discussed in section 3.3.1 of this report.

HRQoL is incorporated in the model by using utility estimates applied to the model health states with decrements to these to reflect the effect of treatment-related adverse events. The MS states the approach used was taken in previous NICE appraisal models for boceprevir[27] and telaprevir[26] and a previous MTA for hepatitis C by Hartwell and colleagues,[32] who had taken utility values from the Mild Hep C trial.[34] These are shown in Table 29 (MS Table 91, p. 159).

Table 29 Baseline health state utilities and sources

Health state	Utility	Source
SVR (from mild disease)	0.82	Wright et al 2006[34]
SVR (from moderate disease)	0.72	
Mild HCV	0.77	
Treatment for mild HCV	0.66	
Moderate HCV	0.66	
Treatment for moderate HCV	0.55	
Cirrhosis	0.55	
Decompensated cirrhosis	0.45	
Hepatocellular carcinoma	0.45	
Liver transplant	0.45	
Post-liver transplant	0.67	

The treatment decrement associated with treatment for hepatitis C is 0.11 in the base case analysis, based upon the estimates made by Hartwell and colleagues[32] for treatment with peginterferon alfa. This treatment decrement was chosen, rather than the values from the clinical trials, after discussion with their clinical experts. The MS compared the EQ-5D data between treatment with boceprevir, telaprevir and simeprevir (Table 92, page 161). They concluded that the results suggest that there are small differences between the treatment combinations in terms of their impact on quality of life during treatment, although these differences were small and may not be statistically significant. The MS has used treatment-specific utility decrements from the clinical trials in a scenario analysis (number 14). The treatment-specific HRQoL utility decrement from the clinical trial data varies between 0.081 (simeprevir) and 0.106 (PR) for treatment-naive patients and between 0.119 (simeprevir) and

0.159 (telaprevir) for treatment-experienced patients. The ERG asked the manufacturer to clarify why utility decrements differed according to treatment naive patients and treatment-experienced treatments. The manufacturer responded that this may be due to treatment-experienced patients being treated with PR for longer than treatment naive patients would be (manufacturer's response to ERG clarification questions, question A3).

When patients achieve SVR, their utility value increases to reflect a higher quality of life associated with response. The utility increment estimated by the Mild Hep C trial was 0.05 and this has been used by the manufacturer to be consistent with previous appraisals. The manufacturer also considers other alternative values in a scenario analysis, such as an utility increment of 0.04, as observed in patients treated with telaprevir + PR in the ADVANCE study.[42]

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.

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 adverse events.

The manufacturer searched the literature for studies on resource use and costs (inclusion criteria presented in Table 93, page 164 of the MS). A total of 21 articles were identified but none related to the UK. The manufacturer followed the approach used by Shepherd and colleagues[33] (NICE TA106) to estimate both treatment and health state resource use.

The estimation of dosage and frequency of administration of the comparator treatments were defined in MS section 1.9. The durations of treatment were as defined in the clinical trials. The dosages used are shown in MS Table 94. A single dose of 150 mg of simeprevir is taken orally once a day. The licensed duration of treatment with simeprevir is 12 weeks, based on the SPC. The model assumes a composite of peginterferon alfa-2a and 2b treatment in the proportion 82.5% and 17.5% respectively based on opinion leader advice. Clinical advice to the ERG considered that the proportion split for peginterferon was consistent with clinical practice.

The manufacturer includes treatment stopping rules, shown in MS Table 80. For simeprevir, the stopping rules state If HCV-RNA $\geq$ 25 IU/ml at week 4, discontinue all treatment and If HCV-RNA is detectable at week 12 or week 24, discontinue all further treatment. Telaprevir and boceprevir also have stopping rules and have RGT, which determine how long treatment should be continued depending on the patient group and treatment response (MS Table 81). Patients meeting RGT criteria have a shortened duration of treatment, whilst those who do not meet RGT criteria go on to have full course of treatment. In the manufacturer's base case, 50% of patients on boceprevir were eligible for RGT and this was varied between 0 and 100% in a scenario analysis. Clinical advice to the ERG confirmed that the proportion of patients on boceprevir eligible for RGT was reasonable. The ERG notes that patients that are treated with peginterferon alfa and ribavirin only are not subject to treatment stopping rules in the model and all have treatment for 48 weeks. The ERG considers that this may be an overestimate of the treatment duration for peginterferon alfa and ribavirin. For example in the QUEST 2 PR treatment arm, the proportion of patients with a PR treatment duration of 48 weeks was 60.4%.

The resource use involved in on-treatment monitoring and management was derived from the previous SHTAC model used in TA106 and TA200,[33] The monitoring resources include regular follow-up, management of adverse effects and investigations to detect adverse effects and asses treatment response. The resource use associated with each health state was derived from the resource use in the previous SHTAC model[33] as similar health states were used in both models. The MS states that the addition of a PI to PR therapy does not affect the cost of initial investigations compared to PR treatment alone. There is an additional cost, for simeprevir and for telaprevir compared to PR alone or boceprevir, for a HCV viral load test performed at week 4, which enables the classification of patients as early or late responders and determines their subsequent treatment duration. Clinical advice to the ERG confirmed that that simeprevir was not likely to require additional monitoring costs than other comparator treatments. An additional test for the Q80K polymorphism is recommended for all genotype 1a patients. Clinical advice to the ERG suggested that the manufacturer has committed to meeting start-up costs associated with introducing Q80K screening and there would be no additional patient hospital visit needed.

The health care resource use associated with treating adverse events was estimated from a study by Thorlund and colleagues[36] This was a budget impact analysis of boceprevir and telaprevir and the resources associated with the management of adverse events (anaemia,

neutropenia, rash and pruritus) were obtained by contacting pharmacies and interviewing practice hepatologists (MS Table 98).

Overall, the relevant resource use appears to have been covered and was consistent with previous NICE appraisals and the SHTAC model.[26;27;33] The approach used is consistent with the reference case as the NHS perspective was adopted.

4.2.7 Costs

The cost analysis was conducted from an NHS and Personal Social Services perspective. The unit costs for simeprevir and other comparators are presented in Table 30 (reproduced from MS Table 94). The cost of treatment for simeprevir has been set by Janssen at £266.64 per day, and so a treatment course of 12 weeks costs is £22,398 per patient. The unit costs of comparator treatments were taken from the BNF 67 2014.[43] Costs were estimated for an average body weight of 80.9 kg, which was the mean patient weight in QUEST 1.

