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Evidence Review Group's Report
Daclatasvir for treating chronic hepatitis C

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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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Beth Woods, Rita Faria, James Lomas wrote the cost effectiveness sections of the report and performed the economic modelling; Alexis Llewellyn and Mark Simmonds wrote the clinical effectiveness sections of the report; Nerys Woolacott was an advisor for the clinical effectiveness sections and commented on drafts of the report. Susan Griffin was an advisor for the cost effectiveness sections and commented on drafts of the report. Melissa Harden wrote the sections of the report dealing with search strategies and provided information support.

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List of abbreviations

BOC Boceprevir

CrI Credibility Interval

CSR Clinical study report

DCC Decompensated cirrhosis

DCV Daclatasvir

DSA Deterministic sensitivity analyses

HCC Hepatocellular carcinoma

HCV Hepatitis C virus

HRQoL Health-related quality of life

ICER Incremental cost effectiveness ratio

LLOQ lower limit of quantification

MAIC Matching-adjusted indirect comparison

MTC Mixed treatment comparison (Network meta-analysis)

NMA Network meta-analysis

PBO Placebo

PI Protease inhibitor

PPSRU Personal Social Services Research Unit

PR Peginterferon + ribavirin

PROM Patient reported outcome measure

PSA Probabilistic sensitivity analyses

QALY Quality Adjusted Life Year

RBV Ribavirin

RNA Ribonucleic acid

RVR Rapid virologic response (4 weeks after start of therapy)

SMV Simeprevir

SOF Sofosbuvir

SPC Summary of product characteristics

STA Single Technology Appraisal

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

TD target detected

TND target not detected

TVR Telaprevir

Glossary

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)

1 Summary

1.1 Critique of the decision problem in the manufacturer's submission

Daclatasvir (brand name Daklinza®) is an inhibitor of non-structural protein 5A which is an essential component in hepatitis C virus replication. The UK Committee for Medicinal Products for Human Use granted marketing authorisation on 22 August 2014 for daclatasvir to be used in combination with other medicinal products for the treatment of chronic hepatitis C virus infection in adults. Whilst this licence is very broad it did include some recommended treatment combinations and therapy durations as presented in Table 1 below.

Table 1: Recommended regimens and treatment duration for Daclatasvir combination therapy

HCV genotype and patient population	Treatment	Duration
Genotype 1 or 4 without cirrhosis	Daclatasvir + sofosbuvir	12 weeks Consider prolongation of treatment to 24 weeks for patients with prior treatment including a NS3/4A protease inhibitor
Genotype 1 or 4 with compensated cirrhosis	Daclatasvir + sofosbuvir	24 weeks Shortening treatment to 12 weeks may be considered for previously untreated patients with cirrhosis and positive prognostic factors such as IL28B CC genotype and/or low baseline viral load. Consider adding ribavirin for patients with very advanced liver disease or with other negative prognostic factors such as prior treatment experience.
Genotype 3 with compensated cirrhosis and/or treatment experienced	Daclatasvir + sofosbuvir + ribavirin	24 weeks. Note [redacted]
Genotype 4	Daclatasvir + peginterferon alfa + ribavirin	24 weeks of Daclatasvir in combination with 24-48 weeks of peginterferon alfa and ribavirin. If the patient has HCV RNA undetectable at both treatment weeks 4 and 12, all 3 components of the regimen should be continued for a total duration of 24 weeks. If the patient achieves HCV RNA undetectable, but not at both treatment weeks 4 and 12, Daclatasvir should be discontinued at 24 weeks and peginterferon alfa and ribavirin continued for a total duration of 48 weeks

The NICE final scope specified, as the intervention of interest, daclatasvir combined with any other medication. The ERG notes that this is a particularly broad scope, permitting a wide range of treatments to be combined with daclatasvir, including both standard treatments (e.g. interferon and ribavirin) and newer licensed treatments (e.g. simeprevir and sofosbuvir). However, the evidence presented in the submission included only a combination of daclatasvir with sofosbuvir (with or

without ribavirin), and with pegylated interferon-alpha and ribavirin (PR). As these are the recommended treatment combinations this was a reasonable approach.

The comparators listed in the scope were:

- Peginterferon alfa and ribavirin (genotypes 1–6)
- Telaprevir in combination with peginterferon alfa and ribavirin (genotype 1 only)
- Boceprevir in combination with peginterferon alfa and ribavirin (genotype 1 only)
- Sofosbuvir in combination with ribavirin, with or without peginterferon alfa (genotypes 1–6)
- Simeprevir in combination with peginterferon alfa and ribavirin (genotype 1 or 4)
- Simeprevir in combination with sofosbuvir, with or without ribavirin (for people who have genotype 1 or 4 disease and are ineligible for or intolerant to interferon treatment) (subject to ongoing NICE appraisal [ID668]).

The submission presented evidence on all of these comparator treatments with the exception of best supportive care (watchful waiting) which was replaced by a no treatment option. No explanation was given as to why this was excluded. In some subpopulations, the manufacturer excluded relevant comparators from some clinical comparisons and the cost-effectiveness analysis on the basis of a lack of evidence.

The final scope issued by NICE for this assessment specified a population of all adults with chronic hepatitis C with either no prior treatment (treatment naïve) or some previous treatment for hepatitis C (treatment experienced). This same population was addressed in the submission. The trials evidence presented focussed on patients with hepatitis C of genotypes 1, 3 and 4 and at all stages of fibrosis (METAVIR score F0 to F4) with both treatment-naive and treatment-experienced patients, which reasonably reflects the distribution of patients with hepatitis C in the UK. The trials of comparator treatments likewise covered the full range of the population with hepatitis C. However, the amount and quality of evidence varied across the subgroups; in particular the evidence for patients with more severe fibrosis (METAVIR F3) and compensated cirrhosis (METAVIR F4) was very limited. Also, there was no evidence for daclatasvir in patients co-infected with HIV.

The ERG concludes that the population considered in the submission reasonably reflects both the NICE scope and the UK population likely to receive daclatasvir. The emphasis of the economic modelling within the submission is on patients with more severe fibrosis (METAVIR F3) and compensated cirrhosis (METAVIR F4), with the full licensed indication being explored in a scenario analysis only.

The submission focussed on sustained virological response (SVR), with evidence presented variously at 12 weeks follow-up post-treatment (SVR12) and 24 weeks follow-up post-treatment (SVR24). The

ERG considers this focus to be appropriate, because sustained virologic response is considered to be a key outcome by clinicians. The other outcomes listed in the scope were development of resistance to daclatasvir; mortality; adverse effects of treatment; health-related quality of life. A range of adverse event data for daclatasvir and comparator treatments was presented. Mortality data were reported, but as, there were no deaths in the two key trials, no further analyses or comparisons with other treatments were performed. The original submission did not report trial evidence on development of resistance to daclatasvir, but data were provided on request for clarification. No data on health-related quality of life were reported.

The final scope suggested that a number of subgroups be considered: genotype; co-infection with HIV; people with and without cirrhosis; patients who have received treatment pre- and post-liver transplant; response to previous treatment (non-response, partial response, relapsed); and people who are intolerant to or ineligible for interferon treatment. The original submission presented evidence for all subgroups except patients post-liver transplant and patients co-infected with HIV, for whom no data were available. Data on interferon intolerant/ineligible patents were not available for daclatasvir trials, but were for some comparator treatments. In previously treated patients, the manufacturer did not present evidence according to response to prior treatment response (non-response, partial response, relapsed).

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The manufacturer's submission on clinical effectiveness contained four reviews: a review to identify trials of daclatasvir; a "benchmarking" review to determine the effectiveness of telaprevir, boceprevir and interferon (PR) treatments; a matching-adjusted indirect comparison review comparing daclatasvir to other treatments; and an unadjusted indirect comparison of daclatasvir to other treatments.

Review of trials of daclatasvir

A systematic review of trials of daclatasvir was reported. It included 5 unique studies of daclatasvir (four trials and one ongoing observational study). All the included studies met the inclusion criteria for at least one of their study arms. The four trials are listed in Table 2:

Table 2: Daclatasvir studies included in the submission

Study	Regimen & duration	Comparator	Design	Patient population
AI444-040	DCV+SOF (±RBV) 12 to 24 weeks	None	Uncontrolled, randomised, open-label, phase II outpatient study	Treatment-naive patients with chronic HCV genotype 1, 2 or 3; treatment-experienced patients (PI triple therapy failures) with chronic HCV

				genotype 1
ALLY-3	DCV+SOF 12 weeks	None	Open-label, parallel arm, phase III study	Treatment-naive and treatment-experienced patients with HCV genotype 3
AI444-042	DCV+PR 24 weeks	Placebo+PR	Randomised, double-blind, phase IIb study	Treatment-naive patients with chronic HCV genotype 4
AI444-010	DCV+PR 12 to 24 weeks	Placebo+PR	Randomised, double-blind, phase IIb study	Treatment-naive patients with chronic HCV genotype 1 or 4
AI444-046	DCV+PR; DCV+SOF±PR; DCV+ASV±PR; others	None	Long-term observational follow-up study (ongoing)	Treatment-experienced patients with chronic HCV genotype 1, 2, 3 or 4

Tables 3 and 4 summarise the daclatasvir SVR results presented in the submission – for the whole trial populations and for patients with METAVIR F4/compensated cirrhosis.

Table 3: Summary of Sustained Virologic Response at Follow-up Week 12 (SVR12)*: Daclatasvir trials

	Treatment naïve	**Treatment experienced**	**Data source**
Genotype 1			
DCV+SOF (12-24 weeks)	100% (70/70)	100% (21/21)	AI444-040
DCV+SOF+RBV (12-24 weeks)	98% (55/56)	100% (20/20)	AI444-040
DCV+PR (12 weeks)	60% (88/146)	No data	AI444-010
Genotype 3			
DCV+SOF+RBV (24 weeks)	100% (5/5)	No data	AI444-040
DCV+SOF (24 weeks)	85% (11/13)	No data	AI444-040
DCV+SOF (12 weeks)	90% (91/101)	86% (44/51)	ALLY-3
Genotype 4			
DCV+SOF	No data	No data	
DCV+PR (24 weeks)	82% (67/82)	No data	AI444-042
DCV+PR (12 weeks)	100% (12/12)	No data	AI444-010

* SVR defined as(< LLOQ, TD or TND). Patients who had missing data at follow-up Week 12 were considered responders if their next available HCV RNA value was <LLOQ
LLOQ: lower limit of quantification; TD: target detected; TND: target not detected; HCV RNA: hepatitis C virus ribonucleic acid

Table 4: Summary of Sustained Virologic Response at Follow-up Week 12 (SVR12)* in patients with METAVIR F4/ compensated cirrhosis: Daclatasvir trials

	Treatment naïve	Treatment experienced	Data source
Genotype 1			
DCV+SOF (12-24 weeks)	[redacted]	[redacted]	AI444-040
DCV+SOF+RBV (12-24 weeks)	[redacted]	[redacted]	AI444-040
DCV+PR (12-24 weeks)	[redacted]	[redacted]	AI444-010
Genotype 3			
DCV+SOF+RBV (24 weeks)	[redacted]	[redacted]	AI444-040
DCV+SOF (24 weeks)	[redacted]	[redacted]	AI444-040
DCV+SOF (12 weeks)	58% (11/19)	69% (9/13)	ALLY-3
Genotype 4			
DCV+SOF	No data	No data	
DCV+PR (24 weeks)	[redacted]	[redacted]	AI444-042
DCV+PR (12-24 weeks)	[redacted]	[redacted]	AI444-010

* SVR defined as(< LLOQ, TD or TND). Patients who had missing data at follow-up Week 12 were considered responders if their next available HCV RNA value was <LLOQ
LLOQ: lower limit of quantification; TD: target detected; TND: target not detected; HCV RNA: hepatitis C virus ribonucleic acid

Benchmarking review

[redacted]

Matched adjusted indirect comparison review

This MAIC analysis was conducted because the single arm trials of daclatasvir lack a common comparator, and this prevented conventional indirect comparison. This analysis consisted of a review of all studies of telaprevir, boceprevir, sofosbuvir or simeprevir, all combined with PR, or PR alone, to identify the expected SVR24 or SVR12 response for these treatments. This was compared to the observed response with daclatasvir with sofosbuvir (with or without ribavirin) in trials AI444-040 and ALLY-3, adjusted to match the demographic characteristics of patients in the other trials. Incidence of adverse events was also compared.

The MAIC analysis concluded that SVR rates were higher for daclatasvir (combined with sofosbuvir, with or without ribavirin) than for other treatments (sofosbuvir, telaprevir or boceprevir) in genotype 1 patients. Adverse events rates were also generally lower with the interferon-free daclatasvir regimen than in the interferon-containing regimens. In genotype 3 patients, daclatasvir plus sofosbuvir had

higher SVR rates than PR alone, but no difference in rates was found when daclatasvir with sofosbuvir was compared to sofosbuvir alone.

Naive indirect comparison of trial results

A review of "best available evidence" identified trials of relevant comparators combinations including sofosbuvir, simeprevir, telaprevir, boceprevir and peginterferon alfa with ribavirin. SVR results were presented in tables, side by side with daclatasvir trial results. Most were not based on formal comparisons such as head-to-head or adjusted indirect comparisons, and therefore most comparisons between treatments are observational and not randomised. The SVR rates for the selected trials were reported according to patient genotype status, treatment history or eligibility and by baseline fibrosis severity (F0-F4; F3 to F4 non-cirrhotic; compensated cirrhosis).

The results from these naïve indirect comparisons were reported only in tables, with no formal conclusions made on the relative effectiveness of different treatments.

Non-RCT data

The MS identified one non-RCT study from a review of BMS databases: AI444-046 is an ongoing multicentre open-label observational study enrolling [redacted] patients, with a planned maximum duration of 144 weeks. The primary aim of the study was to evaluate the durability of virologic response, Of [redacted] patients who had received daclatasvir with PR, and [redacted] who had received daclatasvir with sofosbuvir (with or without ribavirin) who had achieved SVR12 in their parent study [redacted] of the [redacted] and [redacted] of the [redacted] had virologic relapse.

Resistance

Overall, the evidence regarding the association between baseline NS5A polymorphisms and virologic failure was mixed and inconclusive. However, there was some limited evidence to suggest that specific baseline NS5A polymorphisms may be associated with virologic failure in genotype 1, 3 and 4 patients. The evidence is limited by the use of different drug combinations (for instance, use of sofosbuvir may have reduced virologic failure rates) and small sample sizes.

Mortality

Across the four trials there were two deaths (both in AI444-010): both patients were in the daclatasvir 20 mg+PR group. The manufacturer stated that both deaths were deemed unrelated to study therapy by the investigator. There was therefore no evidence that daclatasvir use led to any increase in mortality.

Adverse effects

Overall, there were few serious adverse event rates associated with interferon-free daclatasvir regimens. Rates appeared comparable with placebo in the two trials that evaluated daclatasvir in combination with PR. Serious adverse event rates associated with daclatasvir were low. From the MAIC analyses adverse event rates using daclatasvir (with sofosbuvir, with or without ribavirin) were generally similar to or lower than rates when using boceprevir, telaprevir, sofosbuvir or simeprevir (all combined with PR).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

Review of trials of daclatasvir

The manufacturer's systematic review of clinical effectiveness is of a reasonable quality. The review of trials of daclatasvir used appropriate systematic review methods, with adequate searching of the literature, selections of studies, data extraction and quality assessment of the included trials.

All included studies addressed NICE's final scope. The ERG agrees with the manufacturer that baseline demographics of recruited patients were broadly comparable to the demographics of patients with chronic hepatitis who may be offered treatment in the UK, although difficult to treat populations such as patients with HIV or post liver transplant were excluded.

The manufacturer provided a quality assessment of the four relevant trials of daclatasvir and the ERG mostly concurs with the manufacturer's assessment of quality for the four trials. However, the ERG had concerns about the reliance on single-arm studies, which are at a high risk of bias, and also some minor concerns associated with the definition of primary outcomes in three trials analyses and methods for blinding. All four trials were small in size, and so for many key subgroups, such as patients with compensated cirrhosis or with treatment experience, data were extremely limited.

Benchmarking review

The searches for and the selection of studies included in the benchmarking analysis were generally acceptable. The analysis approach was considered to be reasonable, given that the daclatasvir trials had no comparator arm. The lack of a comparator arm in AI444-040 means the results may be biased if characteristics of patients, or trial conduct were significantly different in AI444-040 than in comparator trials. The ERG considers the results of this analysis to be reasonably reliable, and it was unclear why the results were not used in the overall conclusions.

MAIC

The searches for and the selection of studies included in the MAIC analysis were generally acceptable. However the MAIC analyses are not based on randomised evidence as the two daclatasvir trials AI444-040 and ALLY-3 had no placebo or other comparator arm, and placebo arms from the

trials of other treatments were not included in the analysis. Although the matching-adjusted indirect comparison (MAIC) method aims to adjust results to account for possible differences between trials, the adjusting may be flawed if important unobserved characteristics were not accounted for.

The MAIC analyses results for genotype 1 patients are strongly dependent on the fact that AI444-040 achieved a near perfect SVR12 success rate, and any adjustments to SVR rate are dependent on the characteristics of the one patient who did not achieve SVR. The ERG therefore considers the MAIC analysis to be unreliable and should be treated as if it were an unadjusted comparison of results from different trials, with substantial potential for bias or misleading conclusions.

Because of the potential for bias the ERG is of the opinion that the evidence that daclatasvir plus sofosbuvir is superior to other treatments in treatment-naïve patients of genotype 1 should be treated with caution. However, it is reasonable to conclude that daclatasvir plus sofosbuvir is unlikely to be inferior to other treatments. Data on patients with genotype 3 were more limited, so the ERG believes that no firm conclusions can be drawn on the relative effectiveness of daclatasvir-based regimens in these patients.

No results were presented specifically for treatment-experienced patients with genotype 1 and for patients with genotype 4. No separate adjusted analyses were presented for patients with more severe disease (either cirrhosis or at METAVIR stages F3 to F4). No conclusions can therefore be drawn from the MAIC analysis as to the effectiveness of daclatasvir in those patients.

Naive indirect comparison of trials

Is not clear whether the review of studies informing the “best available evidence” efficacy tables is either systematic or comprehensive. It is therefore not clear whether the trials included were all the relevant trials of hepatitis C treatments, or whether those included were representative of likely effects of the treatments. However, the ERG found no evidence to suggest that significant trials had been omitted.

Most results presented in the “best available evidence” efficacy tables are not based on formal comparisons such as head-to-head or adjusted indirect comparisons. Therefore most comparisons are observational and have significant limitations. In addition, concerns about the appropriateness and consistency of assumptions made to address missing data (such as assuming equivalence across genotypes. disease severity and treatment experience status), the limited evidence (particularly for patients with compensated cirrhosis) means that it was largely unclear whether the results for other treatments were comparable with those presented for daclatasvir-based regimens.

The ERG concluded that the evidence for comparing daclatasvir-based regimens to other treatments is weak and may be prone to considerable bias. The ERG therefore considers that these uncontrolled

indirect comparisons did not provide robust evidence that daclatasvir is superior to other treatments, although they provide some weaker evidence that daclatasvir is at least not inferior to other treatments.

Non-trial data

SVR results of AI444-046 appear reliable, although these are based on interim analyses, and there are uncertainties regarding the selection of patients from the daclatasvir plus sofosbuvir (with or without ribavirin) group. Although interim results from AI444-046 appear promising, the ERG considers that this study does not, at present, provide conclusive evidence on the long-term effectiveness of daclatasvir.

Mortality and adverse events

The evidence presented by the manufacturer on mortality and on-treatment adverse events is based on a reasonably well conducted review and appears reliable. There were very few deaths in the trials of daclatasvir, and the ERG accepts the manufacturer's statements that these mortalities were unrelated to daclatasvir use. Adverse event data from the two randomised trials is likely to be reliable and shows that daclatasvir (when combined with PR) has an adverse event profile no worse than for placebo with PR. Adverse event data for daclatasvir combined with sofosbuvir were presented primarily in the MAIC analysis, with the same limitations as for the analysis of SVR rates in the analyses described above. However the ERG concludes that the evidence suggests that adverse event rates with daclatasvir combined with sofosbuvir are no higher than for other treatments (sofosbuvir, simeprevir, telaprevir or boceprevir, all combined with PR). Long-tern adverse events were not discussed for any treatment regimen.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

The *de novo* cost-effectiveness assessment conducted by the manufacturer evaluated the costs and health benefits daclatasvir-containing regimens (daclatasvir+sofosbuvir (DCV+SOF), daclastavir+sofosbuvir+ribavirin (DCV+SOF+RBV) and daclatasvir+pegylated interferon+ribavirin (DCV+PR)) for the treatment of patients with chronic hepatitis C. The subpopulations considered were patients with HCV genotype 1, 3 and 4 who are treatment naïve, treatment experienced or interferon ineligible or intolerant, at METAVIR stage F0-F4, F3-F4 non-cirrhotic and compensated cirrhotic. Results for patients with METAVIR stage F0-F2 were presented in the manufacturer's response to the ERG's points for clarification. The manufacturer submission focusses on the F3-F4 non-cirrhotic subpopulation and on the compensated cirrhotic subpopulation. The ERG considers the F3-F4 non-cirrhotic subpopulation to represent largely F3 patients and the compensated cirrhotic subpopulation to be equivalent to patients with METAVIR stage F4.

The model consists of a decision tree combined with a Markov model. The decision tree models the effectiveness and costs of the first year, during which treatment occurs. The Markov model simulates the natural history of the disease over the patients' lifetime. Patients with SVR are assumed not to progress and are subject to general population all-cause mortality. Patients without SVR are at risk of liver disease progression, hepatocellular cancer, liver-related mortality and all-cause mortality. SVR rates were obtained from the uncontrolled (naïve) indirect comparison of individual trial arms. SVR rates for daclatasvir-based comparators came from three clinical studies (AI444-040, AI444-042 and ALLY-3). Data for comparators came from single arms of a wide range of clinical studies.

Quality of life was quantified based on an on-treatment decrement to quality of life, the quality of life associated with being in different disease states and the quality of life associated with achieving SVR. Most quality of life data used in the model related to EQ-5D data elicited from patients. Costs were assessed from an NHS perspective and included: acquisition costs for each treatment, costs associated with monitoring during treatment and costs associated with each health state.

The cost-effectiveness drivers are SVR rates and treatment duration. SVR is associated with a halt in disease progression, greater quality of life and zero costs in the long term. Treatment duration determines the acquisition cost of treatment, which is the largest driver of incremental lifetime costs. Hence, treatments with greater SVR rates and lower treatment durations have more favourable cost-effectiveness profiles.

The manufacturer presented deterministic and pairwise results for the 27 subpopulations as described above. Daclatasvir-containing regimens were cost-effective under the £20,000-£30,000 per QALY gained threshold in the following F3-F4 non-cirrhotic and compensated cirrhotic subpopulations (incremental cost-effectiveness ratios (ICERs) are presented within brackets):

- METAVIR stage F3 (non-cirrhotic): DCV+SOF in genotype 1 treatment naïve (£25,454/QALY), treatment experienced (£4,587/QALY) or interferon ineligible or intolerant (£4,587/QALY), in genotype 3 interferon ineligible or intolerant (£7,523/QALY), and in genotype 4 treatment experienced (£3,750/QALY) or interferon ineligible or intolerant (£3,750/QALY).
- METAVIR stage F4 (compensated cirrhotic): DCV+SOF in genotype 1 treatment experienced (£12,443/QALY), DCV+SOF+RBV in genotype 3 interferon ineligible or intolerant (£11,781/QALY), genotype 4 interferon ineligible or intolerant (£12,443/QALY), and DCV+PR in genotype 4 treatment experienced (£3,841/QALY).

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considers that the manufacturers review was unlikely to have missed relevant cost-effectiveness analyses of daclatasvir-containing regimens. The ERG therefore considers the development of a *de novo* cost-effectiveness model to be appropriate and necessary for this appraisal. In general, the submission meets the NICE reference case and NICE scope for this appraisal. However, the ERG considers the manufacturer's analyses to be both highly uncertain and in places biased:

- *Limitations in the analysis of the F0-F2 population*. The manufacturer presented results for F0-F4 and F0-F2 subpopulations as well as results for the F3 (non-cirrhotic) and F4 (cirrhotic) subpopulations. The F0-F4 analysis is uninformative given the heterogeneity across METAVIR fibrosis states in terms of SVR rates, natural history, licensed and NICE-recommended comparators and licensed treatment durations. The F0-F2 analysis presented by the manufacturer is limited to a subset of selected pairwise comparisons, is not informed by SVR data specific to the F0-F2 population and did not include a watchful waiting strategy (i.e. a no treatment option until a patient reaches F3 or F4). The ERG therefore considers that insufficient evidence has been presented for the F0-F2 subpopulations.
- *Heterogeneity in the treatment experienced subpopulation*. The manufacturer considers the treatment experienced group as a single entity despite evidence that type of prior experience (initial response followed by treatment failure, partial response or null response) is predictive of SVR rates for relevant comparators. Furthermore, the treatment experienced group in genotype 1 comprises only individuals who have failed treatment with a protease inhibitor plus PR. This omits a large group of prevalent genotype 1 patients who will have failed PR. The ERG therefore has concerns that insufficient cost-effectiveness evidence has been presented for this subpopulation.
- *Exclusion of relevant comparators*. The manufacturer excluded important comparators both in terms of drugs and treatment strategies. Specifically, sofosbuvir+PR and simeprevir+sofosbuvir were omitted from a number of analyses on the basis of a lack of data on effectiveness. While this is not unreasonable given the state of available evidence during the period in which the manufacturer conducted its appraisal, it is of particular concern as for some subpopulations these comparators have now been recommended by NICE. "Best supportive care (watchful waiting)" was interpreted as no treatment and the use of daclatasvir-containing regimens as second line following treatment failure was not considered.
- *SVR data*. The SVR data used in the model were obtained from individual trial arms. Effectiveness data for all comparators in the F3 and F4 subpopulations is therefore highly uncertain and at high risk of bias since it is not based on a randomised comparison and no adjustments have been made for differences in trial populations. This uncertainty is

compounded by extrapolations of data to subpopulations with different disease severities, treatment histories and genotypes.

- *Experience of cirrhotic (F4) patients who achieve SVR*. The manufacturer's assumptions that cirrhotic patients with SVR are not at risk of progression, do not incur long term costs and experience an improvement in quality of life greater than patients with milder disease are not supported by the evidence. These assumptions overestimate the benefit of achieving SVR in cirrhotic patients.
- *Natural history model*. The ERG has concerns that the rates of disease progression used in the model do not reflect the natural history of patients with chronic hepatitis C in the UK.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

The manufacturer's submitted evidence on clinical effectiveness broadly covered the final scope set out by NICE. The review of daclatasvir trials included all relevant trials in which daclatasvir had been used. Reviews for other treatments were likely to have identified the majority of trials of other relevant treatments. The submission covers the key clinical outcomes, including SVR rates, adverse events and mortality.

The manufacturers' cost-effectiveness analysis generally follows the NICE reference case and the NICE scope, with the exceptions discussed above. The populations considered generally capture key distinct subpopulations that differ with respect to available treatments and outcomes. The model simulates the costs and benefits over the patients' lifetime. Its structure is appropriate and similar to other models used in previous hepatitis C appraisals. The ERG considers that the manufacturer's model captures most important health outcomes associated with the treatment and natural history of chronic hepatitis C. The ERG considers the selection of data on quality of life and resource use and costs in the model to be generally appropriate.