Table 30 Treatment unit costs

Drug	Unit dose	Cost / unit	Cost per week	Cost over time frame	Source
Simeprevir	150 mg	£266.64	£1,866.50	£22,398	Janssen
Telaprevir	375 mg	£44.44	£1,866.50	£22,398	BNF, 2014 [43]
Boceprevir	200 mg	£8.33	£2,800.00	£16,800[a]	
Peginterferon alfa-2a	180 µg	£124.40	£124.40	£3,133[b]	
Peginterferon alfa-2b	120 µg	£159.51	£159.51		
Ribavirin (Copegus)	200 mg	£2.20	£92.50	£1751[c]	
Ribavirin (Rebetol)	200 mg	£1.91	£80.22		

[a] Value shown for boceprevir 24 weeks [b] Value shown for peginterferon alfa 2a / 2b for 24 weeks [c] Value shown for ribavirin for 24 weeks

The ERG notes that there is now a generic form of ribavirin available and the economic model uses the branded price. For example for a 400 mg, 56-tab packs of ribavirin (copegus) the branded cost is £246.65, however, it seems that ribavirin is available to the NHS at a generic price of £42.05 for equivalent pack size, and dose. (source: eMIT http://cmu.dh.gov.uk/electronic-market-information-tool-emit/). The ERG understands that the generic costs applies to ribavirin used in combination with peginterferon alfa-2b and not

peginterferon alfa-2a. As the majority of patients use peginterferon alfa-2a, the generic form of ribavirin is likely to have a minimal impact on model results.

On-treatment monitoring costs (Table 96 page 167 of the MS) were derived from Shepherd and colleagues[33] inflated to 2012-3 values (from 2003-4 prices) using the HCHS from the PSSRU.[37] These included resource unit costs of outpatient appointments, inpatient care, tests and investigations (virology, chemical pathology, haematology, immunology/chemistry, radiology, molecular pathology, other tests) and procedures (for example liver biopsy).

Health state costs associated with HCV infected patients were adopted from Shepherd and colleagues[33] inflated to 2012-3 prices using the HCHS Index from PSSRU (Table 31).[37] The ERG notes that Shepherd and colleagues 2007[33] used health state costs derived from the Mild Hep C trial[34] and Longworth and colleagues,[44] therefore a more correct approach would be for the manufacturer to have inflated the original costs from those studies, rather than those from Shepherd and colleagues. However, this is unlikely to have a significant impact on model results. All relevant costs seem to have been considered and the manufacturer's approach is consistent with previous NICE appraisals for hepatitis C.[26;27] The manufacturer has used a cost of £48,685 for liver transplant. However, this is likely to be an overestimate of the actual cost. The manufacturer has used a cost of £18,019 for liver transplant in a scenario analysis, as suggested by the ERG for the sofosbuvir NICE appraisal from HRG costs 2011/12.[45]

Table 31 Key health state costs

Health state	Value	Source
SVR F0/F2	£343	Wright et al 2006,[34] inflated to 2012/3
SVR F3	£343	
SVR F4	£753	
F0/F2	£183	
F3	£949	
F4	£1,506	
DCC	£12,069	
HCC	£10,755	
Liver transplant	£48,685	Longworth 2001,[44] inflated to 2012/3
Post liver transplant	£1,833	Longworth 2001,[44] inflated to 2012/3

The cost of managing adverse events was estimated by multiplying the proportion of patients expected to experience an adverse event common to PI + PR and PR (as derived from the MTC) multiplied by the unit cost of the event (MS Table 98). Adverse event costs are taken from a published budget impact analysis of boceprevir and telaprevir treatment by Thorlund and colleagues[36] The source of the costing for this study is unclear as this is not stated in the MS or in Thorlund and colleagues[36]

Overall the ERG note that the approach to valuing the resource use is consistent with the NICE reference case, values are indexed to the current price year and the approach used to uprate published estimates was reported, and the NHS reference costs used are consistent with previous NICE appraisals.[26;27]

4.2.8 Consistency/ Model validation

Internal consistency

The economic model was developed in Microsoft Excel, with three alternative versions submitted for genotype 1, genotype 4 and patients intolerant to or ineligible for SMV+SOF. Random checking of the model has been done for some of the key equations in the model. However, the ERG has not undertaken a comprehensive check of all cells in the model. The ERG checked the model by varying parameter values to see if results produced intuitive results. Changes to the parameter settings in the 'Model settings' worksheet can be used to replicate the results presented in the MS and the deterministic sensitivity analyses for the base case model. The model is generally well presented and user friendly. The ERG views the model as a reasonable approach to modelling the cost effectiveness of simeprevir for hepatitis C and from random checking the 'wiring' of the model appears to be mostly accurate, with minor errors reported in the sections below.

The MS states that the models were quality checked by the model developer, and a second consultancy provided a further review and quality check to validate the structure and functionality of the model. This second reviewer identified some minor functionality errors, which resulted in the adaptation of the model to include more detailed descriptions of the model inputs. The MS states that the MTC and MAIC, that inform the genotype 1 and genotype 4 models respectively, were generated by a statistical team at Janssen and the code and outputs validated by an external agencies. The MTC and MAIC inputs were also quality checked by the

external agency. All model outputs used in the base case, sensitivity analyses and scenario analysis were quality checked by a second reviewer.

The ERG has noted an error in the calculation of the cost of ribavirin in the genotype 1 model. The dose for ribavirin varies by weight. The reference cell used to point to the weight of cohort is incorrect in genotype 1 model 'TxCosts!n21', where the cell should reference to 'modelsettings!D14', rather than 'modelsettings!L26'. So for genotype 1, the wrong dose of ribavirin is used. The ERG has corrected the calculation of the cost of ribavirin.

The ERG has noted that the health state costs used in the simeprevir and sofosbuvir model differ from those reported in the MS and from those used in the other two models. For the simeprevir and sofosbuvir model, the costs have been inflated to 2011/2 instead of 2012/3. The ERG has conducted a corrected analysis using the health state costs inflated to 2012/3 for the simeprevir and sofosbuvir model.

The ERG notes that the ranges used for the sensitivity analyses for SVR for genotype 1 do not use the credible interval ranges from the MTC as reported in MS Table 30, rather they have used +/- 25% as the ranges for the treatment-experienced group, however the ERG has re-run the analyses using the credible interval ranges and the results are not changed substantially (not shown in this report).

External consistency

The MS states the strengths of their analysis. They state that the major strength is that the approach adopted is very similar to that used for previously published cost-effectiveness analyses of treatments for HCV used in NICE appraisals,[26;27;33] and so results can easily be compared to the original models. The MS states that the results generated from the current model are very similar to the results generated from the previous models regarding comparisons of the PI regimens with PR alone. However, the ERG notes that the MS does not contain any such comparison. The MS further states that the models comply with the critical appraisal quality criteria.[46]

For external validation, the ERG has compared the total costs and QALYs predicted by the model for genotype 1 treatment naive patients, with the corresponding values for PR, boceprevir

and telaprevir obtained from the NICE STAs for boceprevir[27] and telaprevir.[26] These figures are given in Table 32.

Table 32 Comparison of total costs and QALYs obtained from NICE STAs for boceprevir and telaprevir with simeprevir model outputs (HCV genotype 1, treatment-naive,)

	Figures from relevant STAs			Figures from this submission (MS Table 117, p. 190.)		
	Total costs (£)	**QALYs**	**ICER (£/QALY)**	**Total costs (£)**	**QALYs**	**ICER (£/QALY)**
Boceprevir STA[27]						
PR	22,128	14.38	-	26,316	11.653	-
Boceprevir + PR	32,699	15.30	11,601	38,898	12.242	21,361
Telaprevir STA[26]						
PR	24,722	13.03	-	26,316	11.653	-
Telaprevir + PR	36,152	13.87	13,553	40,945	12.275	23,509

Table 32 indicates that total costs obtained from the simeprevir economic model are somewhat higher than the base case costs in the boceprevir and telaprevir STA base case. The boceprevir arm costs are around £6,000 higher in the simeprevir model than in the boceprevir STA model, whilst the PR costs are around £4,000 higher. The telaprevir arm costs are around £5,000 higher in the simeprevir model than in the telaprevir STA model, whilst the PR costs are around £2,000 higher. The difference in cost is mainly due to longer treatment duration used in the simeprevir model than the other models. For example, the total drug cost for telaprevir + PR varies between £25,391 and £29,490 for the simeprevir model and the telaprevir STA, respectively. The ERG investigates changing treatment duration in a scenario analysis in section 4.3.2.

The total QALYs estimated by the simeprevir economic model are lower than the QALYs estimated in the boceprevir and telaprevir STAs for PR, boceprevir and telaprevir. For example, the total QALYs estimated for PR are 11.65 in the simeprevir model compared with 13.03 and 14.38 in the telaprevir and boceprevir STAs respectively. The incremental QALY gain is lower for boceprevir and telaprevir compared to PR for the simeprevir model than the other STAs. It is unclear what factors are driving the differences in QALYs between the models, but it may be linked to differences in the baseline populations in the models, such as starting ages and HCV

severity, and in addition there are other small differences between the models, such as differences in the transition probabilities.

The simeprevir economic model thus makes boceprevir appear less cost effective compared to PR than suggested in the boceprevir STA (TA253[27]) (ICER of £21,361/QALY compared to £11,601/QALY using boceprevir STA figures). Similarly the ICERs for telaprevir compared to PR are £23,509/QALY compared to £13,553/QALY using telaprevir STA figures [TA252[26]]).

In summary, the simeprevir model estimates higher total costs and lower QALYs, and generates less favourable ICERs for boceprevir and telaprevir compared to PR than the boceprevir and telaprevir STAs. The ERG does not have access to the economic models used in the boceprevir and telaprevir submissions and so was unable to check in detail for potential causes of this difference.

4.2.9 Assessment of Uncertainty

One-way sensitivity analyses

A series of deterministic univariate sensitivity analyses were carried out on the base case models. All model parameters were varied separately (MS Table 100 for HCV genotype 1; Table 103 for HCV genotype 4 and Table 110 for simeprevir + sofosbuvir), within the limits of their 95% confidence intervals (or credible intervals where applicable). Where confidence intervals were not available, the standard error was assumed to vary 20% around the mean. The ERG notes that the manufacturer has not conducted sensitivity analyses using a range of discount rates.

The MS presents the 15 most sensitive model parameters from the sensitivity analyses and displays these diagrammatically in a tornado diagram. For genotype 1, the results are presented for simeprevir vs. PR (MS Table 123), simeprevir + PR vs. boceprevir + PR (MS Table 124) and simeprevir + PR vs. telaprevir + PR (MS Table 125). The model results were most sensitive to the percentage of patients achieving SVR (for all treatments), the post-treatment transition probabilities and their associated health care costs, together with the utility associated with achieving SVR in treatment-naive and treatment-experienced genotype 1 populations. Simeprevir + PR dominates boceprevir + PR for all sensitivity analyses and dominates telaprevir

+ PR for all sensitivity analyses except for two treatment-experienced patient analyses. For treatment-naive patients, the cost effectiveness estimates vary between £12,119 and £18,116 per QALY gained for simeprevir + PR vs. PR. For treatment-experienced patients, the cost effectiveness estimates vary between £7563 and £14,210 per QALY gained for simeprevir + PR vs. PR.

For genotype 4, the sensitivity analysis results are presented in MS Table 134 for simeprevir + PR vs. PR (as stated earlier, this is the only treatment comparison made for genotype 4 patients). The model is most sensitive to the proportion of patients achieving SVR for both simeprevir + PR and PR, although the effect is greater in treatment-naive patients than treatment-experienced patients. The ICER varies between £4,532 and £36,094 per QALY for simeprevir + PR vs. PR for all treatment-naive sensitivity analyses. For treatment-experienced patients, the ICER varies between £6,660 and £11,854 for all sensitivity analyses.

For the SMV+SOF model, the sensitivity analysis results are presented in MS Table 147 for simeprevir + PR vs. no treatment (NB. MS table 110 gives sensitivity analysis input values for the comparison with telaprevir + PR and with boceprevir + PR, but sensitivity analysis results for these comparisons are not given in the MS. Instead sensitivity analyses results are given for the comparison with no antiviral treatment, which is the comparator that the manufacturer is most appropriate for this patient group). The model results were most sensitive to the post-treatment transition probabilities, in particular the estimate for SVR F4 to decompensated cirrhosis. The ICER varies £10,843 and £21,388 per QALY gained for all analyses (i.e. treatment naive and treatment-experienced).

Scenario Analysis

The manufacturer has conducted several scenario analyses to explore the sensitivity of the model results to key structural assumptions in the model. The scenario analyses are described in MS Table 99. Scenario analyses are conducted for changes to the patients' characteristics, time horizon, transition probabilities, treatment utility decrement, cost of liver transplant, trials used in the NMA, and the proportion of boceprevir + PR patients eligible for RGT.

The results from the scenario analyses are shown in MS Table 126-7 for genotype 1, MS Table 135-6 for genotype 4 and MS Table 148-9 for SMV+SOF. The ERG was not able to replicate all scenario analyses and requested clarification from the manufacturer. The manufacturer

provided corrected scenario analyses in their letter of clarification. The results in the corrected scenario analyses did not differ substantially from those presented in the MS.

Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis can be run by clicking on the 'Run PSA' button on the 'Model settings' worksheet in the Excel model. The number of simulations is set at 3000 for the genotype 1 and the simeprevir + sofosbuvir models, and 1000 simulations for the genotype 4 model. The model ran in about 2 minutes. The MS states that increasing the number of simulations above these values did not stabilise the results further. The input variables reported in MS Table 100 were included in the PSA, as previously reported for the sensitivity analyses. Two further parameters for Metavir fibrosis class and the response to prior treatment were also included in the PSA as correlated variables. The PSA does not contain variation in the input values for some demographic parameters of the model, for example patient age, gender or the proportion of patients with genotype 1 who are genotype 1a and treatment discontinuation, although these parameters were varied in the scenario analyses. Beta distributions were chosen for probabilities and HRQoL, gamma distributions chosen for costs, and log-normal distributions were chosen for clinical parameters. The distributions chosen seemed reasonable.