1.7 Weaknesses and areas of uncertainty

1.7.1 Weaknesses

Some caution is warranted regarding the clinical efficacy of daclatasvir due to the following concerns:

- The two studies that evaluated combinations of daclatasvir and sofosbuvir did not have a control group, and may therefore be at high risk of bias. Despite the objective endpoints employed in the trials the lack of a control group means that the true efficacy of daclatasvir combined with sofosbuvir is uncertain.
- All trials of daclatasvir had small sample sizes, reducing confidence in the reliability of their results.

- SVR12-24 results in patients with METAVIR score F4 or with a diagnosis of compensated cirrhosis or with prior treatment experience were all based on small subgroups and their reliability is limited. Therefore there is great uncertainty around the efficacy of daclatasvir in these important subgroups of patients.
- Evidence was unavailable for daclatasvir based comparators in some patient subgroups in which daclatasvir is licensed:
    - DCV+SOF in genotype 1 treatment-experienced patients. All evidence comes from the AI0444-040 trial which used a 24 week treatment duration in these patients whereas the license for non-cirrhotic patients is 12 weeks.
    - No evidence is available for DCV+SOF in genotype 4 patients.
    - No evidence is available for DCV+SOF in interferon ineligible or intolerant patients across genotypes.
    - No evidence is available for DCV+SOF in genotype 3 treatment-experienced cirrhotic patients for the licensed treatment duration (24 weeks)
    - No evidence is available for DCV+PR in genotype 4 treatment experienced patients.
- All comparisons of daclatasvir with other treatments were based on indirect comparisons. These are neither randomised nor controlled comparisons and so may be prone to error and bias, particularly if trial conditions or patient populations varied across trials

The major weaknesses in the cost-effectiveness submission were discussed above (Section 1.5) and consist of: (i) the limited analysis of the F0-F2 population, (ii) heterogeneity in the treatment experienced subpopulations, (iii) exclusion of relevant comparators, (iv) quality of the SVR data, (v) experience of the F4 (cirrhotic) patients who achieve SVR and (vi) progression of patients with chronic hepatitis C in the natural history model. In addition, the model did not quantify the benefits of reduced onward transmission of hepatitis C in a way that could robustly inform decision making.

1.7.2 Areas of uncertainty

The clinical effectiveness of daclatasvir remains uncertain in a number of areas. As the key daclatasvir trials were not randomised controlled trials some uncertainly remains over the accuracy of estimates of SVR in these trials given their potential for bias. Considerable uncertainty remains over the effectiveness of daclatasvir combined with sofosbuvir in patients with advanced fibrosis or compensated cirrhosis. This arises because of the inconsistency in SVR rates in compensated cirrhosis patients between the AI444-040 and ALLY-3 trials. Because patients in ALLY-3 received a shorter course of treatment without ribavirin it is unclear whether the poorer SVR rates in that trial are due to treatment differences or genuine difference in effectiveness in patients with compensated cirrhosis. Limited or absent data mean the effectiveness of daclatasvir combined with sofosbuvir is uncertain or unknown in a number of key patient subgroups including: patients with treatment experience, patients

intolerant of or ineligible for interferon, patients of genotype 4, patients co-infected with HIV and patients post liver transplant.

A key area of uncertainty is the relative effectiveness of daclatasvir when compared to other treatments (e.g. telaprevir, boceprevir, sofosbuvir, simeprevir). As the key daclatasvir trials did not contain a comparator arm all treatment comparisons are indirect and uncontrolled and hence have the potential for bias. While the submission made some attempts to compensate for such bias it is not certain if this was sufficient. As such it is not possible to reliably determine whether daclatasvir (in combination with sofosbuvir or otherwise) is more or less effective than other potential treatments for HCV.

For the assessment of cost-effectiveness the major area of uncertainty is the treatment effectiveness, i.e. SVR rates, of daclatasvir-containing regimens and their comparators across the different subpopulations. As discussed above, SVR is a key cost-effectiveness driver in that it is associated with a halt in disease progression, increase in quality of life and zero long-term costs. However, SVR rates used in the model were obtained from individual trial arms rather than randomised comparisons or a mixed treatment comparison. They represent an unadjusted non-randomised comparison. SVR rates may be biased if the individual trial arms are not comparable in all factors that affect outcomes. The high risk of bias makes the SVR rates very uncertain. In addition, the SVR rates were frequently extrapolated between subpopulations with different disease severities, treatment histories and sometimes genotypes. This extrapolation compounds the uncertainty in the SVR rates.

Another important area of uncertainty is treatment duration. For two treatments, daclatasvir plus sofosbuvir and sofosbuvir plus PR, the marketing authorisations allow for alterations to the licensed treatment durations for specific subpopulations. Daclatasvir plus sofosbuvir can be increased from 12 to 24 weeks in genotype 1 treatment experienced non-cirrhotic patients and reduced from 24 to 12 weeks in genotype 1 or 4 treatment naïve cirrhotic patients with positive prognostic factors. sofosbuvir plus PR can be extended to 24 weeks in patients with characteristics predictive of low response. The proportion of patients which will require these modifications in practice is a significant source of uncertainty regarding the total cost of these comparators. No evidence has been provided by the manufacturer regarding these proportions.

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook a number of exploratory and sensitivity analyses to the manufacturer's model. Each are summarised below, together with their impact on the results.

1.8.1 ERG's corrections to the manufacturer's model

The ERG corrected the anomalies found in the manufacturer's model. The results of the manufacturer's base-case are similar to the results after the ERG's corrections. The corrections did not change the cost-effective intervention at the £20,000 and £30,000 per QALY gained threshold.

1.8.2 The ERG's base-case

The ERG conducted a number of changes to the manufacturer's model that together constitute the ERG's base-case. The ERG's changes include:

- Inclusion of all relevant comparators and exclusion of the treatment regimens not recommended by NICE in the recent appraisals of sofosbuvir and simeprevir.
- Alternative SVR estimates for DCV+SOF for genotype 1 treatment naïve F3, SOF+RBV for genotype 3 interferon ineligible or intolerant F4, and SOF+PR for genotype 4 treatment naïve F4.
- Using the progression rates for genotype 1 to simulate the natural history of genotype 4 rather than progression rates from non-genotype 1 which mainly refer to genotypes 2 and 3.
- Allow cirrhotic patients with SVR to progress to decompensated cirrhosis or hepatocellular cancer (but at a slower rate than cirrhotic patients without SVR).
- Assign the same improvement in quality of life to cirrhotic patients with SVR as patients with moderate disease with SVR (METAVIR score F2 or F3) at 0.05.
- Assign lifetime monitoring costs for cirrhotic patients with SVR since the UK clinical practice is for these patients to receive 6-monthly ultrasound scans of the liver.

In the ERG's base-case, daclatasvir-containing regimens are cost-effective in the following subpopulations under the £20,000-£30,000 per QALY gained threshold:

- In F3 (non-cirrhotic), DCV+SOF is cost-effective in genotype 1 treatment naïve (ICER=£19,739/QALY), treatment experienced (£15,687/QALY) and interferon ineligible or intolerant (ICER=5,906/QALY); in genotype 3 interferon ineligible or intolerant (ICER=£9,607/QALY); in genotype 4 treatment experienced (ICER=£5,906/QALY) or interferon ineligible or intolerant (ICER=£5,906/QALY).
- In F4 (cirrhotic) patients, daclatasvir-containing regimens are not cost-effective in any of the subpopulations.

The difference in results between the manufacturer's base-case after the corrections by the ERG and the ERG's base-case is driven by the addition of relevant comparators and removal of comparators not recommended by NICE, and by the use of alternative SVR estimates.

The ERG conducted a number of sensitivity analysis to its base-case in order to explore the impact of uncertainties in the evidence on the results:

- In the F3 (non-cirrhotic) subpopulations, DCV+SOF was no longer cost-effective at the £30,000 per QALY threshold when using a higher estimate of SVR for SOF+PR in genotype 1 treatment naïve (to reflect that F3 patients may experience better outcomes than cirrhotic patients) and to assuming a 24 week treatment duration for DCV+SOF in genotype 1 treatment experienced. At a cost-effectiveness threshold of £20,000 per QALY, DCV+SOF is also not cost-effective using alternative rates of progression from F3 to F4 in treatment naïve and experienced genotype 1 patients.
- In the F4 (cirrhotic) subpopulation, DCV-containing regimens became cost-effective at a threshold of £30,000 per QALY in genotype 1 treatment naïve patients when a 12 week treatment duration for DCV+SOF was used and in genotype 3 interferon ineligible or intolerant patients when an alternative SVR rate was used for SOF+RBV. DCV+PR also became cost-effective at a cost-effectiveness threshold of £20,000 per QALY when the duration of SOF+PR was extended to 24 weeks in genotype 4 treatment experienced patients.

Although DCV+SOF emerged as cost-effective in genotype 1 treatment naïve F3 patients, it may be more cost-effective to try these patients on a cheaper less effective regimen and reserve the more expensive regimens, such as DCV+SOF or SOF+PR, as second line for patients who do not achieve SVR. Therefore, the ERG explored the cost-effectiveness of DCV+SOF and SOF+PR as second line treatments for genotype 1 treatment naïve F3 patients who did not achieve SVR with PR or SMV+PR. The results suggest that the cost-effective regimen for this subpopulation is to offer PR as a first line then DCV+SOF as second line for treatment failures.

1.8.3 Conclusions of the exploratory and sensitivity analyses undertaken by the ERG

The ERG concludes that, in the F3 (non-cirrhotic) subpopulations, daclatasvir plus sofosbuvir is cost-effective for genotype 1 treatment naïve, treatment experienced and interferon ineligible or intolerant, for genotype 3 interferon ineligible or intolerant and genotype 4 treatment experienced and interferon ineligible or intolerant. However, results in genotype 1 treatment naïve and treatment experienced are sensitive to the SVR of sofosbuvir plus PR (genotype 1 treatment naïve) and the treatment duration of daclatasvir plus sofosbuvir (genotype 1 treatment experienced), both of which resulted in daclatasvir plus sofosbuvir no longer being cost-effective. In addition, reserving daclatasvir plus sofosbuvir as second line after failure with PR may be a more cost-effective option in genotype 1 treatment naïve patients.

The ERG concludes that, in the F4 (cirrhotic) subpopulations, daclatasvir plus sofosbuvir is not cost-effective. These results were sensitive to a shorter treatment duration for DCV+SOF (in genotype 1 treatment naïve) and lower SVR estimates of the cost-effective comparator SOF+RBV (genotype 3 interferon ineligible or intolerant), both of which resulted in daclatasvir plus sofosbuvir becoming cost-effective. Daclatasvir+PR was not found to be cost-effective in any ERG analyses with the

exception of genotype 4 treatment experienced F4 patients when the duration of therapy with sofosbuvir+PR is extended to 24 weeks for all patients.

2 Background

2.1 Critique of manufacturer's description of underlying health problem.

The submission presents a suitable summary of hepatitis C virus (HCV) infection and its health consequences, including discussion of progression to chronic infection, cirrhosis and liver decompensation.

Chronic HCV infection leads to cirrhosis and liver failure in about 10–20% of cases. Approximately 1–5% of chronically infected individuals develop hepatocellular cancer (HCC) and approximately 5% of infected people die from the consequences of long term infection (HCC or cirrhosis). [1] Eliminating HCV from the body halts, reduces or reverses liver damage, which in turn reduces the risk of developing end-stage liver complications and the need for transplant. It also removes the risk of onward transmission.

In the submission the degree of progression of liver disease is categorised using the METAVIR scoring system. The METAVIR scoring system was specifically designed for patients with hepatitis C to help give an indication to the extent of inflammation and liver damage. Following histological examination of a liver biopsy, the METAVIR scoring system assigns two standardised numbers: one to represent the degree of inflammation (A0–3) and the other the degree of fibrosis (F0–4): F0 = no fibrosis, F1 = portal fibrosis with no septa, F2 = portal fibrosis with few septa, F3 = portal fibrosis with numerous septa and F4 = compensated cirrhosis.

The submission focusses on patients at METAVIR stage F3/F4 stating that this is an important group to consider as advanced disease is associated with faster progression to decompensation (liver failure), HCC, liver transplantation or death, and these late stage complications are associated with significant morbidity and utilisation of healthcare resources. Treatment of such patients is consistent with EASL guidelines, which recommend that treatment be prioritised for patients with significant fibrosis (METAVIR score F3 to F4). [2] and is in line with compassionate use programmes granted for pre-license use of daclatasvir.[3]

2.2 Critique of manufacturer's overview of current service provision

The submission presents a clear, accurate summary of current treatment of chronic hepatitis C infection in the NHS. It notes that interferon-based treatment is the care recommended by NICE (technology appraisals TA200, TA106, TA75, TA14) for all genotypes. Protease inhibitor therapies including boceprevir (TA253) and telaprevir (TA252) combined with peginterferon alfa and ribavirin (PR) are recommended by NICE in genotype 1 patients.

The submission notes that no treatment options are currently recommended for patients who have failed on protease inhibitors, or who are intolerant of, or ineligible for, interferon treatment. The ERG notes that, since the submission was written, sofosbuvir with ribavirin has been recommended for some such patients. Daclatasvir may be of benefit to these patients as it may be used without interferon. Based on licenced indications, daclatasvir may be used in patients of genotype 1, 3 or 4; in patients who are treatment naïve or who have received interferon-based treatment (PR) and/or protease inhibitor treatment; and in patients with compensated cirrhosis. The current standard of care in patients with advanced fibrosis or compensated cirrhosis is of limited efficacy and so identifying an effective treatment for these patients is considered an area of high unmet medical need. The submission therefore emphasises the importance of treating patients with advanced fibrosis (METAVIR score F3 to F4) or cirrhosis.

Two other treatments that may also be used, including in patients who are intolerant of, or ineligible for, interferon treatment are available; namely, sofosbuvir and simeprevir. Final appraisal determination information of these treatments was published after the submission (ID654 and ID668, respectively). Simeprevir (a new protease inhibitor), in combination with PR, is now recommended by NICE within its marketing authorisation as a treatment option for genotype 1 and 4 chronic hepatitis C in adults. Sofosbuvir is also recommended as an option for treating chronic hepatitis C in adults, in combination with ribavirin and with or without peginterferon alfa for genotype 1 patients; treatment naïve genotype 2 patients who are intolerant to or ineligible for interferon; treatment experienced genotype 2 patients; treatment naïve genotype 3 patients with cirrhosis and treatment experienced genotype 3 patients.

The ERG notes that a number of new treatments for chronic HCV are currently undergoing appraisal by NICE or will be appraised in the near future, including: simeprevir combined with sofosbuvir, faldaprevir, ledipasvir with sofosbuvir, ombitasvir/paritaprevir/ritonavir (with or without dasabuvir). Service provision for chronic HCV may therefore change radically in the near future, depending on the conclusions of these assessments.

3 Critique of manufacturer's definition of decision problem

3.1 Population

The final scope issued by NICE for this appraisal specified a population of all adults with chronic hepatitis C with either no prior treatment (treatment-naive) or some previous treatment for hepatitis C (treatment-experienced). This same population was addressed in the submission.

The four trials of daclatasvir in the submission included patients with hepatitis C of genotypes 1 to 4 and at all stages of fibrosis (METAVIR score F0 to F4) with both treatment-naive and treatment-experienced patients. The majority of patients were of genotype 1, followed by genotypes 3 and 4, treatment-naïve and with less advanced fibrosis (METAVIR F0 to F2); this reasonably reflects the distribution of patients with hepatitis C in the UK. The trials of comparator treatments likewise covered the full range of the population with hepatitis C.

The ERG concludes that the population considered in the submission reasonably reflects both that set out in the scope, and the UK population likely to receive daclatasvir. Patients co-infected with HIV and patients prior to or post-liver transplant were not included, as no evidence was available for these groups. The emphasis of the submission is on patients with more severe fibrosis (METAVIR F3 and F4) and compensated cirrhosis.

3.2 Intervention

Daclatasvir (brand name Daklinza®) is an inhibitor of non-structural protein 5A which is an essential component in hepatitis c virus replication. Daclatasvir is designed to inhibit viral RNA replication and virion assembly. The European Medicines Agency approved daclatasvir for compassionate use in November 2013. The UK Committee for Medicinal Products for Human Use granted marketing authorisation on 22 August 2014.

Daklinza® (daclatasvir) is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults. The recommended dose of daclatasvir is 60 mg once daily, to be taken orally with or without meals. Daclatasvir must be administered in combination with other medicinal products. Recommended regimens and treatment duration are provided in Table 5 below:

Table 5: Recommended regimens and treatment duration for Daclatasvir combination therapy

HCV genotype and patient population	Treatment	Duration
Genotype 1 or 4 without cirrhosis	Daclatasvir + sofosbuvir	12 weeks Consider prolongation of treatment to 24 weeks for patients with prior treatment including a NS3/4A protease inhibitor (see sections 4.4 and 5.1)
Genotype 1 or 4 with compensated cirrhosis	Daclatasvir + sofosbuvir	24 weeks Shortening treatment to 12 weeks may be considered for previously untreated patients with cirrhosis and positive prognostic factors such as IL28B CC genotype and/or low baseline viral load. Consider adding ribavirin for patients with very advanced liver disease or with other negative prognostic factors such as prior treatment experience.
Genotype 3 with compensated cirrhosis and/or treatment experienced	Daclatasvir + sofosbuvir + ribavirin	24 weeks. Note [redacted].
Genotype 4	Daclatasvir + peginterferon alfa + ribavirin	24 weeks of Daclatasvir in combination with 24-48 weeks of peginterferon alfa and ribavirin. If the patient has HCV RNA undetectable at both treatment weeks 4 and 12, all 3 components of the regimen should be continued for a total duration of 24 weeks. If the patient achieves HCV RNA undetectable, but not at both treatment weeks 4 and 12, Daclatasvir should be discontinued at 24 weeks and peginterferon alfa and ribavirin continued for a total duration of 48 weeks

The final scope for this assessment reflected the indication in the marketing authorisation. The ERG notes that this is a particularly broad scope, permitting a wide range of treatments to be combined with daclatasvir, including both standard treatments (e.g. interferon and ribavirin) and newer licensed treatments (e.g. simeprevir and sofosbuvir). The manufacturer's submission considered only those combinations of treatments that are currently recommended as described in Table 5 above. The ERG considers this to be appropriate.

The two primary trials considered in the submission (AI444-040 and ALLY-3) both evaluated a combination of daclatasvir with sofosbuvir, with some patients in AI444-040 also receiving ribavirin. The two other trials (AI444-010 and AI44-042) evaluated a combination of daclatasvir with PR.

The ERG considers that the interventions included in the submitted trials meet the NICE scope, and that the focus on the daclatasvir and sofosbuvir combination is appropriate as this is a potentially suitable combination for future use, though daclatasvir+PR is also evaluated. The ERG notes that no information on other potential combinations is available.

3.3 Comparators

The comparators listed in the scope are as follows:

- Peginterferon alfa and ribavirin
- Telaprevir in combination with peginterferon alfa and ribavirin (genotype 1 only)
- Boceprevir in combination with peginterferon alfa and ribavirin (genotype 1 only)
- Sofosbuvir in combination with ribavirin, with or without peginterferon alfa
- Simeprevir in combination with peginterferon alfa and ribavirin (genotype 1 or 4)
- Simeprevir in combination with sofosbuvir, with or without ribavirin (for people who have genotype 1 or 4 disease and are ineligible for or intolerant to interferon treatment) (subject to ongoing NICE appraisal [ID668])
- Best supportive care (watchful waiting)

The submission presented evidence on all of these comparator treatments with the exception of best supportive care (watchful waiting). Instead, for the cost-effectiveness analyses, the manufacturer incorporated a 'No treatment' option without providing an explanation as to why watchful waiting was excluded.

The quantity of data presented for the comparators varied. Systematic reviews with multiple included trials were presented for assessment the clinical effectiveness of interferon, telaprevir and boceprevir; data on sofosbuvir and simeprevir were limited to only a few trials. Given that sofosbuvir and simeprevir are recent medications that have recently undergone appraisal this limitation in the evidence is to be expected. For some subpopulations (see section 5.3.4) some comparators were not included, apparently because of a lack of data in these subpopulations.

The ERG concludes that the comparator treatments considered largely meet the scope. Nonetheless, in some subpopulations the manufacturer has excluded relevant comparators from some clinical comparisons and the cost-effectiveness analysis on the basis of a lack of evidence.

3.4 Outcomes

The outcomes listed in the scope were as follows:

- sustained virologic response
- development of resistance to daclatasvir
- mortality
- adverse effects of treatment
- health-related quality of life.

The original submission reported on sustained virologic response (SVR) although reporting varied between response at 12 weeks (SVR12) and at 24 weeks (SVR24) follow-up. SVR12 has become increasingly accepted as a suitable assessment of virologic response, and has been found to be

strongly correlated with SVR24. The submission reported on a range of adverse effects both for daclatasvir and for comparator treatments. Mortality data were reported, but as there were no deaths in the two key trials (AI444-040 and ALLY-3) no further analyses or comparisons with other treatments were performed. No trial evidence on health-related quality of life were presented for either the four daclatasvir trials, or any trials of comparator treatments.

The original submission did not report on development of resistance to daclatasvir, but data were provided on request for clarification.

The ERG concludes that the submission did generally address the outcomes covered in the scope, although data on health-related quality of life was not included. The report focussed on sustained virologic response as the primary outcome. Based on clinical advice, the ERG considers this focus to be appropriate, because sustained virologic response is considered to be the key outcome by clinicians.

3.5 Other relevant factors

The final scope suggested that the following subgroups be considered:

- Genotype
- Co-infection with HIV
- People with and without cirrhosis
- Patients who have received treatment pre- and post-liver transplant
- Response to previous treatment (non-response, partial response, relapsed)
- People who are intolerant to or ineligible for interferon treatment

The original submission presented evidence for all subgroups except patients post-liver transplant and patients co-infected with HIV. When asked for clarification, the manufacturers confirmed that no data on post-liver transplant or HIV co-infected patients were available. The submission considered the effect of genotype, presence of cirrhosis and whether patients had previously received treatment. The ERG believes that appropriate analyses to consider key relevant subgroups of patients were generally performed though the manufacturer did not present clinical or cost-effectiveness comparisons stratified according to type of response to prior treatment (non-response, partial response, relapsed), and the cost-effectiveness analysis did not evaluate genotype 1 treatment experienced patients with PR-only failures.

The submission reported that a high proportion of patients with HCV genotypes 3 and 4 are non-white. As some existing treatments (e.g. telaprevir) are not licenced in these genotypes this raises

potential equality issues. The submission includes daclatasvir trials with patients with genotype 3 and 4 infection. The ERG therefore considers that the submission provides relevant evidence across genotypes and hence across different ethnicities.

4 Clinical Effectiveness

This section contains a critique of the methods of the review(s) of clinical effectiveness data, followed by a description and critique of the trials included in the review, including a summary of their quality and results and the results of any synthesis of studies.

The manufacturer's submission on clinical effectiveness contained four reviews: a review to identify trials of daclatasvir; a "benchmarking" review to determine the effectiveness of telaprevir, boceprevir and interferon (PR) treatments; a matching-adjusted indirect comparison review comparing daclatasvir to other treatments; and an unadjusted indirect comparison of daclatasvir to other treatments. For clarity each review is discussed in a separate section (Sections 4.1 to 4.4).

For each review a critique of the review methods is provided. For the review of daclatasvir trials (Section 4.1) a description and critique of each of the four trials performed by the manufacturer is presented, with a summary and critique of the quality of these trials and their findings. The reviews of other treatments contained a large number of trials, so a detailed review of each individual trial was not feasible. Instead a description and critique of the results of the syntheses for each review is presented.

4.1 Review to identify daclatasvir studies

This section considers the systematic review of daclatasvir in combination with other agents presented in Sections 6.1 to 6.5, section 6.9 and in Appendix 5 of the manufacturer submission.

4.1.1 Critique of manufacturer's approach to the methods of reviews

4.1.1.1 Searches

The manufacturer's submission described the search strategies to identify relevant clinical effectiveness data on the use of daclatasvir. Separate searches were conducted to identify randomised controlled trials (RCTs), non-RCTs and studies reporting adverse events. The search strategies were described in the main body of the submission in section 6.1, and full details were provided in Appendix 5.

All of the required databases specified by NICE were searched – MEDLINE, EMBASE, PubMed (for MEDLINE in process) and the Cochrane Library. In addition, conference abstracts from four liver disease conferences, 2011-2014, were manually searched. All databases were searched from inception to 21st October 2014. The searches were limited to English language and humans studies.

The searches overall were well documented and, for the most part, included the use of appropriate text word searches, subject indexing terms, field searching, Boolean operators and truncation. However, some issues with the search strategies were found which are outlined below.

Both the brand name and the generic drug names were used in the search strategies which is appropriate. However there is a misspelling in the search strategies reported in Appendix 5, Tables 4, 5, 6 and 7 – Daclinza has been used instead of Daklinza. Therefore it is possible that relevant records were not retrieved.

The search strategies comprised of a set of terms for the drug daclatasvir combined with a study design search filter. It is not clear if these were validated study design search filters. In Appendix 5, tables 1 and 4, the search is restricted to RCTs, in tables 2 and 5 retrieval has been restricted to non-RCTs and in tables 3 and 6 to adverse events. However given the low number of studies retrieved using only terms for daclatasvir (591 in EMBASE, 146 in PubMed, 26 in the Cochrane Library) a more sensitive approach could have been adopted by searching using the terms for daclatasvir only and then screening the results to identify the different study types. This approach would be more likely to retrieve all of the relevant studies on daclatasvir.

Finally, the humans limit used in the searches of PubMed and EMBASE would have restricted the search to those records indexed as humans, however some records appear in both databases without any indexing terms and therefore these records could have potentially been missed.

4.1.1.2 Inclusion criteria

Selection criteria are reported in Appendix 5 of the manufacturer submission, section 1.1.6. Included were studies of daclatasvir in combination with other licenced antiviral agents (sofosbuvir, peg-interferon alpha and ribavirin) in adult patients with chronic HCV infection and compensated liver disease. Both HCV treatment naïve and treatment experienced were included. Studies had to report at least SVR. RCTs and observational studies were eligible for inclusion, although cohort studies and case control studies were excluded. Single-arm trials were included. The eligibility criteria capture all the licensed indications of daclatasvir and appeared to be appropriate.

4.1.1.3 Critique of data extraction

The data extracted appeared appropriate. It included: study details, data relevant to risk-of bias, demographic details, treatment data (including treatment history), HCV genotype (sections 6.2 and 6.3), efficacy outcomes (sections 6.5 and 6.8) and safety outcomes (including mortality and adverse effects) (6.9).

4.1.1.4 Quality assessment

The quality of the studies was assessed using NICE criteria, and included consideration of randomisation, allocation concealment, similarity of treatment groups, blinding, selective reporting and us of intention-to-treat analysis, as set out in Table 7.

4.1.1.5 Evidence synthesis

The results of the studies were summarised narratively and in tables. Given the differences in designs, interventions and patient characteristics across the studies, the choice of a narrative synthesis appeared appropriate.

4.1.2 Summary and critique of the findings of the review of daclatasvir studies

The submission presented a flow diagram for the clinical effectiveness review of daclatasvir studies (Fig. 3, MS p. 44). The review included 5 unique studies of daclatasvir (four trials and one ongoing observational study, 8 references) out of 836 records, and are shown in Table 6.

Table 6 Daclatasvir studies included in the submission

Study	Regimen & duration	Comparator	Design	Patient population
AI444-040[4 5]	DCV+SOF (±RBV) 12 to 24 weeks	None	Uncontrolled, randomised, open-label, phase II outpatient study	Treatment-naive patients with chronic HCV genotype 1, 2 or 3; treatment-experienced patients (PI triple therapy failures) with chronic HCV genotype 1.
ALLY-3[6]	DCV+SOF 12 weeks	None	Open-label, parallel arm, phase III study	treatment-naive and treatment-experienced patients with HCV genotype 3
AI444-042[7]	DCV+PR 24 weeks	Placebo+PR	Randomised, double-blind, phase IIb study	treatment-naive patients with chronic HCV genotype 4
AI444-010[8]	DCV+PR 12 to 24 weeks	Placebo+PR	Randomised, double-blind, phase IIb study	treatment-naive patients with chronic HCV genotype 1 or 4
[redacted][9]	[redacted]	[redacted]	[redacted]	[redacted]

Study and participant characteristics of daclatasvir trials are presented in section 6.3 of the submission (pp. 50-69), and efficacy results are reported in section 6.5 of the submission (pp. 70-76). All the included studies met the inclusion criteria for at least one of their study arms. Reporting of study and participant characteristics appeared appropriate overall. However, numbers and percentages of patients according to METAVIR stage and treatment experience were not reported consistently across

the daclatasvir trials in the original submission, and further data was provided by the manufacturer in their response to questions for clarification. The ERG agrees with the manufacturer that baseline demographics of recruited patients were broadly comparable to the demographics of patients with HCV to be treated in the UK, and that SVR rates in the UK are likely to be similar to SVR rates seen in trials.

The manufacturer has provided a quality assessment of the four relevant trials of daclatasvir (AI444-040, ALLY-3, AI444-042 and AI444-010) in MS Table 29 (MS p. 70) and MS Appendix 5 (Table 9, p. 8).

The ERG mostly concurs with the manufacturer's assessment of quality for the four trials. However, the ERG had concerns about the design of the single-arm studies, and some more minor concerns associated with definition of primary outcomes, the analyses and blinding methods.

Both AI444-040 and ALLY-3 were single-arm studies. Uncontrolled trials are not usually considered as providing reliable robust evidence of treatment effect. Without a control group it is not possible to be certain that an apparent treatment benefit is real and not just due to a placebo effect or confounded by an unknown variable. In the context of chronic hepatitis C, where the possibility of spontaneous cure is negligible and the measure of treatment benefit an objective one (SVR), the lack of a placebo or no treatment control group is less important than in other therapeutic indications. However, the risk of bias, including selection and confounding bias, cannot be excluded.

The primary outcome considered was sustained virologic response at 12 weeks (SVR12). The ERG had some concerns regarding the definition of this outcome in three of the four daclatasvir trials. In AI444-040, AI444-042, and ALLY3, SVR12 was defined as being below the lower limit of quantification (LLOQ), target detected (TD) or target not detected (TND) at follow-up Week 12. In AI444-042 the percentage of patients with HCV RNA< LLOQ, *TD or TND* was around 5% higher than HCV RNA< LLOQ, *TND only* (73.2% vs 68.3%) in the daclatasvir group (no difference was observed in the PR+placebo group, suggesting that all patients in this arm had TND). Patients with target detected may not necessarily have cleared the hepatitis C virus, and therefore SVR definitions using target detected may overestimate results.

Missing SVR12 data were imputed using the next observation carried backward (or backward imputation) method in AI444-040, ALLY-3 and AI444-042. This means that patients with missing data at follow-up week 12 visit were considered responders if their next available HCV RNA value was <LLOQ. In AI444-042, SVR12 for daclatasvir+PR treated subjects was 73.2% without missing data imputation and 81.7% with backward imputation. Clinical advice to the ERG suggested that virologic response by 12 weeks is generally sustained, and the AI444-010 trial reported high

concordance between SVR12 and SVR24 for HCV genotype 1 (97%) and HCV genotype 4 (100%). However, the ERG notes that backward imputation may bias results by suggesting a response at 12 weeks follow-up when there was none.

Primary analysis for all four trials was based on a modified intention-to-treat basis (mITT, based on patients who were randomised and had received at least one dose). This is not a strict ITT analysis according to Cochrane Collaboration definition (required to include all randomised patients). It is unclear how many patients were enrolled in ALLY-3 but did not receive at least one dose. However, it appears that all patients randomised in AI444-040, and almost all randomised participants in AI444-042 and AI444-010 were included in the analyses, therefore the risk of bias associated with the mITT is likely to be low.

Both AI444-040 and ALLY-3 could not be blinded as they were single-arm trials. The ERG agrees with the MS that lack of blinding of care providers, participants and outcome assessors are unlikely to have introduced bias for relevant efficacy endpoints as they were measured objectively. However, lack of blinding may have increased the risk of bias for patient-reported safety outcomes. In the two placebo-controlled trials, BMS personnel were unblinded at 12 weeks, which may have increased the risk of bias for safety outcomes.

The quality of the ongoing follow-up observational study AI444-046 was not assessed in the MS.

Table 7: Manufacturer and ERG assessments of trial quality for daclatasvir trials

		Single-arm trials		Placebo-controlled trials	
		AI444-040	ALLY-3	AI444-042	AI444-010
1. Was randomisation carried out appropriately?	MS:	Yes	NA	Yes	Yes
	ERG:	Yes[a]	NA	Yes	Yes
[a] randomisation methods in AI444-040 were used for assigning participants to different daclatasvir based regimens stratified by genotype					
2. Was the concealment of treatment allocation adequate?	MS:	NA	NA	Yes	Yes
	ERG:	NA	NA	Yes	Yes
3. Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	MS:	Yes	Yes	Yes	Yes
	ERG:	NA[b]	NA[c]	Yes	Yes
[b] Groups were stratified by genotype. 97.6% of telaprevir or boceprevir triple therapy failures in Groups I and J had non-CC genotypes, compared with 22.0–57.1% of treatment-naive patients in Groups A through H. ALT levels were higher in Groups D and F compared with other groups. Separate fibrosis stage (ie. F0, F1, F2, F3 and F4) and cirrhosis were not reported [c] Group assignment was determined by treatment experience					
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	MS:	NA	NA	Yes	Yes
	ERG:	NA[d]	NA[d]	Yes[e]	Yes[e]
[d] Low risk of bias for objective outcomes, high risk of bias for patient-reported safety outcomes [e] BMS personnel unblinded at 12 weeks. This may have introduced positive bias for safety outcomes					
5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	MS:	No	NA	No	No
	ERG:	No	No	No	Yes[f]
[f] A higher proportion of treated subjects in the DCV/PR group (72.0%) completed the treatment period compared with the placebo/PR group (61.9%). The manufacturer stated this was mainly due to a higher proportion of subjects in the placebo group discontinuing due to a lack of efficacy.					
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	MS:	No	NA	No	No
	ERG:	No	No	Yes[g]	No
[g] The CSR states that "the secondary endpoints SVR24 and SVR48 were unavailable and will be reported in an addendum".					
7. Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	MS:	Yes	Yes	Yes	Yes
	ERG:	Yes[h]	Yes[h]	Yes[h]	Yes
[h] Primary analysis was based on a modified ITT (based on patients who were randomised and had received at least one dose). Patients who had missing data at follow-up week 12 were considered responders if their next available HCV RNA value was <LLOQ. However, concordance between SVR12 and SVR24 is high, and therefore risk of bias associated with backward imputation is likely to be low.					
NA: Not applicable					

4.1.3 Results by Daclatasvir trial

AI444-040 (DCV+SOF±RBV)

Trial AI444-040 was uncontrolled trial in which, 211 patients were stratified by treatment history and genotype and randomised to one of ten arms (A to J – see Table 8) to receive either 12 or 24 weeks DCV+SOF with or without ribavirin; it did not include a non-daclatasvir control arm. Eighty-two genotype 1 participants received 12 weeks treatment with DCV+SOF±RBV (arms G and H). All other

participants received 24 weeks treatment, with a 60mg dose of daclatasvir and 400mg of sofosbuvir. Patients with prior protease inhibitor therapy failure had their treatment duration extended from 12 to 24 weeks during the course of the study. The manufacturer submission presented the study design of AI444-040 in Table 19 (p. 47) which is replicated below in table 8. Participant characteristics were presented in Table 23 of the submission (p. 57). Most included patients had HCV genotype 1 (n=167), followed by genotype 2 (n=26) and genotype 3 (n=18). Baseline characteristics appeared broadly comparable to the demographics of patients with HCV treated in the UK, although individuals co-infected with HIV, who are considered harder to treat, were excluded. The proportion of patients who were white (83%) was lower than the UK population (96%); as other ethnic groups are considered more difficult to treat, this may be conservative for the effect of daclatasvir. People who abused alcohol or drugs were excluded. All patients were without cirrhosis based on a liver biopsy within 24 months of study drug administration, but 14.4% of genotype 1 patients and 11.1% of genotype 3 patients enrolled were given a METAVIR score of F4 by the beginning of the trial baseline period, based on FibroTest and aspartate aminotransferase (AST): platelet ratio index (APRI) score of 2 or below. The clinical advisors to the ERG have indicated that METAVIR F4 is usually considered equivalent to cirrhosis. Table 9 presents a breakdown of patients numbers by METAVIR stage is presented for genotype 1 and 3 patients. The ERG notes that numbers of patients in some subgroups, particularly in genotype 3 and in patients with METAVIR stage F4 were limited.

Table 8: AI444-040 study design

Treatment group	A	B	C	D	E	F	G	H	I	J
Number of patients (n; n = 211)	15	16	14	14	15	14	41	41	21	20
Treatment experience	treatment-naive								TVR or BOC triple therapy failures	
Duration of treatment	24 weeks (48 weeks follow-up)						12 weeks (48 weeks follow-up)		24 weeks[b] (48 weeks follow-up)	
HCV genotype	1	2 or 3	1	2 or 3	1	2 or 3	1	1	1	1
Treatment	SOF 400 mg QD x 7 days then DCV 60 mg QD + SOF 400 mg QD		DCV 60 mg QD + SOF 400 mg QD		DCV 60 mg QD + SOF 400 mg QD + RBV		DCV 60 mg QD + SOF 400 mg QD	DCV 60 mg QD + SOF 400 mg QD + RBV	DCV 60 mg QD + SOF 400 mg QD	DCV 60 mg QD + SOF 400 mg QD + RBV

[b] Planned as 12 weeks, extended to 24 weeks during the course of the study

Table 9: AI444-040 patient numbers by METAVIR stage*, genotypes 1 & 3

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

The primary outcome in AI444-040 was sustained virologic response at 12 weeks (SVR12). Table 10 presents SVRs of AI444-040 by treatment history for genotype 1 and 3 patients, and by METAVIR score (<3 and ≥ 3). SVR12 rates were very high, and approaching 100%, and consistently high across both genotypes, treatment experience and METAVIR category.

Table 30 of the submission shows that SVR24 (95.2%, 120/126) was slightly lower than SVR12 (99%, 125/126 with backward imputation) in treatment-naïve patients genotype 1 patients. For individuals who had HCV RNA values at both follow-up weeks 12 and 24, the manufacturer stated that concordance of SVR24 with SVR12 (based on the criteria HCV RNA < LLOQ, TD or TND) was 100.0% in all groups of treatment-naive subjects with GT-1 or GT-2/-3, except for one genotype 1 patient who achieved SVR12 and then relapsed at follow-up Week 24. The trial investigator CSR stated that the relapse was probably due to re-infection. It is unclear whether the remaining patients who had SVR12 but missing SVR24 data had virologic relapse.

Table 10. AI4440-040 SVR results by genotype and treatment experience status

	Genotype 1		Genotype 3	
	Treatment naïve	Prior TVR or BOC triple therapy failures	Treatment naïve	
	DCV+SOF±RBV n = 126	DCV+SOF±RBV n = 41	DCV+SOF n=13	DCV+SOF±RBV n = 126
SVR12*	125 (99%)	41 (100%)	11 (85%)	5 (100%)
METAVIR stage[§]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ F3	41/41 (100.0)	20/20 (100.0)	NR	NR

* <LLOQ, TND or TD ; * Patients who had missing data at follow-up Week 12 were considered responders if their next available HCV RNA value was <LLOQ.;
[redacted]

Overall, the results of this trial indicate that DCV+SOF+ RBV is effective in Genotype 1 patients, whether treatment naïve or experienced. However whilst the effect appears as good in cirrhosis patients, this conclusion must be uncertain being based on only very small patient numbers (n=24) Limited evidence is available for Genotype 3 patients (n=18). The results in treatment naïve patients (n=5) suggest DCV+SOF+RBV is effective. Results from AI444-040 should be interpreted with caution as the lack of control group means the high risk of selection and confounding bias cannot be excluded. The exclusion of patients with HIV means that the applicability of the study findings to the population of UK patients co-infected with HIV and HCV is uncertain.

ALLY-3 (DCV+SOF)

ALLY-3 was an uncontrolled trial that evaluated the efficacy of daclatasvir with sofosbuvir (for 12 weeks without ribavirin) in 152 genotype 3 patients, including 101 treatment naïve and 51 treatment experienced patients. The manufacturer submission presented the study design of ALLY-3 in Figure 6 (p. 47) and participant characteristics in Table 24 (p. 59).). Baseline characteristics appeared broadly comparable to the demographics of patients with HCV treated in the UK, although individuals co-infected with HIV, who are considered harder to treat, were excluded. The proportion of patients who were white (90%) was lower than the UK population (96%); as other ethnic groups are considered more difficult to treat, this may be conservative for the effect of daclatasvir. People who abused alcohol or drugs were excluded.

The primary outcome in ALLY-3 was sustained virologic response at 12 weeks post-treatment follow-up (SVR12). Table 11 presents SVR12 results from ALLY-3 by treatment history and METAVIR stage, based on an unpublished report of final results (Appendix 6 of manufacturer responses and

manufacturer responses to clarification). In ALLY-3, SVR12 rates were 90 % in treatment-naive and 86% in treatment-experienced patients, confirming the results found in AI444-040. SVR12 rates were significantly higher in genotype 3 patients without cirrhosis (96%) than in genotype 3 patients with compensated cirrhosis (63%), and higher in patients with less severe fibrosis (METAVIR F0-F3) (93%) than in those with severe fibrosis (METAVIR F4, (70%). There was no evidence of any difference between treatment-experienced and treatment-naive patients.

Further analyses found no notable differences in SVR12 by gender, age, HCV RNA levels, or IL28B genotype. All patients had HCV RNA undetectable at the end of treatment. A total of 16 (11%) patients had post-treatment relapse. The occurrence of virologic failure was low (1 patient), and no virologic breakthroughs were observed.

Table 11: ALLY-3 SVR12 by liver disease severity and treatment history in genotype 3 patients (DCV+SOF)

	Treatment-naïve N = 101	Treatment-experienced N = 51	Total N = 152
Overall	91/101 (90.1)	44/51 (86.3)	135/151 (88.8)
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
F4	16/22 (72.7)	5/8 (62.5)	21/30 (70.0)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
Absent	73/75 (97.3)	32/34 (94.1)	105/109 (96.3)
Present	11/19 (57.9)	9/13 (69.2)	20/32 (62.5)
[redacted]	[redacted]	[redacted]	[redacted]

Overall, the results of this trial indicate that daclatasvir plus sofosbuvir is effective in Genotype 3 patients, whether treatment naïve or experienced. Results from ALLY-3 should be interpreted with caution as the lack of control group means the high risk of selection and confounding bias cannot be excluded. Whilst SVR12 rates appear high in patient with no cirrhosis, they were significantly lower in patients with compensated cirrhosis, although this finding is based on relatively small subgroups. The ERG notes that treatment duration in ALLY-3 was 12 weeks, and that daclatasvir and sofosbuvir were administered without ribavirin. As greater efficacy may have been achieved with a longer treatment duration and with the co-administration of ribavirin, the results may underestimate what could be achieved with daclatasvir in Genotype 3 patients, particularly in the more difficult to treat subgroups. This is reflected in the marketing authorisation, which recommends daclatasvir and sofosbuvir with ribavirin for 24 weeks in genotype 3 patients with compensated cirrhosis and/or previous treatment experience. However,

[redacted]. Therefore in clinical practice, with daclatasvir administered according to its licence higher rates of SVR might be achieved in patients with cirrhosis, though the data to support this are not available. The exclusion of individuals with HIV means that the applicability of the study findings to the population of UK patients co-infected with HIV and HCV is uncertain.

AI444-042 (DCV+PR)

AI444-042 was an RCT compared the efficacy of daclatasvir + PR with PR alone in genotype 4 treatment naïve patients. Patients received 60mg of daclatasvir for 24 weeks. The manufacturer presented the design of this RCT in Figure 7 (p. 48) and characteristics of the participants in Table 25 (p. 60) of the submission. Baseline characteristics appeared broadly comparable to the demographics of patients with HCV treated in the UK, although individuals co-infected with HIV, who are considered harder to treat, were excluded. The proportion of patients who were white (77%) was lower than the UK population (96%); as other ethnic groups are considered more difficult to treat, the result from the trial may be conservative for the effect of daclatasvir. People who abused alcohol or drugs were excluded. The primary outcome in AI444-042 was sustained virologic response at 12 weeks (SVR12). In trial AI444-042, SVR12 rates were higher for patients receiving daclatasvir compared with placebo, and this difference was statistically significant. Table 12 presents overall response rates at follow-up week 12 and by subgroup.

[redacted] SVR12 rates were similar between patients without cirrhosis (81%) and those with compensated cirrhosis (78%) in the daclatasvir arm, although this finding should be interpreted with caution as it is based on small very subgroups (n= 9 and 4). The ERG concludes that this generally well-conducted RCT provides good evidence that daclatasvir combined with interferon and ribavirin is superior to interferon with ribavirin, although the sample size was comparatively small. The exclusion of individuals with HIV means that the applicability of the study findings to the population of UK patients co-infected with HIV and HCV is uncertain.

Table 12: AI444-042 Summary of Sustained Virologic Response (< LLOQ, TD or TND) at Follow-up Week 12 (SVR12) in genotype 4 patients (n/N (%))[*]

	DCV+PR N=82	Placebo+PR N=42
Overall population	67/82 (81.7)	18/42 (42.9)
Baseline cirrhosis		
Absent	56/69 (81.2)	15/38 (39.5)
Present	7/9 (77.8)	1/4 (25.0)
Not reported	[redacted]	[redacted]
Baseline HCV RNA (IU/mL)		
< 800,000	[redacted]	[redacted]
≥ 800,000	[redacted]	[redacted]
Baseline BMI		
<25 kg/m^2	[redacted]	[redacted]
≥25 kg/m^2	[redacted]	[redacted]
IL-28B Genotype		
CC	[redacted]	[redacted]
CT	[redacted]	[redacted]
TT	[redacted]	[redacted]
VR (4&12)		
Virologic response at 4 and 12 weeks treatment		
Achieved	[redacted]	[redacted]
Not achieved	[redacted]	[redacted]

[*] Patients with missing data at follow-up week 12 visit were considered responders if their next available HCV RNA value was <LLOQ (backward imputation). Only treated patients were analysed (modified-ITT).

AI444-010 (DCV+PR)

Trial AI444-010 was an RCT recruited patients of both genotype 1 and 4, and evaluated the efficacy of two daclatasvir regimens. Participants were randomised 2:2:1 to receive DCV 20 mg, DCV 60 mg, or placebo, plus PR. All participants received DCV (20 or 60 mg)+PR or placebo+PR through Week 12. A second randomization (1:1) occurred at Week 12 for subjects initially randomized to 20 mg or 60 mg DCV who achieved a protocol defined response. These participants either received an additional 12 weeks of DCV (20 or 60 mg)/PR or 12 weeks of placebo+PR. The manufacturer presented the design of this RCT in Figure 8 (p. 49) and characteristics of the participants in Table 26 (p. 61) of the submission. Baseline characteristics appeared broadly comparable to the demographics of patients with HCV treated in the UK, although individuals co-infected with HIV, who are considered harder to treat, were excluded. The proportion of patients who were white (81%) was lower than the UK population (96%); as other ethnic groups are considered more difficult to treat, the results may be conservative for the effect of daclatasvir. People who abused alcohol or drugs were excluded.

Results for HCV genotype 1 are summarised in Table 13 (adapted from the submitted clinical study report for this trial). SVR rates were higher in the two daclatasvir arms (20mg or 60mg, combined with PR) than in the placebo arm, but there were no significant differences between the higher and lower daclatasvir doses. The study found that concordance between SVR12 and SVR24 was high (97%). SVR24 rates were higher in patients genotype 1b (compared with genotype 1a), in patients with baseline HCV RNA<800,000, and in patients with BMI<25kg/m^2. Daclatasvir was consistently more effective than placebo across all subgroups. No significant differences were found between patients with and without cirrhosis, although this finding should be interpreted with caution as the number of patients with cirrhosis was small (13/8/8).

Table 13: AI444-010 Summary of Sustained Virologic Response (< LLOQ, TND) at Follow-up Week 12 and 24 by in genotype 1 patients (n/N (%))[*]

	DCV 20 mg+PR N=147	**DCV 60 mg+PR N=146**	**Placebo+PR N=72**
SVR12	95/147 (64.6)	88/146 (60.3)	26/72 (36.1)
SVR24	[redacted]	[redacted]	[redacted]
SVR24 by subgroup			
HCV genotype			
1a	[redacted]	[redacted]	[redacted]
1b	[redacted]	[redacted]	[redacted]
Baseline cirrhosis			
Absent	[redacted]	[redacted]	[redacted]
Present	[redacted]	[redacted]	[redacted]
Baseline HCV RNA (IU/mL)			
< 800,000	[redacted]	[redacted]	[redacted]
≥ 800,000	[redacted]	[redacted]	[redacted]
Baseline BMI			
<25 kg/m^2	[redacted]	[redacted]	[redacted]
≥25 kg/m^2	[redacted]	[redacted]	[redacted]
IL-28B Genotype			
CC	[redacted]	[redacted]	[redacted]
CT	[redacted]	[redacted]	[redacted]
TT	[redacted]	[redacted]	[redacted]

[*] Patients with missing data at follow-up week 12 visit were considered responders if their next available HCV RNA value was <LLOQ (backward imputation). Only treated patients were analysed (modified-ITT).

SVR12 and SVR24 rates were reported for a subgroup of 30 patients with genotype 4 and no cirrhosis, and are presented in Table 14 (adapted from the submitted clinical study report for this

trial). Response rates were higher for both daclatasvir treatment arms compared with placebo, and higher in the daclatasvir 60 mg arm compared with daclatasvir 20 mg. However, these results should be interpreted with caution due to small patient numbers.

Table 14: AI444-010 summary of Sustained Virologic Response at Follow-up Week 12 and 24 by in genotype 4 patients

	DCV 20 mg+PR N=12	DCV 60 mg+PR N=12	Placebo+PR N=6
SVR12	9/12 (75.0%)	12/12 (100%)	3/6 (50%)
SVR24	8/12 (66.7%)	12/12 (100%)	3/6 (50%)

The ERG concludes that this trial provides good evidence that daclatasvir PR is superior PR alone in genotype 1, treatment-naïve patients. Evidence on genotype 4 patients was too limited to draw any firm conclusions. The exclusion of individuals with HIV means that the applicability of the study findings to the population of UK patients co-infected with HIV and HCV is uncertain.

Summary of SVR across daclatasvir trials

Table 15 and 16 present a summary of SVR12 results across trials by genotype, for overall population and patients with compensated cirrhosis/METAVIR score F4 respectively.

None of the four trials identified in the review of daclatasvir provided evidence for the subgroup of patients who were ineligible or intolerant to interferon treatment. Therefore the efficacy of daclatasvir in this subpopulation is uncertain. As stated above, all daclatasvir trials excluded individuals with HIV, therefore the applicability of the study findings to the population of UK patients co-infected with HIV and HCV is uncertain.

In patients with genotype 1, DCV+SOF ±RBV for 12 or 24 weeks yielded very high SVR rates, regardless of fibrosis severity, including in patients with previous telaprevir or boceprevir triple therapy failures who received DCV+SOF±RBV for 24 weeks. There was no evidence for patients with previous triple therapy receiving only 12 weeks DCV+SOF treatment (a licensed treatment duration). DCV+PR appeared less efficacious.

In patients with genotype 3 DCV+SOF±RBV appears efficacious (but possibly less so than in genotype 1 patients), regardless of previous treatment status. In these patient efficacy may be lower in patients with cirrhosis, although this finding is based on limited data. There was no evidence for the licenced 24 weeks treatment combination DCV+SOF+RBV, and no evidence for DCV+SOF 24 weeks in genotype 3 patients with cirrhosis and/or treatment experience.

In patients with genotype 4, there is no evidence for daclatasvir+sofosbuvir. Daclatasvir+PR appears effective compared to PR alone in treatment naïve patients (there is no data for treatment experienced patients) although this is based on relatively limited patient numbers, and again very few patients with compensated cirrhosis. Results for treatment naïve genotype 4 patients with cirrhosis who received daclatasvir+PR did not differ significantly from the overall population, although this finding is based on a very small sample.

Table 15: Summary of Sustained Virologic Response (< LLOQ, TD or TND) at Follow-up Week 12 (SVR12)*: Daclatasvir trials

	Treatment naïve	Treatment experienced[#]	Data source
Genotype 1			
DCV+SOF (12-24 weeks)	100% (70/70)[£]	100% (21/21)[$]	AI444-040
DCV+SOF+RBV (12-24 weeks)	98% (55/56)	100% (20/20)[$]	AI444-040
DCV+PR (12 weeks)	60% (88/146)	No data	AI444-010
Genotype 3			
DCV+SOF+RBV (24 weeks)	100% (5/5)	No data	AI444-040
DCV+SOF (24 weeks)	85% (11/13)	No data	AI444-040
DCV+SOF (12 weeks)	90% (91/101)	86% (44/51)	ALLY-3
Genotype 4			
DCV+SOF	No data	No data	
DCV+PR (24 weeks)	82% (67/82)	No data	AI444-042
DCV+PR (12 weeks)	100% (12/12)	No data	AI444-010

* Patients who had missing data at follow-up Week 12 were considered responders if their next available HCV RNA value was <LLOQ
[£] Includes 15 patients with 7 days SOF 400mg QD run-in; [#] GT1 experienced patients had all failed previous TVR or BOC triple therapy; in ALLY-3 (GT3), 61% had previous relapse, 14% null response, 2% partial response, 12% intolerance, 10% other; [$] 24 weeks treatment only

Table 16: Summary of Sustained Virologic Response at Follow-up Week 12 (SVR12)* in patients with METAVIR F4/ compensated cirrhosis: Daclatasvir trials

	Treatment naïve	Treatment experienced[#]	Data source[+]
Genotype 1			
DCV+SOF (12-24 weeks)	100% (9/9)[£]	100% (2/2)	AI444-040
DCV+SOF+RBV (12-24 weeks)	100% (7/7)	100% (6/6)	AI444-040
DCV+PR (12-24 weeks)	63% (5/8)[$]	No data	AI444-010
Genotype 3			
DCV+SOF+RBV (24 weeks)	No data	No data	AI444-040
DCV+SOF (24 weeks)	NR (NR/2)	No data	AI444-040
DCV+SOF (12 weeks)	58% (11/19)	69% (9/13)	ALLY-3
Genotype 4			
DCV+SOF	No data	No data	
DCV+PR (24 weeks)	78% (7/9)	No data	AI444-042
DCV+PR (12-24 weeks)	No data	No data	AI444-010

* Patients who had missing data at follow-up Week 12 were considered responders if their next available HCV RNA value was <LLOQ; [#] Genotype 1 experienced patients had failed previous TVR or BOC triple therapy; [£] Includes 2 patients with 7 days SOF 400mg QD run-in; [+] Participants from AI444-040 had METAVIR score F4 based on Fibrotest but no diagnosis of compensated cirrhosis. Participants from ALLY-3, AI444-042 and AI444-010 had a diagnosis of compensated cirrhosis at baseline. [$] SVRat follow-up week 24

Summary and critique of the findings of the review of long-term non-RCT evidence

The MS identified one non-RCT study from a review of BMS databases. AI444-046 is an ongoing multicentre open-label observational study enrolling [redacted] patients, with a planned maximum duration of 144 weeks. The primary aim of the study was to evaluate the durability of virologic response, assessed as time to loss of virologic response in eligible patients who achieved SVR12 in a parent study with daclatasvir and/or asunaprevir. Further details on the methodology and eligibility criteria of the study are summarised in tables 51-52 of the manufacturer submission (pp.101-102), and in the submitted clinical study report. Of [redacted] enrolled patients, [redacted] were eligible, and [redacted] had achieved SVR12 in their parent study ([redacted]). Of those [redacted] patients, [redacted] had received daclatasvir with PR, and [redacted] had received daclatasvir with sofosbuvir (with or without ribavirin) and were included in the interim analysis. Other regimens (including PR only, and combination regimens with asunaprevir, which is beyond the license indication) were evaluated.[redacted] of the [redacted] (1.3%) eligible patients treated with daclatasvir+PR, and [redacted] of the [redacted] eligible patients receiving DCV+SOF±RBV had virologic relapse. Sequencing to determine if the DCV treated subjects who did not maintain their virologic response had a possible re-infection of a different strain of HCV were not completed by the date of the interim report. Data on long-term progression of liver disease (secondary outcome) were not reported in this interim analysis.