The MS presents the results of the PSA as scatterplots and cost effectiveness acceptability curves. For genotype 1, these are presented in MS Figure 49-52. At willingness-to pay thresholds of £20,000 and £30,000, the probability of simeprevir + PR being cost effective against all comparators for treatment naive patients is estimated at 92.9% and 97.5% respectively. For treatment-experienced patients, the probability of simeprevir + PR being cost-effective is estimated at 63.9% and 68.4% at £20,000 and £30,000 per QALY thresholds respectively.

For genotype 4, PSA results are presented in MS Figure 54-57. At willingness-to pay thresholds of £20,000 and £30,000, the probability of simeprevir + PR being cost effective compared to PR for treatment naive patients is estimated at 78.6% and 87.4% respectively. For treatment-experienced patients, the probability of simeprevir + PR being cost-effective is estimated at 97.2% and 99.9% at £20,000 and £30,000 per QALY thresholds respectively.

For the SMV+SOF model, PSA results are presented in MS Figure 61-64. At willingness-to pay thresholds of £20,000 and £30,000, the probability of simeprevir + PR being cost effective

compared to no treatment for treatment naive patients is estimated at 76.7% and 94.3% respectively. For treatment-experienced patients, the probability of simeprevir + PR being cost-effective is estimated at 83.2% and 96.3% at £20,000 and £30,000 per QALY thresholds respectively.

The ERG has run the PSA for each of the manufacturer's models (Table 33 and Table 34). The cost estimates from the PSAs differ slightly from those produced by the deterministic results. For example the ICER for the genotype 1 treatment cohort for simeprevir + PR vs. PR was £11,865 compared to the deterministic results of £14,206 per QALY. For this group, the total QALYs are lower and the total costs are higher for the PSA run than for the deterministic result. The ERG has investigated why the results are different and found that the differences are caused by the sampling of the baseline patient characteristics, i.e. the proportion of patients in each of the HCV groups at baseline. For example in the treatment-naive group, the baseline proportion with F4 in the PSA was about 40%, compared to the proportion in the deterministic case of 20%. When the ERG fixed these proportions, the PSA results were similar to that of the deterministic results.

Table 33 Base case PSA results genotype 1 treatment-naive

	Total		**Incremental**		**ICER v baseline**	**ICER**
	Costs	**QALYs**	**Costs**	**QALYs**		
PR	£31,589	10.530				
Simeprevir + PR	£40,855	11.311	£9,266	0.78	£11,865	£11,865
Boceprevir + PR	£45,512	11.149	£4,657	-0.16	£22,490	Dominated
Telaprevir + PR	£45,859	11.178	£5,004	-0.13	£22,042	Dominated

PR: peginterferon + ribavirin.

Table 34 Base case results PSA genotype 1 treatment-experienced

	Total		Incremental		ICER v baseline	ICER
	Costs	QALYs	Costs	QALYs		
PR	£33,732	10.461				
Simeprevir + PR	£44,211	11.313	£10,479	0.85	£12,292	£12,292
Telaprevir + PR	£44,761	11.285	£550	-0.03	£13,376	Dominated
Boceprevir + PR	£50,492	11.184	£6,281	-0.13	£23,179	Dominated

PR: peginterferon + ribavirin.

4.2.10 Comment on validity of results with reference to methodology used

The structure adopted for the economic model and the input parameters used are reasonable, and consistent with previous economic evaluations developed for HCV. The model introduces a transition from the SVR-cirrhotic health state (SVR F4) to the decompensated cirrhosis that has not been included in previous models.

The model for genotype 1 uses clinical effectiveness parameters from an MTC of the clinical trials. The model assumes that patients with F3 and F4 have the same SVR parameter values. The model uses the OR from the MTC to calculate SVR values for the other treatments in relation to peginterferon alfa, and the same odds ratio is used for the F0-2 and F3-F4 groups. The limitations of the assumptions underpinning this approach are not discussed in the MS. The genotype 4 model uses clinical effectiveness data from a MAIC (treatment naive patients only) as there are no head to head RCTs. However there appear to be limitations in the MAIC used to derive these estimates. For treatment experienced genotype 4 patients an unadjusted indirect comparison with no matching was undertaken.

The methods of analysis are generally appropriate and conform to NICE methodological guidelines. However, there were some discrepancies detected for the parameter values used in the three submitted models. These have been documented in this report along with corrected results.

4.3 Additional work undertaken by the ERG

4.3.1 Corrected base case

The ERG has corrected the errors identified in the genotype 1 model for the calculation of the cost of ribavirin. The corrected base case results are shown below in Table 35 and Table 36 and are similar to the MS base case.

Table 35 Base case cost effectiveness results for genotype 1 treatment-naive with correction

	Total		Incremental		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICER (£/QALY)**
PR	£27,039	11.653			
Simeprevir + PR	£37,128	12.390	£10,089	0.74	£13,698
Boceprevir + PR	£39,442	12.242	£2,315	-0.15	Dominated
Telaprevir + PR	£41,489	12.275	£4,361	-0.11	Dominated

PR: peginterferon + ribavirin.

Table 36 Base case cost effectiveness results for genotype 1 treatment-experienced with correction

	Total		Incremental		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICER (£/QALY)**
PR	£35,147	10.327			
Simeprevir + PR	£44,057	11.258	£8,911	0.93	£9,568
Telaprevir + PR	£45,076	11.226	£1,019	-0.03	Dominated
Boceprevir + PR	£50,225	11.128	£6,168	-0.13	Dominated

PR: peginterferon + ribavirin

The ERG has corrected the health state costs used in the SMV+SOF model that do not match those reported in the MS and used in the other two of the manufacturer's models. The corrected base case results are shown below in Table 37 and Table 38 (restricted to the comparison with no anti-viral treatment) and are similar to the MS base case.

Table 37 Base case cost effectiveness results for simeprevir + sofosbuvir model treatment-naive with correction

	Total			Incremental	
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICER (£/QALY)**
No treatment	£32,851	9.369			
SMV+SOF 12 weeks	£69,213	11.747	£36,362	2.38	£15,287

SOF: sofosbuvir; SMV: simeprevir

Table 38 Base case cost effectiveness results for simeprevir + sofosbuvir model treatment-experienced with correction

	Total			Incremental	
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICER (£/QALY)**
No treatment	£33,438	9.239			
SMV+SOF 12 weeks	£68,268	11.761	£34,830	2.52	£13,809

SOF: sofosbuvir; SMV: simeprevir

4.3.2 Additional scenarios undertaken by the ERG

This section details the ERG's further exploration of the issues and uncertainties raised in the review and critique of the MS cost effectiveness analyses. These analyses concern:

a. Using ONS data for all-cause mortality in genotype 1 patients
b. ITT analysis for simeprevir trials (i.e. including Q80K positive and negative patients)
c. SVRs by separate baseline fibrosis grades for peginterferon alfa and ribavirin taken from the pooled QUEST 1 and 2 trials
d. 1.5% discount rate for costs and outcomes
e. Variations in the transition probability between SVR achieved in the F4 (compensated cirrhosis) health state and the HCC / DCC health states
f. Variations in the transition probability between the F4 and DCC health states
g. Changes in the treatment duration for telaprevir and boceprevir
h. Alternative SVRs for genotype 4 patients
i. An older baseline age for patients intolerant to or ineligible for interferon alfa treated with SMV+SOF