SVR results of AI444-046 appear reliable, although these are based on interim analyses, and there are uncertainties regarding the selection of patients from the DCV/SOF±RBV group. As this is an ongoing observational study rather than a randomised trial it did not contribute to the overall conclusions on efficacy. Although interim results from AI444-046 appear promising, the ERG considers that this study does not, at present, provide conclusive evidence on the long-term effectiveness of daclatasvir.

4.1.3.2 Development of resistance to daclatasvir results

The initial submission did not include a section on development of resistance to daclatasvir. However, the manufacturer provided a summary of resistance in their response to clarification question based on results from the four trials supporting the MS, which is presented below.

[redacted]

[redacted]

AI444-040 (DCV+SOF±RBV)

[redacted]

ALLY-3 (DCV+SOF)

[redacted]

AI444-042 (DCV+PR)

[redacted]

AI444-010 (DCV+PR)

[redacted]all participants who failed treatment with daclatasvir+PR had NS5A resistance-associated substitutions to daclatasvir at or close to the time of virologic failure

[redacted]Overall, the evidence regarding the association between baseline NS5A polymorphisms and virologic failure is mixed and inconclusive. However, there is some limited evidence to suggest that specific baseline NS5A polymorphisms may be associated with virologic failure in genotype 1, 3 and 4 patients. The evidence is limited by the use of different drug combinations (for instance, use of sofosbuvir may have reduced virologic failure rates) and small sample sizes.

4.1.3.3 Mortality results

There were no deaths reported in AI444-040, ALLY-3 and AI444-042. In AI444-010 trial, two patients in the daclatasvir 20 mg+PR group died: one during the treatment period (sudden death due to unknown causes) and one during follow-up (cardiopulmonary failure exacerbated by asthma). The manufacturer stated that both deaths were deemed unrelated to study therapy by the investigator.

[redacted]

There is therefore no evidence that daclatasvir is associated with any excess mortality.

4.1.3.4 Safety results

The manufacturer presented adverse events results in section 6.9 (pp. 106-113) of the MS. A summary of key safety results for the five studies included in the review of daclatasvir is presented in 17 and 18.

AI444-040 (DCV+SOF±RBV)

Based on data presented in Table 56 of the manufacturer submission, most SAEs occurred in patients undergoing 24 weeks treatment (86.7%) compared with 12 weeks therapy (13.3%). The proportion of patients with SAEs was slightly higher in those who had receiving daclatasvir and sofosbuvir with ribavirin (6.7%) compared with those who did not receive ribavirin (5.0%). Two patients had a SAE or AE leading to discontinuation of study therapy (one Grade 3, one Grade 2 cerebrovascular accident), and both were not considered to be related to study therapy by the investigator. Grade 3/4 AEs were reported in 3.3% (7/211) of patients. No Grade 4 laboratory values were reported. The most common adverse events were fatigue (37.0%), headache (28.9%) and nausea (19.4%).

ALLY-3 (DCV+SOF)

The incidence of Grade 3 AEs was low (2%), with no Grade 4 AEs reported. One on-treatment serious adverse events (SAEs) was reported: an event of gastrointestinal haemorrhage that was considered not related to study medications. The manufacturer reported that no adverse events led to treatment discontinuation. The most common AEs were headache (19.7%), fatigue (18.4%), and nausea (11.8%).

Table 17: Summary of adverse events in trials of daclatasvir and sofosbuvir combinations

	AI444-040 DCV+SOF±RBV (n = 211)	ALLY-3 DCV+SOF (n=151)
Adverse events		
SAEs	15 (7.1)	1 (0.7)
AEs leading to discontinuation	2 (0.9)	0
Grade 3/4 AEs	7 (3.3)	3 (2.0)
Most common adverse events		
Fatigue	78 (37.0)	28 (18.4)
Headache	61 (28.9)	30 (19.7)
Nausea	41 (19.4)	18 (11.8)
Arthralgia	21 (10.0)	8 (5.3)
Diarrhoea	21 (10.0)	13 (8.6)
AE: adverse event; DCV: daclatasvir; RBV: ribavirin; SAE: serious adverse event; SOF: sofosbuvir		

AI444-042 and AI444-010 (DCV+PR)

The MS reported that types and frequencies of AEs were generally consistent across treatment group, and found no clinically significant differences in the AE profile of DCV+PR and placebo+PR in AI444-042 and AI444-010 trials. Table 18 results below suggest that serious AEs are generally not associated with daclatasvir.

Table 18: AI444-042 and AI444-010 summary of safety: all treated patients

	Number (%) of patients				
	AI444-042		AI444-042		
	DCV+PR (n = 82)	DCV+PR (n = 82)	DCV+PR (n = 82)	DCV+PR (n = 82)	DCV+PR (n = 82)
SAEs	8 (9.8)	2 (4.8)	12 (7.5)	13 (8.2)	6 (7.7)
AEs leading to discontinuation	3 (3.7)	3 (7.1)	7 (4.4)	7 (4.4)	8 (10.3)
Grade 3 to 4 AEs	19 (23.2)	9 (21.4)	32 (20.1)	23 (14.6)	18 (23.1)

[redacted]

4.1.3.5 Health-related quality of life

No results on Health-related quality of life (HRQoL) were presented. Section 7.4 of the submission presented a systematic review to identify all published studies on generic HRQoL instrument in chronic hepatitis since 2009. The review did not identify studies of daclatasvir-based regimens.

4.1.4 Conclusions of the review of daclatasvir studies

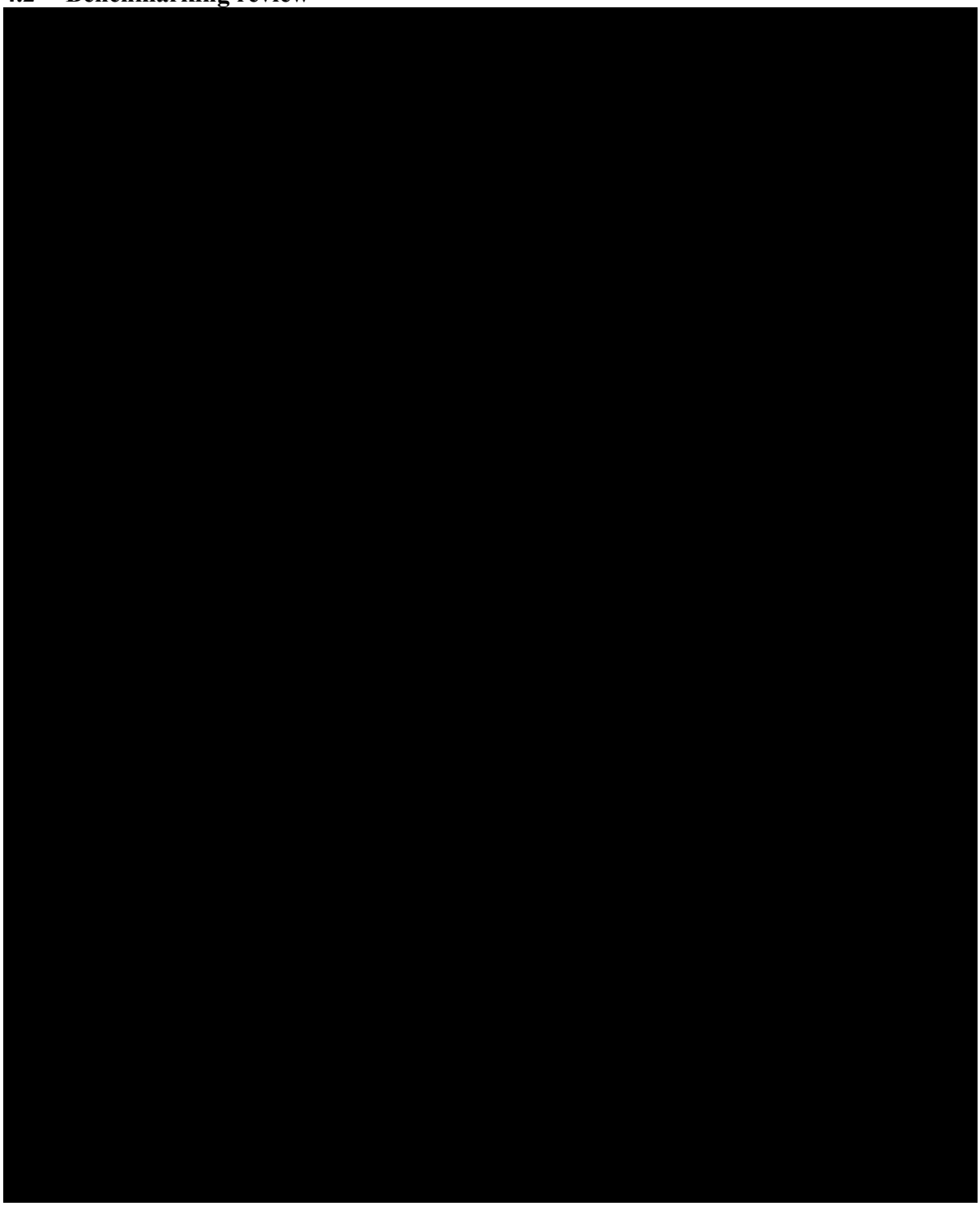
The manufacturer's systematic review of clinical effectiveness is of a reasonable quality. The review included four studies examining the efficacy of daclatasvir in treating chronic hepatitis C, as well as one long-term follow-up observational study. One study compared different treatment regimens of daclatasvir combined with sofosbuvir (with or without ribavirin), one study evaluated daclatasvir combined with sofosbuvir, and two trials compared daclatasvir with PR versus placebo and PR. All studies addressed NICE's final scope.

Based on the evidence presented in the submission, the ERG concludes that daclatasvir appears generally well-tolerated and safe. However, although high rates of SVR12-24 were observed, some caution is warranted regarding the efficacy of daclatasvir due to the following concerns:

- The two studies that evaluated combinations of daclatasvir+sofosbuvir did not have a control group and these trials may be at high risk of bias, therefore the relative efficacy of daclatasvir and sofosbuvir compared with other relevant treatment is uncertain,.
- Evidence from ALLY-3 suggests that the efficacy of daclatasvir+sofosbuvir in genotype 3 patients was significantly lower in patients with compensated cirrhosis (62.5%) compared with patients with no cirrhosis (96.3%). However, these results relate to 12 weeks treatment with daclatasvir+sofosbuvir alone and may underestimate that achieved in clinical practice with the licenced 24 weeks treatment in combination with ribavirin.

- SVR12-24 results in patients with METAVIR score F4 or with a diagnosis of compensated cirrhosis were all based on small subgroups and their reliability is limited. Therefore the effectiveness of daclatasvir in patients with compensated cirrhosis is uncertain.
- No data were presented for patients who were ineligible or intolerant to interferon treatment, or individuals co-infected with HIV. People who abused alcohol or drugs were excluded. Therefore the effectiveness of daclatasvir in these sub-populations is uncertain.

4.2 Benchmarking review



[redacted]

19

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		[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]

[redacted]

[redacted]

4.4 Matching-adjusted indirect comparisons (MAIC) review

This section considers the systematic reviews and matching-adjusted indirect comparisons (MAIC) analyses presented in Section 6.7.1 of the evidence submission and in Appendices 6b, 6c and 6d and appendix 4 of the submitted clarifications. This MAIC analysis consisted of a review of all studies of telaprevir, boceprevir, sofosbuvir or simeprevir, all combined with PR, or PR alone, to identify the expected SVR24 or SVR12 response for these treatments. This was compared to the observed response with daclatasvir in trials AI444-040 and ALLY-3, adjusted to match the demographic characteristics of patients in the other trials. Incidence of adverse events was also compared.

4.4.1 Critique of manufacturer's approach to the methods of reviews

4.4.1.1 Searches

The searches for this indirect and mixed treatment comparison are not described in the main submission but can be found in Appendices 6b, 6c and 6d.

No searches are reported by the manufacturer for trials of telaprevir and boceprevir. The studies included in the comparison for both drugs were identified through previous systematic literature reviews by Chou et al. and Cooper et al. referenced in Appendix 6b. However information on a further set of searches were submitted by the manufacturers in response to the points of clarification.

For sofosbuvir and simeprevir in genotype 1 a search of PubMed only was conducted, therefore this did not meet the NICE minimum requirements for databases to be searched Some important synonyms are missing from the search strategies: the brand names sovaldi and olysio were not been included nor was the abbreviation HCV. Therefore this may have led to relevant studies not being retrieved. A limit to the clinical trial publication type [ptyp] was also used which is quite restrictive. Not all clinical trials in PubMed will have this tag applied so it would have been more appropriate to have used a validated sensitive RCT search filter to limit the results.

For comparator treatments in genotype 3 patients all of the NICE specified databases were searched (MEDLINE, MEDLINE in process, EMBASE and the Cochrane Central Register of Controlled Trials). No additional searches of unpublished data were reported. The period covered by the searches was not reported. The search strategy presented had several limitations. The search was limited to the mp field which searches in the title, abstract, subject headings and keywords. However it is

impossible to tell with an mp. search whether the correct subject headings have been automatically applied. A safer option would have been to include searches of the relevant subject headings separately in addition to the mp. search. The brand names Pegasys, Peg-intron, sofaldi and copegus were not included in the search strategy. It is therefore possible that all relevant studies were not identified by the search strategy.

4.4.1.2 Inclusion criteria

For genotype 1 all studies of telaprevir, boceprevir, sofosbuvir or simeprevir, (all combined with PR) in patients with chronic HCV who were treatment-naïve were included. For genotype 3 all studies of sofosbuvir with ribavirin, or PR alone in patients with chronic HCV were included. Patients with treatment experience were considered only in the analysis of sofosbuvir with ribavirin in genotype 3. Reporting of SVR rates was required.

The inclusion criteria for this review appeared to be appropriate and likely to include most treatments regimens to which daclatasvir should be compared given its licensed therapeutic indication. The restriction to treatment-naïve patients in genotypes 1 means results are unlikely to generalise to treatment-experienced patients or to other genotypes. Some important treatment combinations (particularly, simeprevir with sofosbuvir) were not included in the analysis. No analysis was presented for genotype 4 patients, and there was no separate analysis of patients by fibrosis severity. It was not clear whether this was an intentional exclusion or due to a lack of published trials on treatment combinations.

Reasons for excluding potentially relevant TVR, BOC, SOF and SIM trials were presented in the MAIC analysis for GT1 treatment naïve patients (Appendix 6b, tables 2-5). Two trials [10 11] were excluded because “a more advanced phase trial with a larger population was available”. It is unclear why these trials were not pooled with other included studies. Reasons for exclusion of potentially relevant comparator trials in genotype 3 patients (Appendix 6c-d) were not provided, making study selection bias difficult to assess.

4.4.1.3 Critique of data extraction

Limited information was provided on data extraction. It appeared that, in general, sufficient data on SVR rates and on demographic and patient characteristics needed to perform an adjusted analysis were extracted. In the analysis of PR only baseline HCV RNA data was extracted in order to perform the adjusted analysis, because of limited data availability. Data did not appear to be extracted on key subpopulations (such as patients with advanced fibrosis or compensated cirrhosis) because no adjusted analyses were performed on these subpopulations. It was not clear if this was because data were lacking on these subpopulations.

4.4.1.4 Quality assessment

No plan for a quality assessment was described and the details of the quality of included trials were not discussed in detail.

4.4.1.5 Evidence synthesis

The trials were synthesised using a matched-adjusted indirect comparisons (MAIC) method. This method aims to adjust the outcome in trials for which individual participant data are available to match the demographic characteristics of other trials. In this case the SVR rate or incidences of adverse events in the AI444-040 and ALLY-3 trials were adjusted to match the characteristics of the trials of other treatments identified in the systematic review. This was achieved by re-weighting the patients in AI444-040 and ALLY-3 using a propensity score to match the characteristics of patients in other trials, and then adjusting the SVR or incidence of adverse events according to this re-weighting.

This approach is not a controlled or a randomised comparison and so has the potential for bias, particularly if patient characteristics or clinical conditions were very different in the various trials. While the adjustment process sought to correct for some of these potential differences the reliability of the adjustment is strongly dependent on correctly adjusting for the factors which influence outcomes: if a critical factor that influences outcome is not adjusted for then the results may be misleading. The analysis considered a range of patient characteristics including: age, sex, ethnicity obesity, plasma HCV RNA count, HCV genotype and METAVIR fibrosis stage. These appear to be an appropriate set of covariates but the possibility that there are other critical factors that were not adjusted for cannot be ruled out. In the analyses of PR only baseline HCV RNA was used for adjustment due to a lack of data on other factors, so the adjustments may not have been sufficient to account for all differences across trials in the POR analysis.

4.4.2 Critique of the findings of the MAIC analysis

Table 20 summarises the trials identified by the various systematic reviews, according to treatment and genotype.

Table 20: Trials included in the MAIC analyses

Genotype	Treatment	Trial name	Trial design	Sample size in analysis
1	Boceprevir +PR	SPRINT-2[12]	Phase III double-blind placebo RCT	368
	Telaprevir +PR	ADVANCE[13] ILLUMINATE	Phase III double-blind placebo RCT Open-label randomised trial without placebo	903 across both trials
	Sofosbuvir +PR	NEUTRINO[14]	Single–arm trial	327 *
	Simeprevir +PR	QUEST-1 QUEST-2[15]	Phase III double-blind placebo RCT Phase III double-blind placebo RCT	521 across both trials
3	PR alone	Ferenci[16] Foster[17] Shiffmann[18]	Randomised trial without placebo/comparator RCT with placebo arm Randomised trial without placebo/comparator	129 9 369
	Sofosbuvir with ribavirin	VALENCE[19 20]	Phase III open-label placebo RCT	250 **

* not all genotype 1; ** VALENCE was compared to ALLY-3, and included both treatment-naive and treatment-experienced patients

The data on comparison treatments was therefore limited, with only 10 trials considered, and for both sofosbuvir and boceprevir only one comparison trial was identified. For daclatasvir treatment most comparisons were made with the 125 genotype 1 patients in trial AI444-040, for the genotype 3 comparison with PR alone the comparison was based on only 18 daclatasvir patients. Most of the evidence was in treatment-naïve patients, with only the VALENCE trial containing treatment-experienced patients.

No detailed review of trial quality was reported, however most of the trials in patients with genotype 1 were Phase III placebo controlled and double-blinded trials, so are likely to be of high quality. The trials are likely to be of higher quality than the daclatasvir trials, which had no comparator arm. The NEUTRINO trial of sofosbuvir had no comparator arm, and so may be of lower quality, and more prone to bias than other trials. Although the trials may be of high quality only the active treatment arm was used in the MAIC analysis, so the comparison with daclatasvir is not randomised. None of the trials of genotype 3 patients included a placebo group and so were not controlled trials and may be of lower quality.

The small size of the daclatasvir (with sofosbuvir and ribavirin) trials means that the MAIC adjustment is very unreliable. Only 1 patient in AI444-040 and 17 in ALLY-3 did not achieve SVR12. Any adjustment of the SVR rate in these trials to match the characteristics in other trials is therefore extremely sensitive to the characteristics of these few non-successes, and so adjustments are heavily influenced by chance and are unlikely to represent realistic estimates of what SVR rates might have been in other trials. The ERG therefore considers that the MAIC analyses are no more statistically reliable than unadjusted analyses.

The results of the MAIC analyses for SVR rates are summarised in Table 21. For all analyses in patients with genotype 1 daclatasvir (with sofosbuvir and ribavirin) was found to have higher SVR rates than all the comparator treatments, and all findings were statistically significant. For patients with genotype 3 daclatasvir was found to be superior to PR alone, but there was no statistically significant evidence of superiority when compared to sofosbuvir with ribavirin.

Table 21: Summary of results of MAIC analyses of SVR rates

Genotype	Treatment	SVR % rate		
		Comparator	Daclatasvir (AI444-040 or ALLY-3)	
			MAIC adjusted	Unadjusted
1	Boceprevir	66.6	98.9	98.4
	Telaprevir	73.0	91.5	95.1
	Sofosbuvir	89.6	98.0	98.4
	Simeprevir	80.6	99.2	98.4
3	PR alone	66.1	89.1	88.9
	Sofosbuvir with ribavirin	87.2	89.6	90.3

Table 22 summarises the adverse event rates for the comparator treatments, compared to the MAIC adjusted rates for daclatasvir in genotype 1 patients. Results for patients of genotype 3 were broadly similar (see tables 41 to 47 of submission for full details). In the analyses of adverse events daclatasvir was generally found to have a lower incidence of adverse events than all the other comparator treatments, with most comparisons giving statistically significant results. There were no reported adverse events where incidence was statistically significantly higher on daclatasvir, after MAIC adjustment.

Table 22: Adverse event rates for comparator treatments and adjusted rates in daclatasvir patients of genotype 1.

Tolerability outcome	Incidence of adverse events by treatment (%)				
	Daclatasvir (Adjusted *)	Boceprevir +PR	Telaprevir +PR	Sofosbuvir +PR	Simeprevir +PR
Discontinuation due to AE	0.8%	12.2%	14.5%	1.5%	2.3%
Nausea	27.7%	47.6%	45.3%	34.3%	NR
Anaemia	7.3%	49.5%	7.3%	20.8%	14.8%
Fatigue	40.7%	53.3%	63.8%	58.7%	37.4%
Headache	46.8%	45.7%	39.0%	36.1%	34.0%
Chills	1.6%	36.4%	NR	NR	NR
Pyrexia	5.5%	33.4%	NR	NR	NR
Dysgeusia	0.8%	37.2%	NR	NR	NR
Insomnia	15.3%	31.8%	33.1%	24.8%	NR
Rash	15.4%	NR	37.1%	NR	25.3%
Diarrhoea	12.4%	NR	29.5%	NR	NR
Pruritis	11.5%	NR	50.3%	NR	19.8%

* Adjusted results varied according to treatment comparison: highest adjusted or unadjusted result given
NR = Not reported

4.4.3 Conclusions for the MAIC analysis

The MAIC analysis concluded that SVR rates were higher for daclatasvir (combined with sofosbuvir with or without ribavirin) than for other treatments (sofosbuvir, simeprevir, telaprevir or boceprevir) in genotype 1 treatment naïve patients. Adverse events rates were also generally lower with daclatasvir. In genotype 3 patients daclatasvir had higher SVR rates than PR alone, but no difference in rates was found when daclatasvir was compared to sofosbuvir.

These conclusions are not based on randomised evidence as the two daclatasvir trials AI444-040 and ALLY-3 had no placebo or other comparator arm, and placebo arms from the trials of other treatments were not included in the analysis. The results may therefore be biased if characteristics of patients, or trial conduct were significantly different in the AI444-040 and ALLY-3 trials than in trials or other treatments. Although the matching-adjusted indirect comparison (MAIC) method aims to adjust results to account for possible differences between trials, the adjusting may be flawed if important characteristics were not adjusted for. The approach also does not adjust for differences in trial conduct, such as how treatment was administered, which may produce very different results in different trials.

The evidence base for daclatasvir is small with only 125 genotype 1 patients and 18 genotype 3 patients in trials AI444-040. These analyses also are strongly dependent on the fact that AI444-040 achieved a near perfect SVR12 success rate, and any adjustments to SVR rate are dependent on the characteristics of the one patient who did not achieve SVR. Hence the adjusted SVR rates from the MAIC analysis are largely the consequence of chance. The ERG therefore considers the MAIC analysis to be unreliable and should be treated as if it were an unadjusted comparison of results from different trials, with substantial potential for bias or misleading conclusions.

Because of the potential for bias the ERG is of the opinion that the evidence that daclatasvir is superior to other treatments in treatment-naïve patients of genotype 1 should be treated with caution. However, it is reasonable to conclude that daclatasvir is unlikely to be inferior to other treatments. Data on patients with genotype 3 were more limited, so the ERG believes that no firm conclusions can be drawn on the relative effectiveness of daclatasvir in these patients.

Limited analyses were presented for treatment-experienced patients in genotype 3, with no analyses or for patients of other genotypes. No adjusted analyses were presented for patients with more severe disease (either cirrhosis or at METAVIR stage F3 to F4). No conclusions can therefore be drawn from the MAIC analysis as to the effectiveness of daclatasvir in those patients.

4.5 Naive indirect comparison of trials

This section considers the unadjusted and indirect comparison of daclatasvir to relevant treatment combinations including sofosbuvir, simeprevir, telaprevir, boceprevir and PR. This is found in section 6.7.2 of the submission, and particularly in Table 48 (overall population, F0-F4), Table 49 (significant fibrosis, F3 to F4 non-cirrhotic) and Table 50 (compensated cirrhosis) and also in Tables 75-85. These tables present SVR12 and SVR24 rates for genotypes 1, 3 and 4, each subdivided into treatment naïve, treatment experienced and interferon intolerant/ineligible individuals.

Although results from different HCV therapies are presented side-by-side, most are not based on formal comparisons such as head-to-head or adjusted indirect comparisons. Therefore most comparisons are implicit and have significant limitations.

4.5.1 Critique of manufacturer's approach to the methods of reviews

4.5.1.1 Searches

The submission provided no specific details of how the trials included in this review were sought. It appeared that at least some trials were identified as part of the other searches conducted, particularly the searches for the MAIC review discussed in Section 4.3. The ERG notes that is not clear whether the identification of studies was either systematic or comprehensive. It was therefore not clear

whether the trials included were all the relevant trials of HCV treatments, or whether those included were representative of likely effects of the treatments.

4.5.1.2 Inclusion criteria

No specific inclusion criteria were provided. The manufactures stated that included trials were chosen to match as closely as possible the characteristics of the daclatasvir trials (AI444-042, ALLY-3 and AI444-042). How this matching was assessed was not described in the manufacturer submission [redacted] Reasons for selecting comparator trials in tables 48-50 of the submission were not stated, making the assessment of study selection bias difficult. However, it appears that some comparator trials included in the efficacy tables 48-50 may have been identified through the searches conducted for the MAIC analyses (ADVANCE, ILLUMINATE, SPRINT-2, NEUTRINO, QUEST-1, QUEST-2, VALENCE). In addition, the ERG reviewed the product licences and previous manufacturer submissions of all comparators and found no evidence to suggest that significant trials had been omitted.

4.5.1.3 Critique of data extraction

No data extraction process was described. SVR rates were reported for each trial, along with treatment follow-up duration and treatment regimen. Standard errors of SVR estimates were reported in Tables 74-85, along with data on rates and timing of discontinuation rates, and safety data. Patient characteristics of trials included in the MAIC and in the efficacy tables 48-50 were reported in Appendices 5b-d. It does not appear that any other data were extracted.

The ERG checked the accuracy of SVR rates and sources of evidence used. SVR rates appeared generally accurate. However, data sources could not always be verified due to limited reporting. In particular, the sample size and proportion of patients with advanced fibrosis in participants included in "F3-F4 subgroup analyses" could not be verified for data extracted from the pivotal trial AI444-040. (for further detail, see section 4.4.2 and ERG report Appendix 1)

4.5.1.4 Quality assessment

No quality assessment process or quality data was reported for the comparator trials.

4.5.1.5 Evidence synthesis

The SVR rates for the selected trials were reported according to patient genotype status, treatment history or eligibility and liver fibrosis severity in Tables 48-50, Tables 74-85 of the MS. Selected data were also presented in Figures 13-16 of the MS. Where relevant, results from the syntheses in the

previous sections (i.e from the benchmarking and MAIC analyses) were used. With the exception of adjusted results from MAIC analyses for overall population (F0-F4), no adjustments or corrections were made for potential differences in patient characteristics or trial conduct.

4.5.2 Critique of the findings of the naïve uncontrolled indirect comparison

Tables 48–50 in the submission provide a side-by-side comparison of SVRs for all comparator treatments included in the NICE scope. On clarification the manufacturer provided additional information on sample sizes, follow-up duration, data source and assumptions made to address missing data. Appendix 1 present an updated version of the original tables presented in the submission, with further details on sample sizes and assumptions made by the manufacturer, along with comments by the ERG. Tables 23-24 below present a selection of specific issues associated with SVR rates presented in the manufacturer submission, along with suggestions for preferred SVR values.

The ERG identified a number of issues associated with the efficacy tables 48-50, including the quality of evidence identified, reporting quality, gaps in the evidence and limitations of methods used to address them, and limitations of uncontrolled indirect comparisons.

Quality of evidence

No detailed review of trial quality was reported, however most trials of comparator treatments appeared to be well-conducted RCTs, with the exception of sofosbuvir trials NEUTRINO and LONESTAR-2, and simeprevir trial RESTORE, which were open-label single-arm studies and may therefore be at higher risk of bias.

Patient populations across regimens were small. In daclatasvir trials, sample sizes of extracted populations ranged from 5 to 70; in comparator trials, from 2 to 271. Nearly all SVR rates informing "best available evidence" for populations with more severe fibrosis (METAVIR ≥F3, Tables 49-50) were based on small subgroups from single trials.

Quality of reporting

The definition of "F3 to F4 non-cirrhotic" (Table 49 of the submission) was unclear, partly because a METAVIR score of F4 is generally considered to be cirrhosis. In clarifications, the manufacturer stated that where the F3 to F4 subpopulation is referred to, this is considered to be those patients with significant cirrhosis, but without a diagnosis of cirrhosis confirmed by liver biopsy. No trial included in the efficacy tables reported data for "F3 to F4 non-cirrhotic" patients, although AI444-040 included patient with F4 but no confirmed cirrhosis based on biopsy. This means that populations across treatments may have had differences in baseline disease severity, thereby limiting the extent to which they could be compared (see below for further comments).

For trial arms including daclatasvir, in several instances the exact subgroup from which the data were extracted was unclear. In particular, data informing SVR rates for patients with more severe fibrosis (METAVIR ≥F3) who received daclatasvir+sofosbuvir ("F3 to F4 subgroup analyses" in tables 49-50) appeared to be based on subgroups including a significant proportion with less severe liver damage (F0-F2). For instance, in AI444-040, 23 (rather than 41, as presented in the tables) of the 70 treatment naïve patients who received daclatasvir+sofosbuvir had METAVIR score of F3 to F4.

Treatment doses and duration used in trials of comparator treatments were not reported. The ERG checked all trials of comparators included in the efficacy tables, and found that treatment doses and duration used in trials of comparator treatments generally matched their respective licences. However, there was one exception: SVR12 results of sofosbuvir+ribavirin in genotype 3 interferon ineligible/intolerant patients with cirrhosis were based on data from the POSITRON trial, which used a 12 weeks regimen, instead of the licenced 24 weeks treatment duration. In patients with cirrhosis, evidence for 24 weeks treatment yielded significantly higher SVR12 rates (92% in treatment naïve and 60% in treatment experienced patients in the VALENCE trial) than participants from the POSITRON trial (21%). Therefore the inclusion of a sub-optimal treatment duration for sofosbuvir+ribavirin may have introduced bias against this comparator in this subpopulation of genotype 3 individuals.

Gaps in the evidence and limitations of methods to address missing data

The manufacturer identified a number of gaps in the evidence. In particular, there was no trial evidence for:

- daclatasvir and sofosbuvir with or without ribavirin in genotype 1 patients with confirmed compensated cirrhosis
- daclatasvir in genotype 1, 3 and 4 in patients who were intolerant to or ineligible for interferon therapy
- daclatasvir and sofosbuvir (12 weeks duration) in non-cirrhotic genotype 1 patients with treatment experience (the treatment licence recommends 12 weeks duration, with possible prolongation to 24 weeks treatment in BOC/TVR experienced patients)
- daclatasvir and sofosbuvir with ribavirin in genotype 3 treatment experienced patients with compensated cirrhosis : no data in treatment experienced patients and none based on 24 weeks treatment in patients with cirrhosis
- daclatasvir and sofosbuvir 24 weeks duration in genotype 3 patients with compensated cirrhosis
- daclatasvir and sofosbuvir in genotype 4 patients

The manufacturer submission states that some assumptions were necessary to fully populate the efficacy tables, and that in case of missing SVR data for specific populations in DCV trials, SVRs from an alternative population were assumed where it was considered 'clinically appropriate' (p.96). Such assumptions included:

- generalising across disease severity (assuming patients without cirrhosis are similar to those with compensated cirrhosis)
- generalising treatment-naïve results to treatment experienced and interferon ineligible/intolerant
- generalising across genotypes (assuming genotype 4 is the same as genotype 1, as per EMA licencing)

The first two assumptions appear clinically inappropriate and may have introduced bias favouring daclatasvir. Although the third assumption (equivalence between genotypes 4 and 1) was considered appropriate by the EMA at the time of licencing, lack of trial data for genotype 4 patients needs to be taken into account when interpreting the evidence for daclatasvir with sofosbuvir.

The ERG also notes that these assumptions were applied consistently for daclatasvir trials, but not for sofosbuvir and simeprevir in populations that had not been evaluated. The manufacturer provided no justification for this decision in the submission. In clarifications, [redacted] The ERG believes that this justification is inconsistent and unfounded, particularly because several assumptions made to address missing daclatasvir trial data appeared inappropriate.

Further issues relating to data reporting and assumptions made to address missing data, as well as suggestions for alternative efficacy data are presented in Tables 23-24 below.

Issues with comparability across treatments

The comparability of HCV therapies was greatly limited due to a lack of head-to-head trials. None of the comparisons with daclatasvir were randomised, except for comparisons between daclatascir+sofosbuvir and PR in cirrhotic and non-cirrhotic treatment naïve genotype 4 patients (trial AI444-042).

Except for those treatment comparisons considered in the matching-adjusted indirect comparisons analysis (see Section 4.3), all comparisons between patients receiving daclatasvir and other treatments were not adjusted for differences in baseline characteristics between trials. The manufacturer stated that

[redacted]

[redacted]. It is generally unclear whether patient characteristics data from comparator trials matched those of patients receiving daclatasvir. In particular, definitions of disease severity were not consistently reported across the studies, as acknowledged by the manufacturer (some were based on METAVIR scores, whereas some were defined as "cirrhosis" or no "cirrhosis"). It appears that no data included in the efficacy tables were extracted from populations that matched the "F3 to F4 non-cirrhotic" category (AI444-040 may have included F4 patients with cirrhosis, but none were confirmed with biopsy). Characteristics of treatment-experienced patients (e.g. proportion with relapse, virologic breakthrough or no response to prior treatment) and interferon ineligible/intolerant subgroups were also not consistently reported. Therefore there may be differences in disease severity and treatment experience status across populations (as well as other unknown differences). This means that unadjusted comparisons across HCV therapies are subject to significant uncertainty and may not be reliable.

Concerns about the appropriateness and consistency of assumptions made to address missing data, the limited evidence (particularly for patients with bridging fibrosis and compensated cirrhosis), and general lack of formal comparisons mean that it is largely unclear whether the results presented for treatments other than daclatasvir represent a fair comparison with the specific daclatasvir data presented.

Table 23: Compiled SVR rates based upon best available evidence: significant fibrosis (F3 to F4 non-cirrhotic) population: issues identified by the ERG and suggestions for alternative values

HCV genotype	Treatment experience/ Eligibility	Treatment regimen	SVR n/N (%)	SVR 12 or 24	Source	Manufacturer comments	ERG comments	ERG: Preferred value n/N (%)	Rationale for preferred value
1	Naive	DCV+SOF (vs TVR)	95	SVR24	MAIC[21]	F3 to F4 subgroup analyses	Unclear. Possible pooled F3-F4 naïve across regimens	[redacted]	Includes [redacted] patients with F3 to F4 only from arm G (12 weeks treatment, no RBV, as per marketing authorisation)
		SOF+PR	81	SVR12	MAIC[21] NEUTRINO	F3 to F4 subgroup analyses	This is based on data from patients with compensated cirrhosis: 42/52 (80.8%), likely to underestimate response for F3-F4 without cirrhosis.	86.5%	NEUTRINO. Mid-point between non-cirrhotic 92% and compensated cirrhosis 81%.
	Experienced	SOF+PR	No data				Alternative clinically relevant data was used in SOF NICE appraisal	78%	FDA data (extracted from SOF FAD, p.36)
3	Naive	DCV+SOF+RBV	5/5 (100.0)	SVR12	AI444-040[4 5]	All genotype 3, F3 to F4 subgroup analysis	Source of data unclear. Data from arm F, subgroup with genotype 3? If so, [redacted]	None	NA
		DCV+SOF	[redacted]	SVR12	ALLY-3[22]	Treatment-naïve, pooled F3 and F4 subgroup analyses	Treatment-naïve, pooled F3 and F4 subgroup analyses. Table 12 manufacturer response reports [redacted]	27/36 (75.0%)	Based on data provided by manufacturer response to clarification, Table 12

	Experienced	DCV+SOF+RBV	5/5 (100.0)	SVR12	AI444-040[4 5]	Assumed as naïve GT3 and GT1 PI failures, since no drop in SVR was seen for HCV genotype 1 treatment-experienced patients (who had received PI triple therapy and would be considered harder to treat than PR failures	Data source and fibrosis stage unclear	None	NA
	Interferon ineligible/ Intolerant	DCV+SOF	[redacted]	SVR12	ALLY-3[6]	Assumed as naive	Treatment-naïve, pooled F3 and F4 subgroup analyses. Table 12 manufacturer response reports [redacted]	[redacted]	As per Table 12 of manufacturer response. assumed as naive
4	Interferon ineligible/ Intolerant	SMV+SOF	No data				Alternative clinically relevant data was used in SMV NICE appraisal	89.5%	COSMOS (genotype 1 TN, F3-F4) as per the NICE appraisal of SMV[23]

BOC: boceprevir; DCV: daclatasvir; SMV: simeprevir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SOF: sofosbuvir; TVR: telaprevir; MAIC: matching-adjusted indirect comparison; SVR: sustained virologic response; FDA: Food and Drug Administration

Table 24: Compiled SVR rates based upon best available evidence (compensated cirrhosis population): issues identified by the ERG and suggestions for alternative values

HCV genotype	Treatment experience/ Eligibility	Treatment regimen	SVR n/N (%)	SVR12 or 24	Source	Manufacturer comments	ERG comments	ERG: Preferred value n/N (%)	Rationale for preferred value
1	Experienced	SOF+PR	No data				Alternative clinically relevant data was used in SOF NICE appraisal	78%	FDA data (extracted from SOF FAD)
3	Naive	DCV+SOF+RBV	5/5 (100.0)	SVR12	AI444-040[4 5]	All genotype 3, F3 to F4 subgroup analysis	Is this SVR12 result from arm F, subgroup with genotype 3? If so, [redacted]	None	NA
		SOF+PR	No data				Alternative clinically relevant data was used in SOF NICE appraisal	10/12 (83.3%)	LONESTAR-2[24] (genotype 3 TE, 83.3% response observed both in 12 cirrhotic and 12 non-cirrhotic patients), assumed as TE, as in the NICE appraisal of SOF[25]
	Experienced	DCV+SOF+RBV	5/5 (100.0)	SVR12	AI444-040[4 5]	Assumed as naïve GT3 and GT1 PI failures, since no drop in SVR was seen for HCV genotype 1 treatment-experienced patients (who had received PI triple therapy and would be considered harder to treat than PR failures	Arm F, subgroup with genotype 3? If so, [redacted]	None	NA

	Interferon ineligible/intolerant	SOF+RBV	3/14 (21.4)	SVR12	POSITRON[20]	12-week regimen, cirrhosis	Only 12 weeks treatment, whereas marketing authorisation recommends 24 weeks. There is no data on ineligible/intolerant patients for 24wks treatment, but VALENCE reports SVR rates for naïve cirrhotics: 92% (12/13)	12/13 (92%)	VALENCE (G3 TN cirrhotic) [19 20]Manufacturer used POSITRON data which used a 12 week rather than the 24 week license duration of therapy. Response for this comparator has been shown to be associated with treatment duration.
4	Naive	SOF+PR	1/2 (50.0)	SVR12	NEUTRINO[14]	Pooled genotypes 4, 5 and 6, "cirrhosis"	Very small sample size. In NEUTRINO, 43/54 patients with cirrhosis (genotypes 1,4,5,6 combined) had SVR12, and 27/28 patients with genotype 4 (all fibrosis stages combined) HCV achieved SVR12.	43/54 (79.6%)	Manufacturer used an SVR based on a sample size of 2, extend to genotypes 1, 4, 5, 6 TN cirrhotic subpopulation to increase sample size to 54.
	Experienced	SOF+PR	No data				ERG agrees no data are available. However, assumptions may be made to inform the economic model	68.6%	Treatment naïve data for SOF+PR (79.6% for G1-6 in NEUTRINO), minus the decrement assumed by the FDA for treatment experienced in genotype 1 (11%), as per SOF FAD p.36
	Interferon ineligible/intolerant	DCV+SOF	41/41 (100.0)	SVR12	AI444-040[14 20]	Assumed as naive	Assumed as naïve genotype 1. Data are presumably from treatment naïve group G, which includes F0 to F4 ?	[redacted]	Only include F4 patients from arm G, assume as naïve with compensated cirrhosis

		SMV+SOF	No data		89.5%	COSMOS (genotype 1 TN, F3-F4) as per the NICE appraisal of SMV[23]
DCV: daclatasvir; SMV: simeprevir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SOF: sofosbuvir; MAIC: matching-adjusted indirect comparison; SVR: sustained virologic response; FDA: Food and Drug Administration						

4.5.3 Conclusions from the naïve uncontrolled indirect comparison

The manufacturer stated that SVR rates with daclatasvir-based regimens remain consistent across fibrosis stages for treatment naïve genotypes 1 and 3, whereas the efficacy of comparator regimens drops with increasing disease severity. The manufacturer acknowledged that these results should be interpreted with caution due to the lack of formal comparisons, differences in disease severity definitions across trials and small sample sizes.

The ERG agrees that SVR from AI444-040 remain consistently high across fibrosis stages and genotypes. However, this trial included a relatively small number of patients with METAVIR F4 stage (30 patients) based on Fibrotest, and no patients had a diagnosis of compensated cirrhosis confirmed with more reliable diagnostic methods such as liver biopsy. Evidence from the ALLY-3 trial in genotype 3 patients is more mixed. ALLY-3 shows that SVR12 rates are significantly lower in patients with METAVIR F3-F4 versus F0-F2, and in patients with compensated cirrhosis versus those without cirrhosis regardless of treatment experience. Although treatment duration of patients in ALLY-3 was lower than the recommended dosage for patients with compensated cirrhosis and did not include ribavirin (which is recommended for patients with negative prognostic factors in the current license), the conclusion that daclatasvir-based regimens remain consistent across fibrosis stages for treatment naïve genotype 1 and 3 is not supported by good evidence and may not be reliable.

No conclusions were stated for genotype 4 patients, or treatment experienced and interferon ineligible/intolerant genotype 1 and 3 patients.

The ERG concludes that, because the evidence for comparing daclatasvir to other treatments is largely based non-randomised and uncontrolled comparisons across trials with potentially very different populations and trial methodologies, it is weak and may be prone to considerable bias. This potential for bias is increased by the numerous assumptions made (such as assuming equivalence across disease severity and treatment experience status). The ERG therefore considers that these comparisons do not provide robust evidence that daclatasvir is superior to other treatments, although it provides some weaker evidence that daclatasvir is at least not inferior to other treatments.

4.6 Summary of clinical effectiveness

This section considers the overall interpretation of the clinical evidence presented by the manufacturer in Section 6.10 of the submission and summarises all the clinical evidence from the review discussed in the sections above.

The manufacturers' submission made three key claims for the benefit of daclatasvir-based combination treatments for HCV:

1. Daclatasvir offers very high SVR rates, across genotypes, regardless of disease severity or prior treatment status.
2. The rate and severity of adverse events are significantly decreased with daclatasvir combined with sofosbuvir only.
3. Daclatasvir is easily administered orally without interferon. This may contribute to better rates of treatment adherence.

For patients of genotype 1, the evidence for high SVR rates is primarily drawn from the AI444-040 trial of daclatasvir combined with sofosbuvir and ribavirin. This trial was a small (167 patients) phase II trial and had no randomised comparator group. It achieved a near-100% SVR rate. The trial had very few patients with treatment experience or with compensated cirrhosis, so the high SVR rates in these small subgroups of patients may be due to chance.

For patients of genotype 3, the evidence was largely drawn from the ALLY-3 trial, with a small number of patients in the AI444-040 trial. ALLY-3 showed a high SVR rate in treatment naïve (90.1% in 101 patients) and experienced patients (86.3% in 51 patients), although possibly not as high as for genotype 1. SVR rates in ALLY-3 were lower for patients with cirrhosis (62.5% in 32 patients). This contrasts with the near-100% success rate in AI444-040, meaning there is some uncertainty as to the efficacy of daclatasvir in patients with compensated cirrhosis.

For genotype 4 the data was drawn from two small randomised controlled trials (AI444-010 and AI444-042). These were trials of daclatasvir +PR compared with PR alone, and did not include sofosbuvir, however they achieved high SVR rates on daclatasvir (82% in AI144-042 in 82 patients and 100% in AI444-010 in 12 patients). In general, comparisons in effectiveness across genotypes, treatment experience and disease severity were limited by the small sample sizes; and so estimated SVR rates in these small subgroups of patients may be subject to considerable uncertainty. Comparison across the four daclatasvir trials does however suggest a similarity in effect across genotypes as the trials achieved similar SVR rates in different genotypes. Data were more limited on treatment-experienced patients, with only 92 such patients across trials AI444-040 and ALLY-3.

What data there are, however, do not suggest any difference in effectiveness between treatment-naïve and treatment-experienced patients.

In general, comparisons in effectiveness across genotypes, treatment experience and disease severity were limited by the small sample sizes; and so estimated SVR rates in these small subgroups of patients may be subject to considerable uncertainty. Comparison across the four daclatasvir trials does however, suggest a similarity in effect across genotypes as the trials achieved similar SVR rates in different genotypes. Data were more limited on treatment-experienced patients, with only 92 such patients across trials AI444-040 and ALLY-3. What data there are, however, do not suggest any difference in effectiveness between treatment-naïve and treatment-experienced patients.

The ERG cannot concur with the conclusion of similarity in effectiveness across disease severities. This conclusion is based on the small number of cirrhotic patients in trial AI444-040, all of whom achieved SVR (exact numbers of cirrhotic patients was unclear). The results from ALLY-3 suggested a rather poorer SVR in cirrhotic patients (62.5% in 32 patients), although these patients were treated for only 12 weeks and did not receive ribavirin. This results means there is some uncertainty around the effectiveness of daclatasvir in cirrhotic patients and in patients with more severe fibrosis (METAVIR stages F3 and F4).

While the submitted trials demonstrate a generally high SVR rate the manufacturers' discussion of the clinical evidence does not consider whether daclatasvir is superior to other available treatments. The submission provided three reviews and analyses that considered this: the benchmarking review, MAIC review and naive indirect unadjusted comparisons of trials. The ERG considers that the benchmarking review provides the most robust evidence on the efficacy of daclatasvir. That review estimated the SVR rate that daclatasvir plus sofosbuvir would have to achieve to be considered superior to other treatments: approximately 63% for PR and 85% for telaprevir or boceprevir in treatment-naive patients of genotype 1 (all fibrosis stages). Since the SVR rate in AI444-040 was nearly 100% in these patients the ERG considers it reasonable to conclude that daclatasvir is superior to these other treatments. The results were similar for genotype 1, treatment-experienced patients although patient numbers were small so the validity of the conclusion is less certain., The analysis did not demonstrate that daclatasvir plussofosbuvir was superior to PR in genotype 3 patients, although patient numbers were limited. The remaining comparisons between treatments were all based on naïve indirect comparisons of different trials, with no randomised comparisons. As such the ERG considers this evidence to be of limited quality.

The presented evidence in genotype 1 treatment-naive patients does suggest that daclatasvir (with sofosbuvir, with or without ribavirin) has higher SVR rates than PR, telaprevir, boceprevir, and possibly than simeprevir and sofosbuvir (although these treatments have higher SVR rates). Evidence

was more limited in patients with treatment experience and in those of genotype 3 and 4, so the ERG does not think any conclusions may be safely made on the relative efficacy of daclatasvir with other treatments in these patients. Because of the inconsistency between AI444-040 and ALLY-3 in SVR rates in patients with advanced disease (METAVIR stages F3 and F4) the ERG cannot draw any firm conclusion on the relative efficacy of daclatasvir in those patients.

5 Cost Effectiveness

This section comprises of the ERG comment on the manufacturer's review of cost-effectiveness evidence (Section 5.1), a summary of the MS on cost-effectiveness (Section 5.2) and the critical appraisal of the MS on cost-effectiveness (Section 5.3). Throughout these sections, the following abbreviations are used: daclatasvir (DCV), sofosbuvir (SOF), pegylated interferon alpha with ribavirin (PR), ribavirin (RBV), simeprevir (SMV), telaprevir (TVR) and boceprevir (BOC).

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

The manufacturer conducted a systematic review of the cost-effectiveness evidence on chronic hepatitis C. The aim of the review was to identify new studies published since the systematic review by Hartwell et al.[26]However, Hartwell et al only conducted a systematic review of RCTs. Therefore, the utility of Hartwell et al to inform the manufacturer's systematic review on cost-effectiveness evidence is unclear.

5.1.1 Searches

Appendix 7 of the MS presents the search strategies. The search terms included terms relate to chronic hepatitis C, cost-effectiveness analysis, and European countries. Searches were conducted in PubMed, MEDLINE and MEDLINE in process, EMBASE, EconLit and the Cochrane Library containing the NHS Economic Evaluation Database (NHS EED).

The ERG considers that the searches were generally well conducted. The manufacturer reports that the searches of MEDLINE, EMBASE and NHS EED were limited to 2009 onwards. A restriction to 2009 onwards is unlikely to have excluded studies on direct-acting anti-viral agents for chronic hepatitis C since these agents have only been licensed since 2011. A number of features of the searches may have limited their sensitivity. The use of country terms to restrict the search may have missed some studies since the terms "UK", "Great Britain" and "Europe" were not included, and the country may not be specified in the title, abstract or indexing terms of database records. It is also unclear whether a validated search filter for cost-effectiveness studies was used in EMBASE, MEDLINE and PubMed which may have limited the sensitivity of the search. Restriction of the Cochrane library NHS EED search to economic studies is unnecessary and may have missed some relevant studies. EMTREE indexing terms appear to have been used to search MEDLINE which may have excluded some relevant results. However, as the manufacturer separately searched PubMed using the correct MeSH indexing terms this should have captured relevant records from MEDLINE and MEDLINE in process.

5.1.2 Inclusion/exclusion criteria used for study selection

Table 67 in the MS (p123) summarises the inclusion and exclusion criteria. Broadly the manufacturer included model-based economic evaluations of currently licensed regimens used in adult patients with chronic hepatitis C. DCV-containing regimens were not separately included. Studies were restricted to those conducted in European Union countries. The inclusion and exclusion criteria are mostly adequate although restrictive. Although cost-effectiveness studies on DCV-containing regimens were not explicitly included, any cost-effectiveness study of DCV containing regimens would have almost certainly contained one or more of the included interventions as comparators. The ERG therefore considers that this is unlikely to have resulted in exclusion of relevant studies.

5.1.3 Studies included and excluded in the cost effectiveness review

Nineteen studies were included in the review. Appendix 7 of the MS presents the data extraction tables and quality assessment for these studies. The included studies evaluated protease inhibitors regimens (11, 58%),[27-37], SOF-containing regimens (5, 26%) [32 34 36 38 39] or interferon based regimens (12, 63%).[30 31 33 34 37 39-45]No study evaluated DCV-containing regimens. Six studies were in the UK setting.[30 31 36 40 42 43] Of these, one included SOF-containing regimens[36], three included protease inhibitor regimens [30 31 36], and five included interferon-based regimens [30 31 40 42 43]:

- Cure et al evaluated the cost-effectiveness of TVR+PR compared with PR or BOC+PR in treatment naïve patients with chronic hepatitis C genotype 1.[30]
- Cure et al evaluated the cost-effectiveness of TVR+PR compared with PR and BOC+PR in treatment experienced patients with chronic hepatitis C genotype 1.[31]
- Grishchenko et al evaluated the cost-effectiveness of PR compared with no treatment in treatment naïve patients with chronic hepatitis C. Subpopulations included HCV genotype (1 vs non-1), baseline fibrosis stage defined by Ishak score, age at presentation for treatment and sex.[40]
- Martin et al evaluated the cost-effectiveness of PR in injecting drug users compared with no treatment or treating only ex or non-injecting drug users with chronic hepatitis C. The patient population considered was patients infected with genotype 1, 2 and 3 who are treatment naïve or re-infected. [42]
- McEwan et al evaluated the cost-effectiveness of response guided therapy with PR compared with standard duration therapy with PR and no treatment in treatment naïve patients with chronic hepatitis C genotype 1 using the same model as the manufacturer (the MONARCH model).[43]
- Tsochatzis et al evaluated the cost-effectiveness of four test-and-treat strategies: testing with non-invasive tests and treating patients with fibrosis stage≥F2; testing with liver biopsy and treating patients with ≥F2; treat none; and treat all irrespective of fibrosis.