All analyses use the corrected versions of the manufactured models, referred to in the analyses as the amended model.

a) All-cause mortality

The manufacturer's economic models use different all-cause mortality probabilities: the genotype 1 model uses mortality rates from the Government's Actuary Department, whilst the genotype 4 and SMV+SOF models use mortality rates from the ONS. It is unclear from the MS which of these is the manufacturer's preferred source, as the reference given is incorrect. The ERG assumes that the manufacturer intended to use ONS data for all models and has conducted a scenario analysis for this and the results are shown in Table 39 and Table 40. Changing the mortality rate produces an ICER of £12,077 per QALY gained for the treatment naive population for simeprevir + PR versus PR, compared to the base case corrected ICER of £13,698 per QALY (Table 35). For the treatment-experienced population, the ICER changes to £8,229 per QALY (from a corrected base case of £9,568 per QALY, Table 36). For both analyses simeprevir + PR continues to dominate boceprevir + PR and telaprevir + PR.

Table 39 Cost effectiveness results for genotype 1 treatment naive using mortality rates from ONS with amended model

	Total		Incremental		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICER (£/QALY)**
PR	£27,880	12.225			
Simeprevir + PR	£37,567	13.027	£9,687	0.80	£12,077
Boceprevir + PR	£39,953	12.868	£2,386	-0.16	Dominated
Telaprevir + PR	£41,980	12.904	£4,413	-0.12	Dominated

PR: peginterferon + ribavirin.

Table 40 Cost effectiveness results for genotype 1 treatment experienced using mortality rates from ONS with amended model

	Total		Incremental		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICER (£/QALY)**
PR	£36,426	10.792			
Simeprevir + PR	£44,801	11.810	£8,376	1.02	£8,229
Telaprevir + PR	£45,834	11.775	£1,033	-0.03	Dominated
Boceprevir + PR	£51,036	11.669	£6,234	-0.14	Dominated

PR: peginterferon + ribavirin.

b) ITT analysis from trial data

The MS base case analyses assumes that all patients with genotype 1a would be tested for the presence of the NS3 Q80K polymorphism, and only those who are negative would receive simeprevir (using data from the sub-group of Q80K negative patients from the simeprevir RCTs). In this scenario, the ERG uses the odds ratio from the ITT analysis from the simeprevir RCTs (i.e. regardless of Q80K status) and the results are shown in Table 41 and Table 42 (Note that there would therefore be no cost for Q80K testing in this analysis). For the treatment naive population, the ICER for simeprevir + PR vs. PR increases to £17,038 per QALY (compared to a corrected base case of £13,698 per QALY, Table 35) and simeprevir + PR continues to dominate telaprevir + PR and boceprevir + PR. For the treatment-experienced population, the ICER for simeprevir + PR vs. PR increases to £10,507 (compared to a corrected base case of £9,568 per QALY, Table 36), telaprevir + PR becomes more effective than simeprevir + PR with an ICER of £49,130 per QALY, and boceprevir + PR continues to be dominated.

Table 41 Cost effectiveness results for genotype 1 treatment naive using ITT trial data with amended model

	Total		Incremental		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	
PR	£27,039	11.653			
Simeprevir	£37,971	12.295	£10,932	0.64	£17,038
Boceprevir	£39,442	12.242	£1,471	-0.05	Dominated
Telaprevir	£41,489	12.275	£3,518	-0.02	Dominated

PR: peginterferon + ribavirin.

Table 42 Cost effectiveness results for genotype 1 treatment experienced using ITT trial data with amended model

	Total		Incremental		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	
PR	£35,147	10.327			
Simeprevir	£44,463	11.214	£9,316	0.89	£10,507
Telaprevir	£45,076	11.226	£613	0.01	£49,130
Boceprevir	£50,225	11.128	£5,149	-0.10	Dominated

c) Direct trial evidence from Quest 1 and 2

The manufacturer uses the MTC for estimates for treatment effectiveness in the base case results for genotype 1 patients. The manufacturer has assumed that PR treated patients with fibrosis grades F3 and F4 would have the same SVR and that the proportional differences between the F0-F2 and F3-F4 subgroups remain constant (and the same as for PR) for all comparators. In this scenario, shown in Table 43, the ERG has used the pooled data from the PR arm of the QUEST 1 and 2 trials (SVRs: F0-F2 55%; F3 = 37.5%, F4 = 34.4%) (MS Table 17, p. 51). The ICER for simeprevir + PR increases to £16,717 per QALY compared to PR (compared to a corrected base case of £13,698 per QALY).

Table 43 Cost effectiveness results for genotype 1 treatment-naive patients for with SVR estimates from the QUEST 1 and 2 trials with amended model

	Total		Incremental		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICERs(£/QALY)**
PR	£26,795	11.689			
Simeprevir + PR	£37,686	12.340	£10,892	0.65	£16,717

PR: peginterferon + ribavirin.

d) Discount rate 1.5% for costs and outcomes

The MS does not examine the effect of changes to the discount rate in sensitivity analyses. The NICE Methods Guide[47] advises that sensitivity analyses using discount rates of 1.5% for both costs and health effects may be presented alongside the base case analysis. This analysis is shown in Table 44. A discount rate of 1.5% for costs and outcomes produces more favourable ICERs for simeprevir + PR versus PR of £7,604 per QALY gained for treatment-naive and £4,424 per QALY gained for treatment-experienced patients. In a similar manner, in genotype 4 patients the ICER for simeprevir versus PR reduced to £6,024 per QALY gained for treatment naive and £3,818 per QALY gained for treatment experienced patients respectively. For treatment naive patients unsuitable for interferon, the ICER reduced to £8,073 per QALY for simeprevir and sofosbuvir vs. no treatment and for treatment experienced patients unsuitable for interferon, the ICER decreased to £7,104 per QALY.