Treatment consisted of triple therapy with BOC+PR, TVR+PR or SOF+PR (exploratory analysis). [36]

5.1.4 Conclusions of the cost effectiveness review

The manufacturer did not use the results of the review to inform the *de novo* economic evaluation. Although studies were searched systematically and data extracted, there was no synthesis or interpretation of the results.

The ERG considers that the manufacturers review was unlikely to have missed relevant cost-effectiveness analyses of DCV-containing regimens. The ERG therefore considers the development of a *de novo* model to be appropriate and necessary for this appraisal.

5.2 ERG's summary of manufacturer's submitted economic evaluation

An overall summary of the manufacturer's approach and signposts to the relevant sections in the MS are reported in Table 25 below.

Table 25 Summary of the manufacturer's economic evaluation (and signposts to MS)

<table>
<tr><th>Element</th><th>Approach</th><th>Source/Justification</th><th>Location in MS</th></tr>
<tr><td>Intervention</td><td>DCV-containing regimens:
Genotype 1: DCV+SOF.
Genotype 3: DCV+SOF, DCV+SOF+RBV.
Genotype 4: DCV+PR, DCV+SOF.</td><td>As per NICE scope and marketing authorisation for DCV.[46 47]</td><td>Section A – Decision problem (p27); Table 71-73 (p133-135).</td></tr>
<tr><td>Comparators</td><td>The Table below summarises the comparators included in the MS:
<table>
<tr><th></th><th>Treatment-naive</th><th>Treatment-experienced</th><th>Interferon-ineligible/intolerant</th></tr>
<tr><td>Genotype 1</td><td>DCV+SOF
SOF+PR
SMV+PR
TVR+PR
BOC+PR
PR
No treatment</td><td>DCV+SOF
<u>SOF+PR(excluded in F3, F4, F0-F4 patients)</u>
No treatment</td><td>DCV+SOF
SOF+RBV
SMV+SOF
No treatment</td></tr>
<tr><td>Genotype 3</td><td>DCV+SOF+/-RBV
<u>SOF+PR (excluded F3, F4)</u>
SOF+RBV
PR
No treatment</td><td>DCV+SOF+/-RBV
SOF+PR
SOF+RBV
PR
No treatment</td><td>DCV+SOF+/-RBV
SOF+RBV
No treatment</td></tr>
<tr><td>Genotype 4</td><td>DCV+SOF
DCV+PR
SOF+PR
SMV+PR
PR
No treatment</td><td>DCV+SOF
DCV+PR
<u>SOF+PR(excluded in F3, F4, F0-F4 patients)</u>
SMV+PR
PR
No treatment</td><td>DCV+SOF
<u>SOF+SMV(excluded in F3, F4, F0-F4 patients)</u>
<u>SOF+SMV(excluded in F3, F4, F0-F4 patients)</u>
No treatment</td></tr>
<tr><td colspan="4">Bold indicates daclatasvir-containing regimens.
Italic+underlined indicates comparators considered by the manufacturer as relevant but not included in the economic evaluation for some or all subgroups due to lack of data.</td></tr>
</table></td><td>The comparators considered agree with those described in the NICE scope;[47] however, some were excluded from the cost-effectiveness analysis for specific subgroups due to lack of data on their effectiveness.

NT was included since there is a proportion of patients who are currently diagnosed but do not receive treatment.

Watchful waiting was not included. The manufacturer did not justify not including watchful waiting as a comparator.</td><td>Table 1 (p15; also in Table 9 p29, in Table 70 p130 and Table 71-73 p133-135).
Tables 74-85 (p137-148).</td></tr>
<tr><td>Population and subgroups</td><td>Population: adults with chronic hepatitis C.
Subgroups considered in the MS:
By genotype: 1, 3 and 4.
By METAVIR stage: F0-F4, F3-F4 non-cirrhotic; compensated cirrhotic.
By treatment status: treatment naïve, treatment experienced, ineligible for or intolerant to interferon.
In their response to the ERG's points for clarification, the manufacturer presented results for the</td><td>As per NICE scope.[47]

The manufacturer's base-case focusses on the F3-F4 non-cirrhotic subpopulation and the compensated cirrhotic subpopulation. The F3-F4 non-cirrhotic subpopulation corresponds to patients who are F3 or those that could be</td><td>Table 16 (p41).</td></tr>
</table>

Element	Approach	Source/Justification	Location in MS
	subpopulation F0-F2 treatment naïve, treatment experienced and interferon ineligible or intolerant for a selection of pairwise comparisons between DCV-containing regimens and some comparators.	considered as F4 according to FibroTest but in whom biopsy indicates the absence of cirrhosis. The ERG considers that the F3-F4 non-cirrhotic subpopulation consists largely of F3 patients. The compensated cirrhotic subpopulation is considered equivalent to METAVIR stage F4. The NICE scope also included subgroups by co-infection with HIV, by receipt of liver transplant (pre or post liver transplant) and by response to previous treatment (non-response, partial response and relapsed). The MS did not present the subgroup analyses by co-infection with HIV and by receipt of liver transplant because the available clinical trials did not include these patient subgroups. The manufacturer did not justify not presenting an analysis by response to previous treatment. Treatment experienced patients in the manufacturer's analysis are restricted to those whom have received a protease inhibitor with PR in genotype 1 and those who have received PR in genotypes 3 and 4.	
Model	Decision tree with Markov model: • The decision tree models the effectiveness of each treatment regimen as the proportion of patients who achieved SVR and tracks their costs and HRQoL over the course of treatment and up until the end of year 1. Patients enter the model in a health state that corresponds to their baseline METAVIR fibrosis score (F0, F1, F2, F3, F4). During the planned treatment period patients experience a treatment-specific probability of discontinuing treatment due to adverse events. Patients can also stop treatment early due to early signs of a strong response. The cycle length is 4 weeks. At the end of the first year, patients are partitioned between those with and those without SVR. • The Markov model simulates the natural history of the disease over the patients' lifetime. Patients enter the Markov model in the health state in which they reside at the end of the 1 year decision tree model. The health states are: METAVIR fibrosis states: F0, F1, F2, F3, F4 (compensated cirrhosis), decompensated cirrhosis, hepatocellular cancer, liver transplant year 1, liver transplant year 2+ and death. Patients who achieve SVR are subject to general population risks of all-cause mortality and therefore remain in their baseline SVR fibrosis stage until death. Patients without SVR are at risk of liver disease progression and hepatocellular cancer. Each health state is associated with a specific HRQoL and cost. The cycle length is annual.	A systematic review of the model-based cost-effectiveness analyses concluded that all studies used Markov model with a similar model structure to simulate the natural history of the disease.[48]	Sections 7.2.2-5 (p127-129).
Treatment effectiveness	Treatment response (SVR) rates were obtained from an uncontrolled (naïve) indirect comparison of individual trial arms. Data for daclatasvir were obtained from three clinical studies identified via systematic review (the AI444-040, AI444-042 and ALLY-3 trials). It is unclear how the studies for comparators were	The manufacturer stated that attempts were made to use the most appropriate and robust source of data taking in to account patient and disease characteristics and licensed treatment	Tables 74-85 (p137-148). Manufacturer response to ERG

Element	Approach	Source/Justification	Location in MS
	identified. In order to reflect the characteristics of the target subpopulations, data was often taken from subgroup analyses of individual trials and generalised across genotypes, treatment histories and disease severities.	regimens.	points for clarification p6-7.
Adverse events	Considered only in HRQoL decrements during treatment duration. The costs of adverse events are not considered in the base-case analysis.	The costs from adverse events were not included due to their inconsistent reporting and low impact on results.	Section 7.5 (p165-167).
Health-related quality of life	Expressed in QALYs. Each model state is associated with a specific HRQoL; more severe states are associated with lower HRQoL. Achieving SVR is associated with a higher HRQoL. Achieving SVR in the compensated cirrhosis state (F4) is assumed to be associated with the same HRQoL as achieving SVR in the moderate (F2-F3) states. Each treatment regimen is associated with a HRQoL decrement to reflect the impact of adverse events.	HRQoL associated with each model state (pre- and post-SVR) was obtained from Wright et al (2006)[49]. The assumption that HRQoL associated with achieving SVR in the cirrhotic state (F4) is equivalent to achieving SVR in the moderate states (F2-F3) was based on other cost-effectiveness analyses with the same assumption. The HRQoL decrements associated with the comparator regimens were obtained from other manufacturer submissions to NICE and a conference abstract. The HRQoL decrement associated with SOF+RBV and DCV-containing regimens were calculated as a weighted average of HRQoL decrements weighted by the incidence of each event. HRQoL decrements were obtained from a time trade-off study conducted by the manufacturer. The incidence of adverse effects was obtained from a published study for SOF+RBV and the clinical trial reports on AI444-040 and AI444-042.	Section 7.4 (p155-161)
Resource use and costs	Costs were expressed in UK pound sterling at a 2012-13 price year from an NHS perspective. The costs included were: • Acquisition costs for each treatment. • Costs associated with monitoring during treatment • Costs associated with each health state The costs of mild (F0-F1), moderate (F2-F3) and cirrhotic (F4) disease after achieving SVR are only accrued in the first year.	The costs were obtained from different sources: • Acquisition costs for each treatment were obtained from the BNF. • Costs associated with monitoring during treatment were obtained from Shepherd et al.[50] • Costs associated with each health state were obtained from Martin et al.[42] The costs from adverse events were not included due to their inconsistent reporting and low impact on results. The cost of SVR surveillance was not included; no justification was given in the MS.	Section 7.5 (p162-167).
Discount	3.5% for both costs and HRQoL.	As per the NICE reference case.[51]	Table 69 (p130).

Element	Approach	Source/Justification	Location in MS
rate			
Sensitivity analysis	The manufacturer conducted scenario, univariate, threshold and probabilistic sensitivity analyses: • Scenario analysis on the DCV-containing regimen for the subpopulation with genotype 3. • Scenario analysis on the treatment duration of a selection of treatment regimens. • Univariate sensitivity analysis on age, proportion of males, time horizon, discount rate, transition probabilities, discontinuation rates, HRQoL associated with health states and treatment, and costs associated with health states, adverse effects and monitoring. • Probabilistic sensitivity analysis including a wide range of parameter inputs. • Threshold analysis on SVR rate.	The scenario analysis on the DCV-containing regimen for the subgroup with genotype 3 were conducted because there are two sources of data on effectiveness of DCV+SOF for this population, the AI444-040 and ALLY-3 trials. The scenario analysis on treatment duration was conducted to reflect the product license for DCV which permits a range of treatment durations in some subgroups. The manufacturer did not justify the univariate analyses undertaken with the exception of exclusion of monitoring costs from DCV+SOF regimens. The rationale for this analysis was that DCV+SOF regimens may incur less monitoring costs.	Section 7.6 (p168-169). Section 7.7.9 (p186-187). The threshold analysis on SVR rate was provided in the manufacturer response to the ERG points for clarification Table 6 (p12)
Results	For the base-case, the manufacturer presented deterministic pairwise results for the subpopulations defined according to genotype (1, 3 and 4), severity (F3, F4 and entire population F0-F4) and treatment status (treatment naïve, treatment experienced and interferon ineligible or intolerant). Probabilistic results were presented as pairwise comparisons for these subpopulations. For the sensitivity analyses, the manufacturer presented results for subpopulations defined according to the same genotypes and treatment status but restricted attention to patients with severity F3 and F4. In their response to the ERG's points for clarification, the manufacturer presented full incremental deterministic results for the subpopulations defined according to genotype (1, 3 and 4), severity (F3, F4) and treatment status (treatment naïve, treatment experienced and interferon ineligible or intolerant). The DCV-containing regimens appeared cost-effective at cost-effectiveness threshold values of £20,000 - £30,000 per QALY in the following subgroup populations: • F3: DCV+SOF in genotype 1 treatment naïve, treatment experienced or interferon ineligible or intolerant, in genotype 3 interferon ineligible or intolerant, and in genotype 4 treatment experienced or interferon ineligible or intolerant. • F4: DCV+SOF in genotype 1 treatment experienced, in genotype 3 interferon ineligible or intolerant, and genotype 4 interferon ineligible or intolerant; DCV+PR in genotype 4 treatment experienced. The manufacturer also presented pairwise deterministic results for the F0-F2 subpopulation for the pairwise comparisons in which the DCV-containing regimen was cost-effective in the F0-F4 population.	The manufacturer did not justify the presentation of pairwise comparisons. The manufacturer justified the focus on F3 and F4 populations for many of the analyses on the basis that these are the subpopulations in which DCV-containing regimens were expected to offer the largest incremental clinical benefit compared to alternative therapies.	Section 7.7.6 – 7.7.11 (p171-220). See also manufacturer response to ERG points for clarification Table 36-41 (p97 -102)

BOC: boceprevir; DCV: daclatasvir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir. NT: no treatment. NICE: National Institute for Health and Care Excellence. MS: manufacturer's submission. HRQoL: Health-related quality of life.

5.2.1 Model structure

The model structure comprises a one-year decision tree and a Markov model which captures outcomes in the rest of the cohorts' lifetime. Each is discussed in turn below:

5.2.1.1 Decision Tree

The decision tree predicts the proportion of patients who achieve SVR during treatment, and the health-related quality of life (HRQoL) and costs during the first year of the model. It consists of a treatment period, which corresponds to the treatment duration of each regimen under comparison, and an off-treatment period, which is the remainder of the year. Patients enter the model in a health state that corresponds to their baseline METAVIR fibrosis score (F0, F1, F2, F3, F4).

Planned treatment period: During the planned treatment period, patients experience the HRQoL associated with their baseline METAVIR fibrosis state. Patients are at risk of discontinuing treatment due to adverse events. These risks are specific to each regimen under comparison. In addition, Patients receiving TVR+PR, BOC+PR and DCV+PR also stop treatment early if they experience extended rapid virologic response (eRVR). Those on treatment incur treatment and monitoring costs and treatment-specific reductions to their HRQoL. Costs associated with adverse events are not incorporated in the base case analysis. Patients do not progress during the treatment period (i.e. all patients remain alive at their baseline fibrosis stage).

Remainder of the first year: At the end of the treatment period, patients are partitioned between those with an SVR response and those without an SVR response according to treatment-specific SVR rates. All patients remain in a state corresponding to their baseline METAVIR fibrosis score but those achieving SVR gain an improvement in HRQoL. This occurs as soon as treatment is completed rather than at the time point at which SVR is assessed (typically 12 or 24 weeks after treatment completion).

The decision-tree model uses a cycle length of 4 weeks.

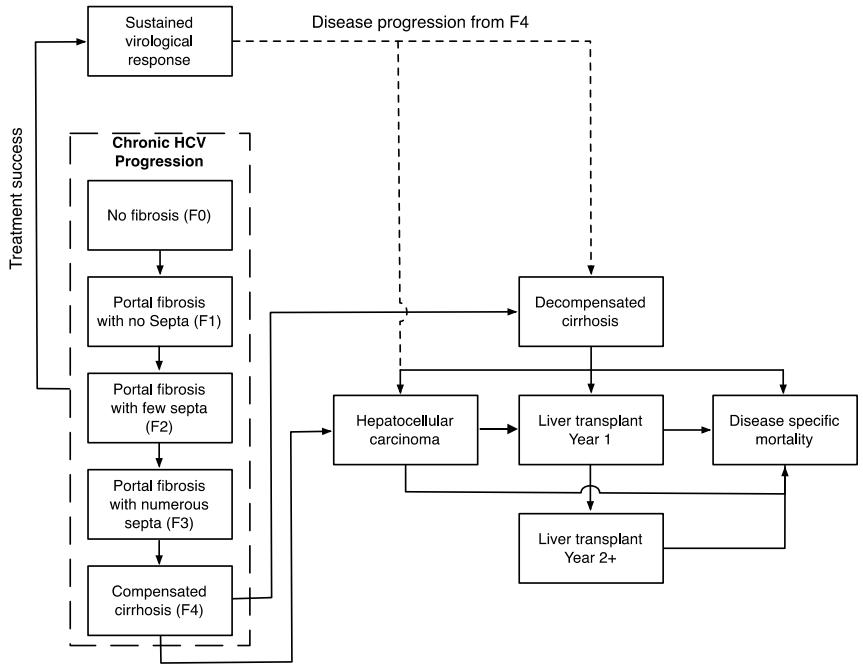
5.2.1.2 Markov model

Figure 1 describes the allowed transitions in the Markov model. Patients enter the Markov model in the health state in which they reside at the end of the 1 year decision tree model (i.e. F0, F1, F2, F3, F4, SVR F0, SVR F1, SVR F2, SVR F3 or SVR F4). Costs and QALYs generated by the Markov model differ only to the extent that the distribution of patients over these different health states differs across treatments. The distribution across these health states is determined by the baseline distribution across METAVIR states F0-F4 and by the SVR associated with each treatment.

Patients who achieve SVR are only subject to general population risks of all-cause mortality and therefore remain in their SVR fibrosis stage until death. Patients without SVR are subject to

probabilities of disease progression. Patients progress sequentially through the METAVIR fibrosis states. Patients are at risk of progression to decompensated cirrhosis or HCC at the most severe METAVIR fibrosis state (F4, compensated cirrhosis). Patients can progress from decompensated cirrhosis to HCC or liver transplant and from HCC to liver transplant. Liver transplant is associated with two health states (year 1 and year 2+) to allow for the elevated risk of death, reduced utility and high upfront cost associated with the first year of transplant. Patients with decompensated cirrhosis, HCC or liver transplant face an elevated risk of death; all patients also face the general population risk of death. All health states are assigned constant health state utilities, costs and transition probabilities. The Markov model uses a cycle length of one year.

Figure 1 Model structure schematic (adapted from Figure 21 p127 of the MS)



Section 4.2 of the manufacturer's submission describes a disease transmission model that is used to estimate the additional benefit of treating hepatitis C in terms of the reduction in onward transmission of the virus. The disease transmission model is not incorporated in the manufacturer's base case and is discussed further in Section 5.3.11 Transmission model of hepatitis C infection.

5.2.2 Population

5.2.2.1 Population and subgroups

The population considered in the model comprises adult hepatitis C patients without end stage liver disease. The MS considered patients with genotypes 1, 3 or 4 and within each genotype patients whom are treatment naïve, treatment experienced, or ineligible for or intolerant to interferon-based therapy. The submission further subdivided these populations in to all patients without end stage liver

disease (those with METAVIR scores F0-F4), those with significant fibrosis (METAVIR score ≥3) but without cirrhosis and those with compensated cirrhosis.

Table 26 shows the 27 subpopulations considered by the manufacturer. In line with the emphasis of the MS, the ERG's summary of the MS focuses on all subpopulations with disease stage F3 and F4. Given the heterogeneity within the F0-F4 population with respect to licensed and NICE recommended comparators, licensed treatment durations and effectiveness the ERG does not consider the F0-F4 pooled analysis to be a useful basis for decision making.

Patients with significant fibrosis but without cirrhosis would seem to include only those with a METAVIR score of F3. However, this group may also include those in whom non-invasive tests such as FibroTest produce results on the borderline between F3 and F4 disease and who have not had cirrhosis confirmed by biopsy (for further detail see *manufacturer response to clarification points* p2-3). In reality, these are expected to be a very small group of patients and the ERG considers the F3-F4 non-cirrhotic subgroup to represent largely F3 patients. The compensated cirrhotic subpopulation is considered equivalent to METAVIR stage F4. Hence, throughout the rest of the report, where the manufacturer has used the term "F3-F4 non-cirrhotic", the ERG has interpreted as referring to the F3 subpopulation, and where it has used the term "compensated cirrhotic", the ERG has interpreted as referring to the F4 (cirrhotic) subpopulation.

Table 26 Patient populations considered by manufacturer

Genotype	Treatment history	Disease stage
1	Treatment naïve	F0-F4
		F3
		F4
	Treatment experienced (prior BOC/TVR+PR)	F0-F4
		F3
		F4
	Ineligible for or intolerant to interferon-based therapy	F0-F4
		F3
		F4
2	Treatment naïve	F0-F4
		F3
		F4
	Treatment experienced (prior PR)	F0-F4
		F3
		F4
	Ineligible for or intolerant to interferon-based therapy	F0-F4
		F3
		F4
3	Treatment naïve	F0-F4

Genotype	Treatment history	Disease stage
		F3
		F4
	Treatment experienced (prior PR)	F0-F4
		F3
		F4
	Ineligible for or intolerant to interferon-based therapy	F0-F4
		F3
		F4

The manufacturer stated that patients in the two more severe groups (significant fibrosis, compensated cirrhosis) were the focus of their submission since these are the patients in whom DCV is expected to offer the largest incremental clinical benefit when compared to alternative treatment options.

In the analysis of patients with genotype 1, treatment experienced patients are restricted to those who have received BOC+PR or TVR+PR; and in patients with genotype 3 and 4 treatment experienced patients are restricted to those who have received PR. The manufacturer justified these restrictions on the basis that these subgroups of treatment experienced patients would make up the majority of prevalent treatment experienced patients in the UK (see *manufacturer response to point for clarification* p69).

The manufacturer has not presented any evidence on the cost-effectiveness of DCV in patients whom are co-infected with HIV or are pre- or post-liver transplant. These indications are not considered outside of the current label for daclatasvir but are excluded from the current submission due to lack of data. Data in these indications are expected to be reported from the ALLY-1 and ALLY-2 trials in 2015 (see *manufacturer response to point for clarification* p55).

In response to the ERG's points for clarification, the manufacturer presented results for the F0-F2 subpopulations for a selection of pairwise comparisons. This will be discussed in more detail in Section 5.3.3.1 Analyses for the milder subpopulation.

5.2.2.2 Characteristics of the patient population

Table 27 shows the baseline characteristics of the patient population. Average age is taken from the HCV research database. Although the study database was provided to the ERG, it is unclear which patients informed the calculation of mean age. The proportion of males was estimated from laboratory reports of HCV infection in England in the period 1996-2013.[52] The distribution of individuals across METAVIR scores was based on a disease burden model.[53] This model predicts the distribution of individuals across mild, moderate and cirrhotic disease states. It is unclear how these states were defined. The manufacturer assumes that mild patients were equally distributed between

METAVIR F0 and F1 and moderate patients between METAVIR F2 and F3. Disease duration, the proportion of individuals who acknowledge injectable drug use as the main risk factor for HCV infection, the proportion of individuals who acknowledge blood or blood product transfusion as the main risk factor, and the proportion of individuals with excess alcohol consumption within 12 months of study entry were estimated as a weighted average of all UK studies included in a systematic review of cohorts of chronic HCV patients.[54] The weighted average included six studies conducted in UK liver clinics (one study also included US patients). With the exception of baseline METAVIR scores, all patient characteristics were assumed to be the same across subpopulations.

Table 27 Baseline characteristics of the patient population in the base-case (F3-F4 non-cirrhotic; adapted from Table 90 p153 of MS)

Parameter	Mean (SE)	Distribution	Source
Age (years)	50 (0.2)	Normal	HCV Research UK database[55]
Male (%)	67 (0.4)	Beta	Hepatitis C in the UK: 2014 report[52]
F3 (%)*	78.62 (2.82)	Beta	Based on updated burden model used in the Hepatitis C in the UK: 2013 report[53]
F4 (%)*	21.38 (5.41)	Beta	
Disease duration	16.93 (3.53)	Normal	Weighted average of all UK studies included in a systematic review of cohorts of chronic HCV patients.[54]
Individuals who acknowledge IDU as the main risk factor for HCV infection (%)	59.34 (3.13)	Beta	
Individuals who acknowledge blood or blood product transfusion as the main risk factor for HCV infection (%)	26.85 (2.85)	Beta	
Individuals with excess alcohol consumption in the past 12 months (%)	23.78 (2.43)	Beta	

*For the analysis on the entire population (F0-F4), the proportion of patients in each METAVIR score is F0=F1=30.89%, F2=F3=16.82, F4=4.57%.

HCV: hepatitis C virus; SE: standard error; IDU: injecting drug users.

5.2.3 Interventions and comparators

5.2.3.1 Interventions and comparators included in the MS

Table 28 presents the interventions and comparators considered by the manufacturer as relevant to the current appraisal. The DCV-containing regimens are in bold. Regimens in italics and underlined were considered by the manufacturer as relevant but were not included in the economic evaluation for some or all subgroups due to a lack of data. The manufacturer excluded SOF+PR in genotype 1 treatment experienced patients for all disease severity subpopulations (F0-F4, F3 and F4), in genotype 3 treatment naïve patients with F3 or F4 disease and genotype 4 treatment experienced patients for all disease severity subpopulations. SMV+SOF was excluded from genotype 4 interferon ineligible or intolerant patients for all disease severity subpopulations.

DCV+SOF is currently only licensed for genotype 3 patients when used in combination with ribavirin for a duration of 24 weeks and only for patients who are treatment experienced or cirrhotic.

[redacted]

Table 28 Comparators included in the MS

	Treatment-naive	Treatment-experienced	Interferon-ineligible/intolerant
Genotype 1	**DCV+SOF** SOF+PR SMV+PR TVR+PR BOC+PR PR No treatment	**DCV+SOF** *SOF+PR* No treatment	**DCV+SOF** SOF+RBV SMV+SOF No treatment
Genotype 3	**DCV+SOF(+RBV for F4)** *SOF+PR (no data F3/F4)* SOF+RBV PR No treatment	**DCV+SOF(+RBV for F4)** SOF+PR SOF+RBV PR No treatment	**DCV+SOF(+RBV for F4)** SOF+RBV No treatment
Genotype 4	**DCV+SOF** **DCV+PR** SOF+PR SMV+PR PR No treatment	**DCV+SOF** **DCV+PR** *SOF+PR* SMV+PR PR No treatment	**DCV+SOF** *SOF+RBV* *SMV+SOF* No treatment

BOC: boceprevir; DCV=daclatasvir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir.
Bold indicates daclatasvir-containing regimens.
Italic+underlined indicates comparators considered by the manufacturer as relevant but not included in the economic evaluation for some or all subgroups due to lack of data.

5.2.3.2 Treatment durations and dosages

Table 29 details the durations of each treatment regimen. These correspond to the treatment durations specified in the relevant SPCs. Treatment durations for cirrhotic patients are noted in brackets where these differ to those used in non-cirrhotic patients. These treatment durations have been applied in the model with the exception of genotype 3 compensated cirrhotic patients, where the model specifies 12 weeks as the treatment duration when the manufacturer states it should be 24 weeks. The doses used by the manufacturer are the licensed doses: DCV 60mg per day, SOF 400mg per day, SMV 150mg per day, TVR 750 mg three times per day, BOC 800mg three times per day, pegylated interferon alfa 180 mcg per week and RBV 1,000 mg per day.

Table 29 Treatment durations for the first and second component of each treatment regimen

Genotype	Treatment-naïve	Duration in weeks (cirrhotic)		Treatment-experienced	Duration in weeks (cirrhotic)		Interferon-ineligible/ intolerant	Duration in weeks (cirrhotic)	
		1	2		1	2		1	2
1	DCV+SOF SOF+PR SMV+PR TVR+PR BOC+PR PR	12 (24) 12 12 12 24-32* (44) 48	12 (24) 12 24 24-48* (48) 28-48* (48)	DCV+SOF SOF+PR	12 (24) 12	12 (24) 12	DCV+SOF SOF+RBV SMV+SOF	12 (24) 24 12	12 (24) 24 12
3	DCV+SOF SOF+PR SOF+RBV PR	12 (24) 12 24 24	12 (24) 12 24 24	DCV+SOF SOF+PR SOF+RBV PR	12 (24) 12 24 48	12 (24) 12 24 48	DCV+SOF SOF+RBV	12 (24) 24	12 (24) 24
4	DCV+SOF DCV+PR SOF+PR SMV+PR PR	12 (24) 24 12 12 48	12 (24) 24-48* 12 24	DCV+SOF DCV+PR SOF+PR SMV+PR PR	12 (24) 24 12 12 48	12 (24) 24-48* 12 48	DCV+SOF SOF+RBV SMV+SOF No treatment	12 (24) 24 12	12 (24) 24 12

BOC: boceprevir; DCV=daclatasvir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir.
* These comparators are subject to early stopping rules based on extended rapid virologic response. See text for further details.

5.2.3.1 Extended rapid virologic response

DCV+PR, TVR+PR and BOC+PR are subject to stopping rules if extended rapid virologic response (eRVR) is experienced. These rules only apply to TVR+PR and BOC+PR when used in non-cirrhotic patients. For DCV+PR and TVR+PR, the PR duration is reduced from 48 to 24 weeks if HCV RNA is undetectable at both weeks 4 and 12. For BOC, the PR duration is reduced from 48 weeks to 28 weeks and BOC duration is reduced from 32 to 24 weeks if RNA is undetectable at weeks 8 and 24. Rates of eRVR applied were 67% for DCV+PR, 58% for TVR+PR, and 44% for BOC+PR. These rates were taken from the AI444-042, ADVANCE [13], and SPRINT-2 [12] trials for DCV+PR, TVR+PR and BOC+PR respectively. These studies also informed the efficacy data for these comparators. However, for TVR+PR in genotype 1 treatment naïve patients without cirrhosis (F0-F4 and F3), the ILLUMINATE study [56] informed clinical outcomes but was not included in when estimating eRVR.

5.2.4 Perspective, time horizon and discounting

The perspective of the manufacturer's analysis was the NHS. Costs falling on the personal social services (PSS) budget were not included. An annual discount rate of 3.5% on both costs and health effects was applied, in line with NICE guidance.[51] The time horizon of the model is lifetime as per the NICE reference case.[51]

5.2.5 Treatment effectiveness and extrapolation

5.2.5.1 SVR rates

SVR rates were obtained from the manufacturers' uncontrolled (naïve) indirect comparison of trials as discussed in Section 4.4 Uncontrolled indirect comparison of trials. The SVR rates used in the model are presented in Tables 24-25 for the F3 and F4 subpopulations (details presented in Appendix 1). SVR rates for the F0-F4 population can be found in Tables 80-83 p143-6 of the MS. SVR rates for the F0-F2 subpopulations can be found in Table 42 p104 of the manufacturer response to the ERG points for clarification.

Although DCV studies were identified by systematic review, it is unclear whether the studies for comparators were identified in a systematic manner. In a number of cases, the manufacturer extrapolates results from a population which differs with respect to the METAVIR fibrosis score, treatment status or genotype of the target population. The SVR data presented for F0-F2, F3 and F4 patients was obtained from single arms of studies with no adjustments or correction for potential differences in patient characteristics or trial conduct. The benchmarking and MAIC studies were not an appropriate basis to inform SVRs in the model for any of these populations as they do not provide results stratified by METAVIR fibrosis stage.

The assumptions made to extrapolate the DCV-containing regimens data to the relevant populations are described in Table 30 for the F3 and F4 subpopulations. As shown in Appendix 1, the manufacturer's presented two SVR estimates for the F3 and F4 subpopulations with genotype 3. For the base-case in F3 genotype 3 treatment naïve, treatment experienced and interferon ineligible or intolerant patients, SVR estimates were obtained from ALLY-3. For the base-case F4 genotype 3 treatment naïve, treatment experienced and interferon ineligible and intolerant patients, SVR estimates were obtained from AI0444-040. This is assumed to be due to the treatment durations for DCV+SOF in each study

[redacted]. In a scenario, the manufacturer tested using the estimates of AI0444-040 in F3 patients and the estimates of ALLY-3 in F4 patients. It should be noted that the 040 trial contained only 2 F4 patients with genotype 3 (neither in the licensed regimen arm) and no treatment experienced patients with genotype 3.

Table 30 Data used to estimate SVRs for DCV-containing regimens in the model subpopulations

Target subpopulation				Source data					
						Does data match target subpopulation and licensed regimen			
Treatment	Genotype	Treatment history	Disease stage	Data source	Sample size	Genotype	Treatment history	Disease stage	Regimen*
DCV + SOF	1	Treatment naïve	F3	040	41	*Yes*	*Yes*	*No (F3-F4)*	*No*[(1)]
			F4	040	20[+]	*Yes*	*No (prior BOC+PR, TVR+PR failures)*	*No (F3-F4)*	*No*[(2)]
		Treatment experienced (prior BOC/TVR+PR)	F3	040	20	*Yes*	*Yes*	*No (F3-F4)*	*No*[(2)]
			F4	040	20	*Yes*	*Yes*	*No (F3-F4)*	*No*[(2)]
		Interferon ineligible or intolerant	F3	040	41	*Yes*	*No (treatment naïve)*	*No (F3-F4)*	*No*[(1)]
			F4	040	20[+]	*Yes*	*No (prior BOC+PR, TVR+PR failures)*	*No (F3-F4)*	*No*[(2)]
	3	Treatment naïve	F3	ALLY-3	36	*Yes*	*Yes*	*No (F3-F4)*	*Yes*
			F4	040	5	*Yes*	*Yes*	*No (F3-F4)*	*No*[(3)]
		Treatment experienced (prior PR)	F3	ALLY-3	21	*Yes*	*Yes*	*No (F3-F4)*	*Yes*
			F4	040	5	*Yes*	*No (treatment naïve)*	*No (F3-F4)*	*No*[(3)]
		Interferon ineligible or intolerant	F3	ALLY-3	36	*Yes*	*No (treatment naïve)*	*No (F3-F4)*	*Yes*
			F4	040	5	*Yes*	*No (treatment naïve)*	*No (F3-F4)*	*No*[(3)]
	4	Treatment naïve	F3	040	41	*No (G1)*	*Yes*	*No (F3-F4)*	*No*[(1)]
			F4	040	20[+]	*No (G1)*	*No (prior BOC+PR, TVR+PR failures)*	*No (F3-F4)*	*No*[(2)]
		Treatment experienced (prior PR)	F3	040	20	*No (G1)*	*No (prior BOC+PR, TVR+PR failures)*	*No (F3-F4)*	*No*[(2)]
			F4	040	20	*No (G1)*	*No (prior BOC+PR, TVR+PR failures)*	*No (F3-F4)*	*No*[(2)]
		Interferon ineligible or intolerant	F3	040	41	*No (G1)*	*No (treatment naïve)*	*No (F3-F4)*	*No*[(1)]
			F4	040	20[+]	*No (G1)*	*No (prior BOC+PR, TVR+PR failures)*	*No (F3-F4)*	*No*[(2)]
DCV + PR	4	Treatment naïve	F3	042	69	*Yes*	*Yes*	*No (non-cirrhotic)*	*Yes*
			F4	042	9	*Yes*	*Yes*	*Yes*	*Yes*
		Treatment experienced (prior PR)	F3	042	69	*Yes*	*No (treatment naïve)*	*No (non-cirrhotic)*	*Yes*
			F4	042	9	*Yes*	*No (treatment naïve)*	*Yes*	*Yes*

BOC: boceprevir, PR: pegylated interferon-alfa+ribavirin, TVR: teleprevir.DCV: Daclatasvir. SOF: Sofosbuvir.
* Whether the data was restricted to the licensed regimen or included unlicensed regimens.
[+] The manufacturer description of the population and the sample size do not match up, population size has been extracted to match manufacturer description of subgroup.
(1) Includes results from all trial arms including treatment naïve genotype 1 patients (arms A, C, E, G and H)
(2) Includes results from all trial arms including treatment experienced genotype 1 patients (arms I and J)
(3) Includes results from all trial arms containing treatment naïve genotype 3 patients (genotype 3 patients in arms B, D and F)

5.2.5.2 Treatment discontinuation

The manufacturer states that the model includes treatment discontinuations due to adverse events (in addition to those due to eRVR). Tables 31 and 32 present the proportion of patients discontinuing due to adverse events in the model for F3 and F4 subpopulation (discontinuation data for the F0-F4 subpopulation are presented on p143-146 of the MS). These proportions were obtained from the clinical trials that were selected to inform the SVR rates. The timing of discontinuations was not clear from many of the studies; hence the manufacturer assumes that the discontinuations occur in the first four weeks of treatment. In its response to the ERG's points for clarification, the manufacturer presented results for the F0-F2 subpopulation. However, parameter inputs for the discontinuation rates and their sources were not reported.

Table 31 Proportion of patients discontinuing treatment due to adverse events in the F3 subpopulations (adapted from Tables 74-76 p137-139 in the MS)

Genotype	Treatment status	Regimen	Discontinuation rate (SE)	Source
1	Treatment naïve	DCV+SOF (vs TVR)	0.005 (0.006)	MAIC (Appendix 6a of MS)
		TVR+PR	0.145 (0.012)	MAIC (Appendix 6a of MS)
		BOC+PR	0.122 (0.017)	MAIC (Appendix 6a of MS)
		SOF+PR	0.015 (0.007)	MAIC (Appendix 6a of MS)
		SMV+PR	0.023 (0.007)	MAIC (Appendix 6a of MS)
		PR	0.264 (0.021)	NV15942[57 58]
		No treatment	0	Assumption
	Treatment experienced	DCV+SOF	0	AI444-040 clinical trial report
		No treatment	0	Assumption
	Interferon ineligible or intolerant	DCV+SOF	0	AI444-040 clinical trial report
		SOF+RBV	0.080 (0.054)	QUANTUM and 11-1-0258 [20 59-61]
		SMV+SOF	0	COSMOS[15 62]
		No treatment	0	Assumption
3	Treatment naïve	DCV+SOF	0	ALLY-3 clinical trial report
		SOF+RBV	0.016 (0.008)	VALENCE[19 20]
		PR	0.222 (0.027)	FISSION[28]
		No treatment	0	Assumption
	Treatment experienced	DCV+SOF	0	ALLY-3 clinical trial report
		SOF+PR	0.083 (0.056)	LONESTAR-2[20 24]
		SOF+RBV	0.016 (0.008)	VALENCE[20 61]
		PR	0.056 (0.009)	HALT-C[15]
		No treatment	0	Assumption
	Interferon ineligible or intolerant	DCV+SOF	0	ALLY-3 clinical trial report
		SOF+RBV	0.019 (0.010)	POSITRON[20]
		No treatment	0	Assumption

4	Treatment naïve	DCV+SOF	0	AI444-040 clinical trial report
		DCV+PR	0.183 (0.043)[b]	AI444-042 clinical trial report
		SOF+PR	0.021 (0.008)	NEUTRINO[14 20]
		SMV+PR	0.009 (0.009)	RESTORE[63]
		PR	0.381 (0.075)	AI444-042 clinical trial report
		No treatment	0	Assumption
	Treatment experienced	DCV+SOF	0	AI444-040 clinical trial report[5 64]
		DCV+PR	0.183 (0.043)	AI444-042 clinical trial report
		SMV+PR	0.009 (0.009)	RESTORE[63]
		PR	0.056 (0.009)	HALT-C[15]
		No treatment	0	Assumption
	Interferon ineligible or intolerant	DCV+SOF	0	AI444-040 clinical trial report
		No treatment	0	Assumption

For the timing of discontinuations see manufacturer submission.

MAIC: Matching-adjusted indirect comparison. BOC: boceprevir; DCV: daclatasvir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir.

Table 32 Proportion of patients discontinuing treatment due to adverse events in the F4 subpopulations (adapted from Tables 77-79 p140-142 in the MS)

Genotype	Treatment status	Regimen	Discontinuation rate (SE)	Source
1	Treatment naïve	DCV+SOF	0	AI444-040 clinical trial report
		TVR+PR	0.262 (0.023)	ADVANC[65]
		BOC+PR	0.413 (0.026)	SPRINT-2[12]
		SOF+PR	0.021 (0.008)	NEUTRIN[14 20]
		SMV+PR	0.002 (0.006)	QUEST 1 and QUEST 2[66-68] [15 67 68]
		PR	0.264 (0.021)	NV15942 [57 58]
		No treatment	0	Assumptions
	Treatment experienced	DCV+SOF	0	AI444-040 clinical trial report[5 64]
		No treatment	0	Assumption
	Interferon ineligible or intolerant	DCV+SOF	0	AI444-040 clinical trial report
		SOF+RBV	0.080 (0.054)	QUANTUM and 11-1-0258[20 57]
		SMV+SOF	0	COSMOS[15 62]
		No treatment	0	Assumption
3	Treatment naïve	DCV+SOF+RBV	0.068 (0.038)	AI444-040 clinical trial report[5 64]
		SOF+RBV	0.016 (0.008)	VALENCE[20 61]
		PR	0.222 (0.027)	FISSION[20 28]
		No treatment	0	Assumption
	Treatment experienced	DCV+SOF	0.068 (0.038)	AI444-040 clinical trial report[5 64]
		SOF+PR	0.083 (0.056)	LONESTAR-2[20 24]
		SOF+RBV	0.016 (0.008)	VALENCE[20 61]
		PR	0.056 (0.009)	HALT-C[15]

		No treatment	0	Assumption
	Interferon ineligible or intolerant	DCV+SOF+RBV	0.068 (0.038)	AI444-040 clinical trial report[5 64]
		SOF+RBV	0.019 (0.010)	POSITRON[69]
		No treatment	0	Assumption
4	Treatment naïve	DCV+SOF	0	AI444-040 clinical trial report[5 64]
		DCV+PR	0.183 (0.043)[b]	AI444-042 clinical trial report
		SOF+PR	0.021 (0.008)	NEUTRIN[20]
		SMV+PR	0.009 (0.009)	RESTORE[63]
		PR	0.381 (0.075)	AI444-042 clinical trial report
		No treatment	0	Assumption
	Treatment experienced	DCV+SOF	0	AI444-040 clinical trial report[5 64]
		DCV+PR	0.183 (0.043)	AI444-042 clinical trial report
		SMV+PR	0.009 (0.009)	RESTORE[63]
		PR	0.056 (0.009)	HALT-C[15]
		No treatment	0	Assumption
	Interferon ineligible or intolerant	DCV+SOF	0	AI444-040 clinical trial report[5 64]
		No treatment	0	Assumption

For the timing of discontinuations see manufacturer submission.

MAIC: Matching-adjusted indirect comparison. BOC: boceprevir; DCV: daclatasvir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir.

5.2.5.3 Transition probabilities

The transition probabilities for the Markov model were obtained from the literature. All transition probabilities (with the exception of all-cause mortality) were assumed to be constant over time, reflecting the estimates available from the literature. Table 33 shows the transition probabilities used in the model. The transitions between METAVIR fibrosis stages, from compensated cirrhosis and from and to liver transplantation are discussed in turn below.

Table 33 Transition rates used in the model (adapted from Table 86-88 p150-151 of the MS)

Transition	Coefficient	Mean	Standard error	Distribution	Source and comments
(i) Transitions between METAVIR fibrosis health states					
F0 to F1	Intercept	-2.01240	0.664*	Normal	Coefficients and standard errors from Thein et al.[54] The manufacturer uses the baseline cohort characteristics (see Table 27) to determine the transition probabilities used in the model.
	Duration	0.07589	0.011*	Normal	
	Design	-0.32470	0.175*	Normal	
	Male	0.50630	0.478*	Normal	
	Genotype	0.48390	0.278*	Normal	
F1 to F2	Intercept	-1.53870	0.818*	Normal	
	Duration	-0.06146	0.014*	Normal	
	Excess alcohol	0.80010	0.391*	Normal	
F2 to F3	Intercept	-1.60380	0.590*	Normal	
	Age	0.01720	0.012*	Normal	
	Duration	-0.05939	0.010*	Normal	
	Excess alcohol	0.45390	0.280*	Normal	

Transition	Coefficient	Mean	Standard error	Distribution	Source and comments
F3 to F4	Intercept	-2.28980	0.773*	Normal	
	Age	0.01689	0.015*	Normal	
	Duration	-0.03694	0.013*	Normal	
	IDU	0.59630	0.316*	Normal	
	BT	1.16820	0.368*	Normal	
	Genotype	-0.46520	0.291*	Normal	
Genotype 3 multiplier for METAVIR transitions	NA	1.31	0.0434	Normal	Multiplier applied to transition rate obtained from the estimates above. Multiplier obtained from Kanwal et al[70]
(ii) Transitions between compensated cirrhosis, decompensated cirrhosis, HCC and death					
F4 to DC	NA	0.039	0.010**	Beta	Fattovich et al[71]
F4 to HCC	NA	0.014	0.010**	Beta	Fattovich et al[71]
DC to HCC	NA	0.014	0.010**	Beta	Fattovich et al[71]
DC to death	NA	0.130	0.010**	Beta	Fattovich et al[71]
HCC to death	NA	0.430	0.030**	Beta	Fattovich et al[71]
Genotype 3 multiplier F4 to HCC	NA	1.44	0.1148	Normal	Multiplier applied to transition rate obtained from the estimates above. Multiplier obtained from Kanwal et al [70]
Genotype 3 multiplier DC to HCC	NA	1.44	0.1148	Normal	Multiplier applied to transition rate obtained from the estimates above. Multiplier obtained from Kanwal et al[70]
(iii) Transitions to and from liver transplantation					
DC to LT	NA	0.030	0.012**	Beta	Siebert et al[72]
HCC to LT	NA	0.030	0.012**	Beta	Siebert et al[72]
LT year 1 to death	NA	0.210	0.046**	Beta	Bennett et al[73]
LT year 2+ to death	NA	0.057	0.012**	Beta	Bennett et al[73]

*Standard Error estimates obtained from the model including all covariates.
** It is unclear how these estimates of standard errors were derived.
Duration: Length of time from the presumed date of infection to the date of liver biopsy; Design: Value=0 if the study design is cross sectional; value=1 if the study design is retrospective-prospective; Male: Proportion of patients that are male; Genotype: Proportion of patients that are genotype 1; Excess alcohol: Defined as alcohol consumption of at least more than 20 g/day over past 12 months. Age: Age at date of infection; IDU: Proportion of patients that acknowledged intravenous drug use as the main risk factor for HCV progression; BT : Proportion of patients that were newly diagnosed with chronic hepatitis C at blood donor screening.
NA – non applicable; CC – compensated cirrhosis; DC – decompensated cirrhosis; HCC – hepatocellular cancer; LT – liver transplantation.

Transitions between METAVIR fibrosis health states

For genotypes 1 and 4, the transitions between METAVIR fibrosis health states were informed by a meta-analysis conducted by Thein et al (2008).[54] Studies included in the meta-analysis were identified by a systematic review aimed at identifying untreated cohorts of hepatitis C patients which reported fibrosis stage and duration of hepatitis C following a period of follow-up. The meta-analysis included 111 studies and 33,121 patients with chronic hepatitis C; patients were followed up for an average of 17.5 years. Studies were generally from after the year 2000 (101/111). The majority of the studies (79/111) were of patients at specialists liver clinics. Other studies were in specialist populations: blood donors, dialysis patients, females, injecting drug users, paediatric population, post-transfusion or renal transplant recipients; and a small number of studies were conducted in the community (4/111). Almost all of the studies (100/111) assessed liver fibrosis contemporaneously

but established the date of infection retrospectively. The other studies included some degree of prospective follow-up. Studies were from a wide range of countries, mainly in Europe or the USA.

The manufacturer uses transition probabilities estimated by Thein et al. using a meta-regression approach. Transition rates are estimated from individual studies using the maximum likelihood method developed by Yi et al (2004).[74]This method estimates the transition rates most likely to have generated the observed distribution across METAVIR fibrosis stages given the duration of follow-up (estimated from mean disease duration). Many studies (approximately half) did not collect METAVIR fibrosis and used other liver fibrosis staging methods. Mapping was therefore required to generate distributions across METAVIR fibrosis stage. Where studies reported mapped or actual METAVIR fibrosis stages aggregated across two METAVIR fibrosis stages, patients were assumed to be equally distributed between these stages. Heterogeneity across studies in progression rates was adjusted for using meta-regression. This explored the impact of study design, population, publication year, gender, age at infection, infection duration, source of infection (injecting drug use, blood/blood product transfusion), excess alcohol consumption, HIV status, HCV RNA positivity and genotype. A backward stepwise procedure appears to have been employed to select variables for the final model but the details of this are unclear.

The manufacturer uses the baseline cohort characteristics to determine the transition probabilities used in the model. For patients with genotype 4, transition probabilities are estimated by setting the proportion of non-genotype 1 patients to 100%. For patients with genotype 3, a multiplier is applied to the transitions rates between METAVIR fibrosis stages for patients in genotype 1 (as estimated from the Thein et al. study). This multiplier was estimated from Kanwal et al (2014).[70] This study analysed the impact of genotype 3 infection on cirrhosis and HCC incidence in 110,484 US veterans diagnosed between 1999 and 2009 followed up for an average of 5.4 years. The impact of genotype was estimated using Cox regression adjusting for age, gender, race, period of service, year of diagnosis, diabetes, alcohol use, HIV status, BMI and antiviral treatment (and response). The hazard ratio estimated for progression to cirrhosis indicates that genotype 3 patients progress to cirrhosis considerably more quickly than genotype 1 patients (HR 1.31 95% CI 122-1.39). This hazard ratio was applied to accelerate all METAVIR fibrosis state transitions (i.e. F0→F1, F1→F2, F2→F3, F3→F4).

Transitions between compensated cirrhosis, decompensated cirrhosis, HCC and death

Transition probabilities from F4 (cirrhosis) to decompensated cirrhosis and HCC, from decompensated cirrhosis to HCC and death and from HCC to death were derived from Fattovich (1997).[71] Fattovich (1997) analysed data from a cohort of 384 patients with compensated cirrhosis enrolled at seven European tertiary referral centres in the period 1982-1992 and followed up for a mean period of 5.2 years. The source of the stated probability of transitioning from HCC to death is

unclear but appears to be approximately correct given the available data. As for transitions between METAVIR fibrosis stages, data from Kanwal et al. were used to estimate an increased rate of progression from F4 and decompensated cirrhosis to HCC in genotype 3 patients. The methods used were as above although the sample size was smaller (21,716) as patients were required to be cirrhotic.[70] The hazard ratio for time from cirrhosis to HCC was applied to the rate of transition for patients who were F4 (cirrhosis) or had decompensated cirrhosis (and were genotype 3).

Transitions to and from liver transplantation

The rate of liver transplant (from HCC and decompensated cirrhosis) is based on an assumption made for an economic evaluation of PR.[72] Survival following liver transplant is informed by three studies involving 2,166 patients undergoing liver transplantation.[73] It is not clear how the studies were pooled or which patients were included in the analysis.

5.2.6 Health related quality of life

5.2.6.1 Systematic review of HRQoL in chronic hepatitis C

The manufacturer conducted a systematic review of the published literature on HRQoL in chronic hepatitis C. This review does not appear to have informed the HRQoL estimates used in the submission. As with the review on cost-effectiveness studies described in Section 5.1, the aim was to identify new studies published since the systematic review by Hartwell et al.[26]. Again, the appropriateness of Hartwell et al to inform the manufacturer's systematic review is unclear since this study included only systematic reviews of RCTs.

The manufacturer reports the search strategies and data extraction tables (see Appendix 8 of the MS); however, no synthesis of the evidence was undertaken. Searches were generally well conducted, however some variations of terms relating to quality of life and measurement scales were not included (e.g. "euroqual" and "sf 36"). Searches of Medline, Embase and the Cochrane Library were restricted to 2009 onwards; this may have missed relevant articles.

Twenty three studies were included by the manufacturer. The ERG reviewed the data extraction tables for the setting and HRQoL instrument used. Of the 23 included studies, only one was conducted in the UK.[75] Most studies were set in Europe (excluding UK and Ireland), one in Ireland,[76] two in the US,[77 78] five in various countries[79-83] and two in Asia.[84 85] Most studies reported SF-36 (n=18) and one reported SF-6D.[80] Four studies collected EQ-5D.[80 86-88]:

- Bjornsson et al evaluated the HRQoL in patients in different stages of hepatitis C infection and compared HRQoL in cirrhosis induced by hepatitis C with cirrhosis due to other causes in Sweden. The mean EQ-5D (standard deviation in brackets) was 0.819 (0.217) for healthy individuals, 0.811 (0.230) for patients with chronic hepatitis C, 0.749 (0.212) for patients with

compensated cirrhosis, 0.656 (0.266) for decompensated cirrhosis and 0.792 (0.209) non-cirrhotic patients who had achieved SVR.[86]

- McDonald et al compared EQ-5D of a sample of people who inject drugs in Scotland who were chronically infected with hepatitis C and aware of their infected status, chronically infected with hepatitis C but unaware, and not chronically infected. The median EQ-5D in each group, respectively, was 0.66, 0.74 and 0.76. [87]
- Scalone et al compared the properties and performance of the EQ-5D-3L with the EQ-5D-5L in patients with chronic hepatitic diseases. The mean EQ-5D (standard deviation) in patients with chronic hepatitis C was 0.823 (0.205) for the EQ-5D-3L and 0.840 (0.178) for the EQ-5D-5L.[88]
- Stepanova et al reported the EQ-5D and SF-6D, both derived from SF-36, collected in patients with chronic hepatitis C during the RCTs and cohort studies evaluating SOF-containing regimens: POSITRON comparing SOF+RBV for 12 weeks vs placebo, FISSION comparing SOF+RBV for 12 weeks with PR for 24 weeks, FUSION comparing SOF+RBV for 16 weeks with SOF+RBV for 12 weeks and NEUTRINO was a cohort longitudinal study of SOF+PR. Table 34 summarises the EQ-5D scores reported in this study. The HRQoL decrement for SOF+RBV (12 weeks treatment duration) ranges from -0.006 (±0.232) in FISSION to -0.075 (±0.180) in POSITRON. The HRQoL decrement associated with regimens containing interferon is much greater at -0.115 (±0.200) for PR in FISSION and -0.149 (±0.209) for SOF+PR in NEUTRINO. [80]

Table 34 EQ-5D scores reported in Stepanova et al 2014 (adapted from Table 3 p683)

Study	Period of time	Baseline	Decrement from baseline		
			End of treatment	Follow-up at week 4	Follow-up at week 12
POSITRON	SOF+RBV for 12 weeks	0.717±0.214	-0.075±0.180	-0.026±0.188	-
	Placebo	0.673±0.227	-0.029±0.138	-0.019±0.172	-
FISSION	SOF+RBV for 12 weeks	0.740±0.232	-0.006±0.201	-	0.035±0.173
	PR for 24 weeks	0.771±0.236	-0.115±0.200	-	-0.035±0.156
FUSION	SOF+RBV for 16 weeks	0.745±0.211	-0.020±0.167	-0.005±0.175	0.054±0.179
	SOF+RBV for 12 weeks	0.753±0.231	-0.059±0.191	-0.012±0.177	0.021±0.184
NEUTRINO	SOF+PR	0.793±0.219	-0.149±0.201	-0.044±0.209	0.0003±0.1874

The manufacturer provided no synthesis of the findings of the review and the review does not appear to have informed the selection of data for inclusion in the model. We discuss the potential relevance of these data sources in Section 5.3.7.5 The systematic review on HRQoL.