Table 44 Cost effectiveness results using a discount rate of 1.5% for costs and outcomes with amended model

Indication	Comparison	Base case corrected ICER (£/QALY)	Revised ICER (£/QALY)
Genotype 1 TN	Simeprevir + PR vs. PR	£13,698	£7,604
Genotype 1 TE	Simeprevir + PR vs. PR	£9,568	£4,424
Genotype 4 TN	Simeprevir + PR vs. PR	£11,662	£6,024
Genotype 4 TE	Simeprevir + PR vs. PR	£8,896	£3,818
Genotype 1 UI TN	Simeprevir + sofosbuvir vs. no treatment	£15,287	£8,073
Genotype 1 UI TE	Simeprevir + sofosbuvir vs. no treatment	£13,809	£7,104

PR: peginterferon + ribavirin; TN: treatment naive; TE: treatment experienced: UI: unsuitable for interferon

e) Different estimates for transition between SVR and DCC / HCC

As discussed in section 4.2.1, the manufacturer has used a transition probability from SVR F4 (compensated cirrhosis) to HCC which is informed by a study by Cardoso and colleagues (2010),[39] and which is also used to extrapolate to the SVR F4 to DCC transition. This approach differs from some of the previous economic models, which have not included the transition between SVR F4 and DCC. In addition, the study by Cardoso and colleagues reports a transition probability of 0.0123 for SVR F4 to HCC, rather than 0.005 as used in the economic model. This scenario investigates the effect using a transition probability between SVR F4 and DCC of 0 (base case = 0.014), and between SVR F4 and HCC of 0.0123 and the results are shown in Table 45 and Table 46. Variation in these transition probabilities has only a small effect on the ICERs: changing the transition probability to DCC produces more favourable ICERs and changing the transition probability to HCC produces less favourable ICERs.

Table 45 Cost effectiveness results using a different estimate for transition between SVR F4 and DCC with amended model

Indication	Comparison	Base case corrected ICER (£/QALY)	Revised ICER (£/QALY)
Genotype 1 TN	Simeprevir + PR vs. PR	£13,698	£11,489
Genotype 1 TE	Simeprevir + PR vs. PR	£9,568	£7,078
Genotype 4 TN	Simeprevir + PR vs. PR	£11,662	£9,740
Genotype 4 TE	Simeprevir + PR vs. PR	£8,896	£6,493
Genotype 1 UI TN	Simeprevir + sofosbuvir vs. no treatment	£15,287	£11,927
Genotype 1 UI TE	Simeprevir + sofosbuvir vs. no treatment	£13,809	£10,346

PR: peginterferon + ribavirin; TN: treatment naive; TE: treatment experienced: UI: unsuitable for interferon

Table 46 Cost effectiveness results using a different estimate for transition between SVR F4 and HCC with amended model

Indication	Comparison	Base case corrected ICER (£/QALY)	Revised ICER (£/QALY)
Genotype 1 TN	Simeprevir + PR vs. PR	£13,698	£14,625
Genotype 1 TE	Simeprevir + PR vs. PR	£9,568	£10,545
Genotype 4 TN	Simeprevir + PR vs. PR	£11,662	£12,417
Genotype 4 TE	Simeprevir + PR vs. PR	£8,896	£9,812
Genotype 1 UI TN	Simeprevir + sofosbuvir vs. no treatment	£15,287	£16,845
Genotype 1 UI TE	Simeprevir + sofosbuvir vs. no treatment	£13,809	£15,401

PR: peginterferon + ribavirin; TN: treatment naive; TE: treatment experienced: UI: unsuitable for interferon

f) Different estimates for transition between F4 and HCC

The MS used a transition probability for F4 to HCC of 0.014 from the Fattovich and colleagues.[40] A more recent study by Cardoso and colleagues[39] reports an incidence of HCC of 5.85 per 100 person years for patients (i.e. annual probability of 0.0568) with bridging fibrosis (F3) or cirrhosis (F4) with no SVR. The study reports that there was no difference between the incidence of HCC in patients with bridging fibrosis or cirrhosis. The ERG has conducted a scenario using a transition probability for F4 to HCC of 0.0568, as per the study by Cardoso and colleagues, and the results are shown in Table 47. Changes to the transition probability causes more favourable results for simeprevir + PR in all analyses.

Table 47 Cost effectiveness results using a different estimate for transition between F4 and HCC with amended model

Indication	Comparison	Base case corrected ICER (£/QALY)	Revised ICER (£/QALY)
Genotype 1 TN	Simeprevir + PR vs. PR	£13,698	£11,455
Genotype 1 TE	Simeprevir + PR vs. PR	£9,568	£7,852
Genotype 4 TN	Simeprevir + PR vs. PR	£11,662	£9,933
Genotype 4 TE	Simeprevir + PR vs. PR	£8,896	£7,406
Genotype 1 UI TN	Simeprevir + sofosbuvir vs. no treatment	£15,287	£11,991
Genotype 1 UI TE	Simeprevir + sofosbuvir vs. no treatment	£13,809	£10,814

g) Treatment duration

The manufacturer's model uses treatment durations for the comparator treatment which are longer than used previous NICE STAs.[26;27] These previous appraisals used the treatment duration of the treatments seen in the comparator clinical trials.

For the treatment naive population, the telaprevir STA economic model[48] used 36.3 weeks treatment for PR; 10.7 weeks telaprevir and 26.9 weeks PR from the ADVANCE trial (Telaprevir MS, p. 68[48]). The boceprevir STA economic model[49] used 22.6 weeks of boceprevir and 30 weeks PR, from the SPRINT trial (estimated from results presented in boceprevir MS, p. 240[49]).

For the treatment experienced population, the telaprevir STA economic model[48] used 30 weeks treatment for PR; 10.7 weeks treatment telaprevir and 38.6 weeks PR from the REALIZE trial (Telaprevir MS, p. 74[26]). The boceprevir STA economic model[49] used 28 weeks boceprevir and 30 weeks PR, from the SPRINT trial, estimated from results presented in boceprevir MS, p. 246[27]).

The ERG conducted analyses with these treatment durations for telaprevir and boceprevir and the results are shown in Table 48. For the treatment naive population, the total cost for boceprevir + PR is now lower than for simeprevir + PR and has an ICER of £16,630 per QALY vs. PR. Simeprevir + PR has an ICER of £22,541 per QALY versus boceprevir + PR and telaprevir + PR remains dominated by simeprevir + PR. Similarly for the treatment-experienced population, the ICER for boceprevir + PR vs. PR is £15,344, simeprevir + PR has an ICER of £6,885 vs. boceprevir + PR and telaprevir + PR remains dominated by simeprevir + PR (Table 49).

Table 48 Cost effectiveness results for genotype 1 treatment naive patients using different estimates of treatment duration for comparators with amended model

	Total		Incremental		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICER (£/QALY)**
PR	£24,481	11.677			
Boceprevir + PR	£34,089	12.255	£9,607	0.58	£16,630
Simeprevir + PR	£37,128	12.390	£3,039	0.13	£22,541
Telaprevir + PR	£37,307	12.294	£179	-0.10	Dominated

PR: peginterferon + ribavirin.

Table 49 Cost effectiveness results for genotype 1 treatment-experienced patients using different estimates of treatment duration for comparators with amended model

	Total		Incremental		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICER (£/QALY)**
PR	£31,212	10.364			
Boceprevir + PR	£43,344	11.155	£12,131	0.79	£15,344
Simeprevir + PR	£44,057	11.258	£714	0.10	£6,885
Telaprevir + PR	£44,614	11.225	£557	-0.03	Dominated

PR: peginterferon + ribavirin.

h) Genotype 4 model SVR estimates

The manufacturer's model uses a MAIC to obtain values for genotype 4 treatment naive patients. This scenario investigates alternative SVR values for genotype 4 treatment naive patients. The MAIC matches patients from the RESTORE study and Rumi and colleagues.[20] The ERG has concerns with the MAIC (section 3.1.7). The ERG notes that the SVR for PR ranges from 44.4% (Rumi and colleagues[20]) to 70.6% (Kamal and colleagues[50]) across the studies considered for potential inclusion in the MAIC. For simeprevir + PR, SVR values of 82.9% (compared to 77.1% SVR used in the MS base case) were taken from the RESTORE study and for PR the SVR values from Kamal and colleagues were used. Changing these SVRs produces an ICER of £39,422 per QALY for simeprevir + PR vs. PR compared to the base analysis ICER of £11,662 per QALY (Table 50).

Table 50 Cost effectiveness results for genotype 4 treatment-naive patients using different SVR estimates

	Total		Incremental		ICER (£) (QALYs)
	Costs (£)	QALYs	Costs (£)	QALYs	
PR	£22,068	12.836			
Simeprevir + PR	£34,577	13.154	£12,509	0.32	£39,422

PR: peginterferon + ribavirin.

The manufacturer did not identify any PR studies for treatment experienced genotype 4 patients. They derived the SVRs for this group by assuming the same proportional decline in SVR between treatment naive and treatment experienced patients from the MTC for genotype 1 patients for PR. This assumption was used with the SVR values for treatment naive patients from the MAIC and results in a SVR of 15% for PR. The ERG scenario used alternative SVR values by using the same assumption of proportional decline with the Kamal and colleagues study for treatment naive patients, which gives an SVR of 23.8%. Changing the SVR produces an ICER of £13,614 per QALY compared to the base analysis of £8,896 per QALY (Table 51).

Table 51 Cost effectiveness results for genotype 4 treatment-experienced patients using different SVR estimates

	Total		Incremental		ICER (£) (QALYs)
	Costs (£)	QALYs	Costs (£)	QALYs	
PR	£34,866	10.935			
Simeprevir + PR	£45,591	11.722	£10,726	0.79	£13,614

PR: peginterferon + ribavirin.

i) Patient age in simeprevir and sofosbuvir model

In the MS the mean age of patients in the model cohort is 50 years, however in cohort 2 of the COSMOS study the median age was 58 years. In this scenario patients' age is set to 58 years to match the study (NB. no distinction was made between the ages of treatment naive and treatment experienced patients as this information was not reported in the MS). The ICERs for SMV+SOF vs. no treatment increase to £21,625 per QALY for treatment naive patients (Table 52) and to £19,673 per QALY for treatment experienced patients (Table 53).

Table 52 Cost effectiveness results for simeprevir and sofosbuvir model for treatment naive patients using age of 58 years with amended model

	Total		Incremental		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICER**
No treatment	£28,151	8.357			
SMV+SOF 12 weeks	£67,967	10.198	£39,816	1.84	£21,625

Table 53 Cost effectiveness results for simeprevir and sofosbuvir model for treatment experienced patients using age of 58 years with amended model

	Total		Incremental		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**ICER**
No treatment	£28,741	8.251			
SMV+SOF 12 weeks	£67,171	10.204	£38,431	1.95	£19,673

4.4 Summary of uncertainties and issues

There is a lack of head to head RCTs comparing simeprevir + PR with alternative anti-viral treatments. The economic evaluation therefore uses an MTC to estimate clinical effectiveness of treating genotype 1 patients. The ERG notes that the MTC is of reasonable quality, though some treatments were connected together only by single trial arms. To accord with the licence for simeprevir the MTC uses SVRs for the sub-group of Q80K polymorphism negative patients in the simeprevir trials. This breaks randomisation, though the MS reports that the majority of patients in the simeprevir study programme were Q80K negative (70%). Clinical effectiveness estimates for genotype 4 patients and patients ineligible for or intolerant to interferon alfa were based on unadjusted indirect comparisons based on small uncontrolled studies, which the ERG notes are subject to limitations. Cost-effectiveness estimates for the latter two patient groups are therefore subject to the greatest uncertainties in terms of clinical effectiveness input data.

The cost-effectiveness of simeprevir + sofosbuvir in genotype 1 patients ineligible for or intolerant to interferon alfa is made in relation to comparators that are either not within the NICE scope (i.e. no anti-viral treatment), or comparison drug regimens that include interferon (i.e. telaprevir + PR, boceprevir + PR) and therefore do not reflect clinical practice for this patient group. No cost-effectiveness evidence was presented for simeprevir + sofosbuvir in genotype 4 patients intolerant to or ineligible for interferon. However, the MS notes that the Committee for Medicinal Products for Human Use (CHMP) recognises that the efficacy of this combination in genotype 1 patients can be assumed for patients with genotype 4.

The base case model does not include genotype 1a patients who are positive for the Q80K polymorphism (assumed to be around 30% of genotype 1a patients). The summary of product characteristics for simeprevir recommends that alternative therapy should be considered for these patients. Alternative therapy could include telaprevir + PR and boceprevir + PR, both of which are recommended by NICE for use in genotype 1a patients. However, these would not be appropriate in Q80K positive genotype 1a patients ineligible for or intolerant to interferon alfa who would therefore lack any alternative therapy.

The cost-effectiveness of simeprevir + PR in patients co-infected with HIV and HCV has not been estimated as the manufacturer has assumed that they are equal in efficacy.

5 End of life

Not applicable.

6 Innovation

The manufacturer makes the case that simeprevir belongs to a new class of PI which has a different mode of binding compared with the first generation PIs, telaprevir and boceprevir (MS p.27). The MS highlights that 'strong efficacy' has been demonstrated, without the poorer tolerability profile associated with the first generation PIs. Simeprevir has the lowest pill burden (one tablet daily) of all PI treatments, and will halve the time on treatment and number of IV injections for many patients. Simeprevir can be used in a broad range of patients, including genotype 1, genotype 4, and HIV co-infected patients, regardless of liver disease severity and prior treatment experience.

Simeprevir is a 'step' change in the management of the following groups of people:

- Patients with genotype 4, as it is the first PI to be licensed for this indication
- Patients intolerant to or ineligible for interferon based regimens, as it is the first treatment to demonstrate efficacy in an interferon-free regimen when combined with sofosbuvir.

The MS also suggests there are likely to be wider societal benefits in the form of reduced onward transmission among patients.

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The manufacturer identified four phase 3 RCTs and two phase 2 RCTs of simeprevir + PR that are relevant to the decision problem; however, although the phase 2 RCTs were included in the MTC they were not discussed within the main body of evidence despite having relevant intervention and comparator arms.

The MTC conducted for comparison of simeprevir + PR against relevant comparators was considered to be well conducted and well reported, but with two caveats that may introduce uncertainty around the reliability of the findings:

- Few studies were available to form the MTC network, with the majority of the comparisons being informed by single trials;

- For consistency with the licensed indication, the MTC excluded HCV genotype 1a patients who had the Q80K polymorphism in the simeprevir + PR arms; this broke the randomisation within the RCTs being compared, meaning that imbalances might occur in the prognostic characteristics of the groups being compared.

The MAIC of simeprevir and comparator studies in HCV genotype 4 patients was considered by the ERG to have serious limitations, as the analytical approach is dependent upon having a reasonable range of baseline characteristics reported for the studies to be matched but in practice this was not feasible. The ERG also had concerns about a lack of clarity regarding the methods employed in the MAIC and the quality of the contributing studies; as well as the lack of any statistical analyses, including analyses of uncertainty, or processes for validating the results.

Data on relevant patient subgroups were provided for HCV genotype 4 patients, HCV genotype 1 patients with HIV co-infection, and HCV genotype 1 patients receiving simeprevir + sofosbuvir therapy (±ribavirin). However, in each of these subgroups data were only available from a single non-RCT study.

At the time of this STA, sofosbuvir is being considered by NICE through the STA programme. If approved, sofosbuvir could be considered as a comparator. The ERG conducted a search for sofosbuvir and identified no relevant trials that could be included in the MTC.

7.2 Summary of cost effectiveness issues

The MS includes evidence on the cost effectiveness of simeprevir + PR in genotype 1 and genotype 4 patients and of simeprevir + sofosbuvir in genotype 1 patients compared with the current treatment standard. The model structure and methods adopted for the economic evaluation are reasonable and generally appropriate. The model structure and model parameters are consistent with previous economic evaluations of anti-viral therapy for chronic hepatitis C.

The ERG identified some inconsistencies in data included in the models (calculation of ribavirin cost, health state costs). Additional analyses have been presented by the ERG for changes to some of the model parameters. While these have some effect on costs and outcomes in the models they do not have a substantial impact on the cost effectiveness estimates for simeprevir.

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9 APPENDICES

9.1 Appendix 1

Summary of key results from Phase 2 RCTs PILLAR and ASPIRE

Fried and colleagues[11] and Zeuzem and colleagues[10] stated that their respective studies PILLAR and ASPIRE were not powered to provide definitive data across subpopulations and observations must be confirmed in larger phase 3 trials; and the MS (p. 34) gives this as a reason for not including these studies in the main clinical effectiveness section (although they are both included in the MTC).

As both of these studies contribute data to the MTC their results are briefly summarised below.

PILLAR

Virologic results from PILLAR (Fried and colleagues[11])

Fried and colleagues[11] noted that the SVR12 rate in the placebo + PR group was higher than expected and it is very different to that obtained in the placebo + PR group of ASPIRE: 66.2% in PILLAR (Table 54) versus 22.7% in ASPIRE (Table 55, part reflecting the population difference of naive vs experienced patients). It should also be noted that PILLAR excluded cirrhotic patients (which were included in other trials) – MS p. 90, section 6.7.9.

Table 54 Virologic results from PILLAR (HCV genotype 1, treatment-naive)

Outcome (from MS Table 184, p.295)	**SMV (12 weeks) +PR (48 weeks)**	**Placebo + PR (48 weeks)**	**Difference between groups**
SVR12, % (n/N) [a]	80.5 (62/77)	66.2 (51/77)	NS
SVR24, % (n/N) [a]	80.5 (62/77)	64.9 (50/77)	p<0.05
Viral breakthrough, % (n/N)	7.8 (6/77)	5.2 (4/77)	NS
Viral relapse, % (n/N)	8.7 (6/69)	17.7 (11/62)	NS

a. Specified as a secondary outcome. NS: not statistically significant; PR: peginterferon + ribavirin; SMV: simeprevir

Fatigue results from PILLAR (from Fried and colleagues[11])

Patient-reported Fatigue Severity Scale (FSS) scores in the simeprevir + PR group increased from baseline, peaking around week 24, and then declined to be at or lower than baseline levels during weeks 36-72. FSS scores in the placebo + PR group showed a similar pattern except that the scores remained relatively high up to week 48 before returning to baseline levels during weeks 60-62. These results indicate that both simeprevir and PR regimens increase fatigue, but effects of simeprevir on fatigue are of shorter duration than those of PR, consistent with the shorter duration of the simeprevir regimen compared to PR.

Adverse events in PILLAR (from MS and Fried and collegues[11])

No mortality occurred. Overall, there were no notable differences in the frequency or types of adverse events in the simeprevir and PR groups. An exception is that a mostly mild (grade 1) elevation in serum bilirubin occurred in the simeprevir group, although bilirubin levels decreased to baseline levels after patients completed simeprevir dosing. The hyperbilirubinaemia led to one discontinuation in the simeprevir group.

ASPIRE

Table 55 Virologic results from ASPIRE (HCV genotype 1, treatment-experienced)

Outcome (from MS (Table 183, p. 294) and paper[10])	**SMV (12 weeks) +PR (48 weeks)**	**Placebo + PR (48 weeks)**	**Difference between groups**
SVR12, % (n/N) [a]			
- overall	66.7 (44/66)	22.7 (15/66)	NS
SVR24, % (n/N) [b]			
- overall	66.7 (44/66)	22.7 (15/66)	p<0.001
- prior null response	52.9 (9/17)	18.8 (3/16)	NS
- prior partial response	65.2 (15/23)	8.7 (2/23)	NS
- prior relapse	76.9 (20/26)	37 (10/27)	NS
Viral breakthrough, % (n/N)	9.1 (6/66)	1.5 (1/66)	NS
Viral relapse, % (n/N)	11.8 (6/51)	44.4 (12/27)	NS
Stopping rule met, % (n/N)	7.6 (5/66)	51.5 (34/66)	NS

a. Specified as a secondary outcome. b. specified as the primary outcome. NS: not statistically significant; PR: peginterferon + ribavirin; SMV: simeprevir

Fatigue results from ASPIRE (from Zeuzem and colleagues[10])

At baseline the FSS scores in the simeprevir + PR and placebo + PR groups were approximately 1 point higher than the established normative value for healthy adults. Zeuzem and colleagues[10] reported narratively that in all study groups the mean FSS score increased from baseline to week 12, remained stable to week 48, and returned to values at or below baseline by weeks 70-72. There were no clinically or statistically significant differences between study groups during the 72-week study period.

Adverse events in ASPIRE (from MS and Zeuzem and colleagues[10])

One death (due to bacterial meningitis) occurred and this was in the simeprevir + PR group, but was not deemed related to the simeprevir treatment. The incidence of adverse events was generally comparable between the study groups, although pruritus and neutropenia were ≥10% more frequent in the simeprevir + PR group (pruritus 30.3% vs 16.7%; neutropenia 27.3% vs 16.7%).[10] The only clinically significant change in laboratory parameters was hyperbilirubinaemia which occurred in all treatment groups during the first 2 weeks, with bilirubin levels subsequently returning to baseline values or below by week 52.