5.2.6.2 HRQoL in the model

HRQoL was expressed in QALYs by quality adjusting the period of time the average patient was alive within the model with the appropriate HRQoL weight. HRQoL was captured in two

components: (i) HRQoL associated with the natural history of chronic hepatitis C as defined by the model states and (ii) the decrement in HRQoL associated with adverse effects from treatment. In addition, and following a request by the ERG, the manufacturer included an age-related HRQoL decline in the model.[89] Each component of HRQOL is discussed in turn below. Table 35 summarises the HRQoL values used in the economic model.

Table 35 HRQoL values used in the model (adapted from Table 93-95 p160-1 of the MS)

Health State or Regimen	Mean	SE	Source
HRQoL associated with each model state			
Mild (F0- F1)	0.77	0.015	Wright et al[49]
Moderate (F2- F3)	0.66	0.031	Wright et al[49]
Cirrhosis (F4)	0.55	0.054	Wright et al[49]
SVR in mild disease (F0-F1)	0.82	0.043	Wright et al[49]
SVR in moderate or cirrhotic disease (F2-F3 and F4)	0.72	0.048	Wright et al (assumption made for F4) [49]
Decompensated cirrhosis	0.45	0.031	Wright et al[49]
Hepatocellular cancer	0.45	0.031	Wright et al[49]
Liver transplant year 1	0.45	0.031	Wright et al using data from Ratcliffe et al.[49 90]
Liver transplant	0.67	0.066	
HRQoL decrement associated with each regimen			
PR Treatment naïve	0.109	0.010	Janssen submission to NICE on TVR for the treatment of genotype 1 chronic hepatitis C[91]
PR Treatment experienced	0.126	0.036	
TVR+PR	0.102	0.010	
BOC+PR	0.0671	0.00671*	MSD submission to NICE on BOC for the treatment of genotype 1 chronic hepatitis C[92]
SMV+PR	0.0798	0.00798*	Janssen submission to NICE on SMV for the treatment of genotype 1 and genotype 4 chronic hepatitis C (SMV+SOF assumed to be equal to SMV+PR)[63]
SMV+SOF	0.0798	0.00798*	
SOF+PR	0.148	0.0148*	Younossi et al 2014[93]
SOF+RBV	0.048	0.0048*	Osini et al. for adverse event rates, [61] manufacturer time trade off study for adverse event HRQoL decrements.
DCV+SOF	0.035	0.0035*	DCV clinical trials for adverse events, manufacturer time trade off study for adverse event HRQoL decrements.
DCV+PR	0.137	0.0137*	
DCV+SOF+RBV	0.059	0.0059*	

*SE assumed to be 10% of the mean value.

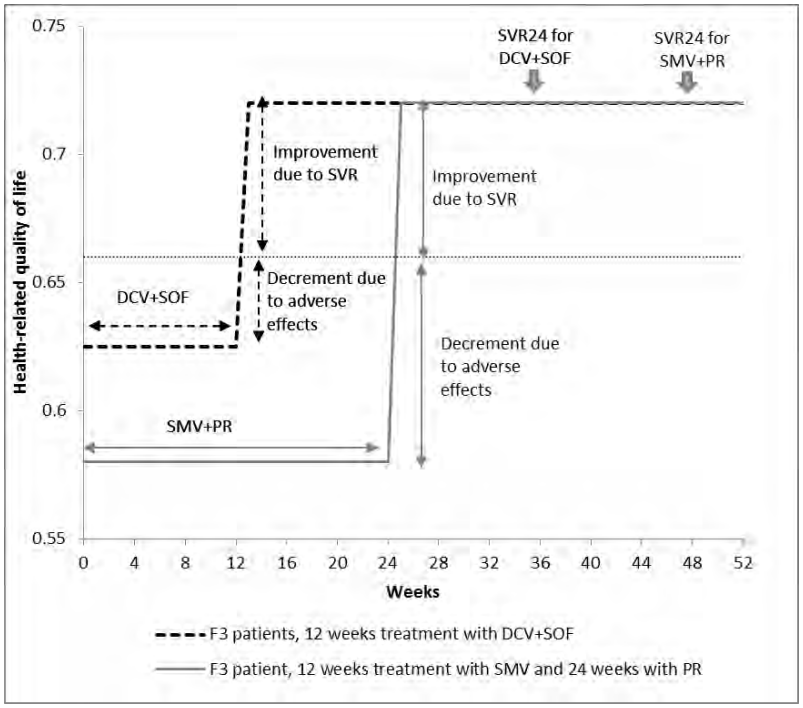
SVR: sustained virologic response. HRQoL: health-related quality of life. MSD: Merck Sharp & Dome.

PR: pegylated interferon alpha with ribavirin. SMV: simeprevir. SOF: sofosbuvir. TVR: telaprevir. BOC: boceprevir. DCV: daclatasvir.

Figure 2 exemplifies how HRQoL was incorporated in the manufacturer's model during the first year for a patient who achieved SVR. This example shows the HRQoL profile of a patient with genotype 1 who is treatment naïve, has F3 disease severity and is treated with DCV+SOF or SMV+PR. During the treatment period, patients experience the HRQoL associated with their disease severity (F0, F1, F3, F4) minus the HRQoL decrement associated with the adverse events from treatment. Patients in F3 enter the model with a utility of 0.66. The HRQoL decrement (0.04 for DCV+PR and 0.08 for SMV+PR) is applied for the treatment duration of the longest component of the treatment regimen. The treatment duration for DCV+SOF is 12 weeks and for SMV+PR 12 weeks for SMV and 24 weeks for PR. The HRQoL decrement associated with DCV+SOF is therefore applied over 12 weeks and the HRQoL decrement associated with SMV+PR is applied over 24 weeks. Although SVR is commonly tested for at 24 weeks after the end of treatment, in the model the HRQoL improvement associated with SVR is experienced immediately after the end of the treatment. Patients with SVR are assumed to remain in their health state throughout their lifetime (i.e. in F3 with SVR in this example). Age-related decrements were applied following the ERG's request in the points for clarification to reflect the HRQoL decrement from aging. If this patient had not experienced SVR they would have returned to their baseline HRQoL (0.66) at the end of treatment and then faced risks of further liver-related events which reduce their quality of life.

The assumptions that the benefit of SVR is achieved immediately after treatment is complete and that the HRQoL decrement associated with adverse events is experienced for the duration of the longest component of therapy were not justified by the manufacturer.

Figure 2 HRQoL in the model during the treatment year



HRQoL for each health state

The HRQoL for each health state was obtained from Wright et al.[49] Wright et al is a Health Technology Assessment (HTA) monograph reporting an RCT and an economic evaluation comparing PR with no treatment for mild chronic hepatitis C. Mild chronic hepatitis C was defined as patients with an Ishak necroinflammatory score <4 or a fibrosis score <2. Wright et al collected EQ-5D data directly from patients during the RCT (baseline, treatment weeks 12, 24, 48 and follow-up weeks 12, 24 and 48). The HRQoL score of mild disease was taken as the mean EQ-5D score collected in the RCT at baseline. The EQ-5D at 24 and 48 weeks post-treatment was used to estimate the HRQoL associated with achieving SVR in patients with mild disease using an ANCOVA model to adjust for treatment group (NT or treatment) and for whether SVR was achieved. A separate observational sub-study also reported in Wright et al provided EQ-5D scores for patients with moderate chronic disease with and without SVR and for patients with cirrhosis without SVR. This sub-study included 71 patients with moderate disease and 40 patients with cirrhosis.

In order to incorporate this data in to the model mild chronic hepatitis C was assumed equivalent to the METAVIR stages F0-F1 and moderate to METAVIR stages F2-F3. The manufacturer justified this assumption with reference to the study by Martin et al.[42]. However, the cost-effectiveness analysis by Martin et al did not use METAVIR score to distinguish severity of chronic hepatitis C and hence does not provide a justification for this assumption.

Wright et al. does not provide data on the HRQoL of patients with cirrhosis (METAVIR stage F4) who achieve SVR. These patients were assumed to experience the same HRQoL as moderate patients with SVR. This implies a greater HRQoL *improvement* than patients with moderate and mild disease with SVR (0.17 for F4 (cirrhotic) vs 0.05 in mild and 0.06 in moderate disease). The manufacturer justified this assumption with reference to four published studies which used this approach.[33 94-96]

The HRQoL scores associated with decompensated cirrhosis or hepatocellular cancer were obtained from the Brunel transplantation study.[90] The HRQoL associated with decompensated cirrhosis or hepatocellular cancer was taken as the EQ-5D score of patients with chronic hepatitis C at transplant listing. The manufacturer also used this value for the HRQoL over the first year after transplant. The HRQoL after liver transplantation was take as the mean EQ-5D score at one year post transplant. All EQ-5D profiles were scored using the UK tariff in their original studies.

HRQoL decrement associated with adverse effects

The HRQoL decrement associated with adverse effects from treatment is also presented in Table 35. The decrements for the comparator regimens PR, TVR+PR, BOC+PR, SMV+PR, SMV+SOF, SOF+PR were obtained from submissions to NICE for TVR,[91] BOC[92] and SMV[63]. The HRQoL decrement for PR and for TVR+PR corresponds to the decrease between baseline EQ-5D and

the average EQ-5D score during treatment as collected in the ADVANCE and REALIZE RCTs.[91] The HRQoL decrement for BOC+PR was referred to having been obtained from the submission to NICE for BOC by Merck Sharp and Dome (MSD; manufacturer of BOC) ;[92] however, this value was not quoted in this submission. The source of the HRQoL decrement for BOC+PR is therefore unclear. The HRQoL decrement for SMV+PR and SMV+SOF corresponds to the reduction in EQ-5D from the QUEST 1 and 2 trials in patients receiving SMV+PR. This was assumed to apply to SMV+SOF and used in the cost-effectiveness submission for SMV for genotype 4.[63] The HRQoL decrement for SOF+PR was obtained from a conference abstract. This reported the EQ-5D scores mapped from SF-36 and SF-6D data from RCTs evaluating SOF-based regimens (POSITRON, FISSION, FUSION and NEUTRINO). The HRQoL decrement for SOF+PR corresponds to the mapped EQ-5D decrement obtained from NEUTRINO. [81]

The HRQoL decrements for SOF+RBV and for the DCV-containing regimens (DCV+SOF, DCV+PR and DCV+SOF+RBV) were calculated as a sum of the product of the incidence of a range of adverse effects and decrement in HRQoL associated with those adverse effects. The adverse effects considered were mild anaemia, severe anaemia, flu-like symptoms, mild rash, severe rash and depression. The incidence of these adverse effects was obtained from Osini et al for SOF+RBV and from the clinical trial reports for the DCV-containing regimens.[61] The HRQoL decrement was estimated in a study conducted by the manufacturer. This study was conducted in a sample of the UK general population (n=182) and used the time-trade off method to value vignette descriptions of chronic hepatitis C health states, with and without treatment and with and without the different adverse effects considered.[97]

5.2.7 Resources and costs

5.2.7.1 Systematic review of resource use and costs in chronic hepatitis C

The manufacturer conducted a systematic review of the published literature on resource use and costs in chronic hepatitis C. This review did not inform the estimates of resource use and costs used in the model. As with the review on cost-effectiveness studies and HRQoL, the aim was to identify new studies published since the systematic review by Hartwell et al 2009.[98] Again, the utility of Hartwell et al to inform the manufacturer's systematic review is unclear since this study included only systematic reviews of RCTs.

The manufacturer reports the search strategies and data extraction tables (Appendix 9 of the MS); however, no synthesis of the evidence was undertaken. Searches were generally well conducted. However, as with the cost-effectiveness searches an attempt has been made to restrict the searches by country, which may have resulted in some studies being missed. Omission of terms for costs and economics may have also missed some relevant studies, as may restriction of the searches of MEDLINE, EMBASE and the Cochrane Library to 2009 onwards.

Five studies were included in the review. The ERG identified the one study that reported costs in the UK setting, Backx et al.[99] This study conducted a costing study of the resource use and costs falling on the NHS budget associated with the monitoring of patients with chronic hepatitis C genotype 1 with and without SVR. Patients entered the study at the end of a minimum of 2 months of treatment with PR. The resource use collected consisted of outpatient clinic visits, HCV RNA tests, liver-related imaging, day case visits and inpatient hospital days. Unit costs for hospital resource use were obtained from the NHS payment by results database (price year not specified); drug acquisition costs were obtained from the BNF.

Backx et al obtained data from 193 patients (108 SVR and 85 non-SVR) who were non-cirrhotic, cirrhotic or had decompensated cirrhosis prior to treatment. The average follow-up was 3.5 years for SVR patients and 4.9 years for non-SVR patients. None of the SVR patients experienced disease progression over the period of follow-up. Some of the non-SVR patients progressed. Of the 65 non-cirrhotic patients, 17 progressed to cirrhotic (2 of whom subsequently decompensated) and 2 progressed directly to decompensation. Of the 36 cirrhotic patients, 7 progressed to decompensated disease. SVR patients with cirrhosis (n=6) or decompensation (n=2) at pre-treatment were not discharged from clinic. All SVR patients without cirrhosis at pre-treatment were discharged during the study follow-up: 42 patients at 6 months post therapy and the remaining 58 within 2 years of achieving SVR.

For the non-cirrhotic patients, the average annual cost per SVR patient was £54 and per non-SVR patient was £506. Since all of the SVR patients were discharged, their resource use and costs decline over time. Costs were greater in more severe patients: the average annual cost per SVR patient with cirrhosis was £556 and per SVR patient with decompensated cirrhosis was £663. The corresponding costs for non-SVR patients were £667 and £3,394 respectively. Table 36 presents the cost estimates from the generalised linear model (gamma family with log link) for SVR vs non-SVR.

Table 36 Cost estimates from generalised linear model for SVR vs non-SVR who were not retreated (adapted from Table 5 of Backx et al 2014) [99]

Severity of disease pre-treatment	SVR status	Number of patients	Average cost per person per year	Lower 95% confidence interval	Upper 95% confidence interval
Non-cirrhotic	SVR	100	£58	£45	£75
	No SVR	54	£589	£417	£833
Cirrhosis	SVR	6	£586	£207	£1,655
	No SVR	27	£914	£560	£1,491
Decompensated	SVR	2	£719	£119	£4,347
	No SVR	10	£4,364	£1,951	£9,757
SVR: sustained virologic response.					

The manufacturer provided no synthesis of the findings of the review and the review does not appear to have informed the selection of data for inclusion in the model. Section 5.3.8.7 Systematic review on costs in chronic hepatitis C discusses the potential relevance of this data source.

5.2.7.2 Costs used in the model

The manufacturer took an NHS perspective for the identification, measurement and valuation of resource use and costs. Costs were expressed in UK pound sterling at a 2012-13 price base. Costs were categorised as: acquisition costs for each treatment, costs associated with monitoring during treatment and costs associated with each health state. Costs associated with adverse events were not considered in the base-case. The rationale for their exclusion was their anticipated marginal impact on the cost-effectiveness results and the inconsistency in the reporting of adverse events across the trial publications for comparator regimens. A sensitivity analysis in the MS explores the impact of including the costs associated the rash and anaemia on the results (see Section 5.2.8 Sensitivity analysis). Table 37 presents the costs used in the model.

Table 37 Costs used in the model (adapted from Table 97-100 p165-167 of the MS)

Health State or Regimen	Mean	SE	Source	Comments
Drug acquisition costs (per week)				
DCV	£2,038.13	NA	BNF[100]	Cost per 28 tablet pack: £8,172.61
SOF	£2,915.24	NA		Cost per 28 tablet pack: £11,660.98
SMV	£1,866.50	NA		Cost per 7 capsule pack: £1,866.50
TVR	£1,866.50	NA		Cost per 42 tablet pack: £1,866.50
BOC	£700.00	NA		Cost per 336 capsule pack: £2,800
RBV	£66.95	NA		Cost per 168 200mg capsules: £321.38
PEG-I	£124.40	NA		Cost per 4 syringes: £497.60
Monitoring costs				
12 weeks of treatment	£710.97	£71.10	Shepherd et al 2007	The manufacturer inflated the costs reported in Shepherd et al from 2003-4 to 2012-13 using the Health and Community Health Services (H&CHS) index.[101] In the model, the standard error was assumed as 10% of the mean value.
24 weeks of treatment	£872.16	£87.21		
48 weeks of treatment	£1,167.03	£116.70		
Costs associated with each model state				
Mild disease (F0 or F1)	£177.47	£35.01	Martin et al 2012 [42]	Martin et al 2012 obtained the cost estimates from Wright et al 2006[49] The manufacturer inflated the costs reported in Martin et al 2012 from 2003-4 to 2012-13 using the Health and Community Health Services (H&CHS) index.[101] The cost of the health states after achieving SVR apply only for the first year post-
Moderate disease (F2 or F3)	£922.08	£97.82		
Cirrhosis (F4)	£1463.50	£297.45		
SVR in mild (F0 or F1) year 1	£333.08	£62.05		
SVR in moderate (F2 or F3) year 1	£922.08	£97.74		

Health State or Regimen	Mean	SE	Source	Comments
SVR in cirrhosis (F4) year 1	£1463.50	£288.07		treatment.
Decompensated cirrhosis	£11,728.61	£1954.09		
Hepatocellular cancer	£10,451.58	£2456.09		
Liver transplant event	£35,147.26	£3,709.93		
Liver transplant year 1	£12,163.29	£3,133.55		
Liver transplant year 2+	£1781.15	£456.57		
SVR – sustained virological response; H&CHS – Health and Community Health Services; DCV – Daclatasvir; SOF – Sofosbuvir; SMV – Simeprevir; TVR – Telaprevir; BOC – Boceprevir; RBV – Ribavirin; PEG-I – Pegylated interferon alpha.				

Drug acquisition costs

Drug acquisition costs were obtained from the British National Formulary (BNF, the manufacturer did not specify the edition). The costs of each regimen were calculated as the acquisition costs of each drug for one week of treatment. This assumes that no wastage occurs, which it may if patients discontinue with prescribed drugs left unused. The manufacturer assumed doses for ribavirin and pegylated interferon alpha of 1,000mg per day and 180mcg per week respectively and chose the brand Rebetol® and Pegasys ® from which to source the unit costs.

Costs associated with each health state

The costs associated with each health state were obtained from Martin et al,[42]which in turn reproduced them from Wright et al,[49] and were inflated from 2003-4 to 2012-13.[101] Wright et al collected the resource use associated with chronic hepatitis C during the mild hepatitis RCT for mild disease and in a separate observational study for moderate, cirrhotic, decompensated cirrhotic and hepatocellular cancer stages. Martin et al assumed that the costs of moderate and cirrhotic disease with SVR were the same as the non-SVR costs. The manufacturer made the same assumption in the first year. In order to translate the resource use data to the METAVIR fibrosis health states used in the model mild disease was assumed to correspond to METAVIR stage F0-F1 and moderate disease to F2-F3. Resource use was identified and measured from a health service perspective and costed using national unit costs. Costs associated with liver transplant were obtained from a UK based liver transplantation study.[102] The manufacturer assumed that the costs of the health states post-SVR are relevant only for the first year after achieving SVR; subsequent years have zero costs. This was justified with reference to the Janssen submission to NICE on TVR for genotype 1 chronic hepatitis C.[91] However, in this submission, the mild and moderate health states post SVR are monitored for one year but cirrhotic patients with SVR are monitored throughout their lifetime.

Costs associated with monitoring during treatment

Table 37 also presents the costs associated with monitoring during treatment. They were obtained from Shepherd et al 2007 and inflated from 2003-4 to 2012-13.[50 101] Shepherd et al reports a systematic review and economic evaluation of pegylated interferon alfa and non-pegylated interferon alfa and ribavirin for the treatment of adults with mild chronic hepatitis C. Resource use associated with monitoring of patients during treatment were identified and measured from clinical guidelines and discussions with hepatologists/specialist nurses at Southampton University Hospitals Trust. The source of the unit costs used by Shepherd et al is not clear from the report. In the manufacturer's model, treatment monitoring costs were grouped in to four-weekly costs and applied for the duration of treatment. The manufacturer tested a scenario in which DCV+SOF is associated with no monitoring costs in the sensitivity analysis (see Section 5.2.8).

5.2.8 Sensitivity analysis

Table 38 documents the manufacturer's sensitivity analysis. The manufacturer presented:

- Scenario analysis regarding DCV effectiveness data and treatment durations for specific sub-populations
- Univariate sensitivity analysis for a range of parameter inputs in all subpopulations with either F3 or F4 severity disease (but not for the F0-F4 severity group).
- Probabilistic sensitivity analysis (PSA). The variables included in the PSA were: baseline characteristics of the patient cohort (age, proportion male, initial disease severity), SVR rate, discontinuation due to adverse events, discontinuation due to early response, transition rates between health states, HRQoL associated with health states, HRQoL decrement associated with each treatment regimen, costs associated with each health state and costs associated with monitoring.
- Threshold analysis on the lowest SVR that DCV-containing regimens would have to attain to achieve cost-effectiveness at a threshold of £20,000 per QALY compared pairwise with each included comparator regimen.

Table 38 Sensitivity analyses presented by the manufacturer

Element	Approach in the base-case	Sensitivity analysis
Scenario analysis		
Intervention	Genotype 3 Non-cirrhotic: DCV+SOF for 12 weeks using effectiveness data from ALLY-3 Cirrhotic: DCV+SOF+RBV for 24 weeks using effectiveness data from AI444-040	Genotype 3 Non-cirrhotic: DCV+SOF+RBV (DCV over 12 weeks and SOF+RBV over 24 weeks) using effectiveness data from AI444-040 Cirrhotic: DCV+SOF for 24 weeks using effectiveness data from ALLY-3
Treatment duration	12 weeks treatment duration with DCV+SOF for the subgroup with genotype 1 or 4 F3 who are interferon-ineligible or intolerant and for treatment	24 weeks treatment duration

	experienced patients.	
	24 weeks treatment duration with DCV+SOF for the subgroup with genotype 1or 4 F4 who are treatment naïve.	12 weeks treatment duration
Univariate sensitivity analysis		
Age	Mean age is 50 years.	Mean age varied by 10 years.
Proportion male	67% male.	Patient cohort assumed to be all male or all female.
Time horizon	Lifetime (100 years of age).	5- and 20-year time horizons.
Discount rate	3.5% for both costs and HRQoL	0% and 6%.
Transition probabilities	Age-dependent transition probabilities based on Thein et al.[54]	Static transition rates.
		Transition rates varied by 20%.
Progression following SVR at cirrhosis (F4)	Patients with cirrhosis (F4) who achieve SVR are not at risk of progression.	Patients with cirrhosis (F4) who achieve SVR are at risk of progression to decompensated cirrhosis or HCC (annual transition rates 0.001 and 0.008 respectively).
Discontinuation	Discontinuation rates from the relevant clinical trials.	No discontinuation from treatment.
HRQoL associated with health states	See Table 35for HRQoL used in the base-case.	HRQoL varied by 20%.
HRQoL decrement associated with treatment	See Table 35 for HRQoL decrements used in the base-case.	HRQoL decrements varied by 20%
Costs associated with health states	See Table 37 for health state costs used in the base-case.	Costs varied by 20%.
Costs associated with adverse events	Not included in the base-case.	Costs associated with rash and anaemia caused by treatment included at £181.34 per rash event and £5,017.57 per anaemia event.
Costs associated with monitoring	All treatment regimens have the same weekly monitoring costs; costs are applied throughout the duration of the treatment.	DCV+SOF does not incur monitoring costs.
Probabilistic sensitivity analysis		
Wide range of parameter inputs	Deterministic: analysis on the mean parameter values.	Probabilistic: analysis ran a large number of times with sampling of the distributions of parameter values.
Threshold analysis on SVR rate		
SVR rate	SVR obtained from the relevant clinical trials.	The lowest SVR that DCV-containing regimens would have to attain to achieve cost-effectiveness at a threshold of £20,000 per QALY compared to individual comparators using pairwise analysis.
HRQoL: health-related quality of life. SVR: sustained virologic response. DCV: daclatasvir. SOF: sofosbuvir. RBV: ribavirin. QALY: quality-adjusted life year.		

5.2.9 Model validation and face validity check

The manufacturer validated the cost-effectiveness model by commissioning its independent review by an external agency for programming errors. Face validity was assessed by:

- Comparing the model structure and its key assumptions with those in the cost-effectiveness studies identified in the systematic review by Townsend et al.[48]
- Comparing the costs, QALYs, incremental cost-effectiveness ratios (ICERs) and events predicted by the model with those predicted in eight cost-effectiveness studies identified in the systematic review by Townsend et al.
- Comparing the all-cause mortality and liver-related mortality predicted by the model with those reported in two UK studies.[103 104]The model produced ranges of liver-related mortality incidence of 0.02-0.041 and 0.061-0.095 compared to observed ranges of 0.011-0.031 and 0.037-0.071 in each study.

5.2.10 Modifications to the model in response to the ERG's points for clarification

In its response to the points for the clarification, the manufacturer submitted a new cost-effectiveness model with some of the corrections suggested by the ERG. The corrections implemented include:

- Incorporate in the model the facility to break down costs into treatment costs, monitoring costs and complication costs.
- Incorporate an age-related decline in HRQoL based on UK population norms.
- Apply the Kanwal et al genotype 3 transition rate multipliers to the transition rates calculated for genotype 1 since the Kanwal et al study reports the multiplier for progression to cirrhosis and HCC for genotype 3 vs genotype 1.[70]
- Incorporate in the model the functionality to run the cost-effectiveness analysis for the F0-F2 subgroup population. The manufacturer conducted the F0-F2 analysis only where the DCV-based regimens were estimated to be cost-effective in the F0-F4 population since cost-effectiveness typically improves with disease severity.

The manufacturer showed in Figure 11 (p73 of the manufacturer's response to the ERG's points for clarification) that the implemented corrections made little difference to the results.

Some of the corrections suggested by the ERG were not implemented, namely:

- Correction of the PSA to exclude baseline characteristics as probabilistic inputs. The manufacturer responded that baseline characteristics are not sampled when the model is run deterministically.
- Incorporate in the model the functionality to evaluate multiple treatment comparisons simultaneously and to calculate fully incremental comparisons for each subgroup population. The manufacturer responded that the model does not generate an automated fully incremental analysis but that this can be calculated from the model outputs.

- Incorporate in the model the functionality to run all the relevant comparators as stated in the MS. The manufacturer commented that lack of data on comparative effectiveness precluded the incorporation of all relevant comparator regimens.
- Incorporate in the model the functionality to compare PR as first line followed by second-line direct antiviral agent to first-line direct antiviral agents in treatment naïve patients. The manufacturer commented that assessing optimal treatment sequencing was outside the scope of this technology appraisal and would constitute a major piece of research.

5.2.11 Cost effectiveness results

5.2.11.1 Base-case results

Table 39 summarises the deterministic cost-effectiveness results for all F3 and F4 subpopulations by showing the cost-effective regimen at a threshold of £20,000-£30,000 per QALY. Full incremental results are presented in Tables 40-41. All results were obtained from the manufacturer's response to the ERG's points for clarification. The DCV-containing regimens are cost-effective in the following subpopulations:

- F3 subpopulation (patients with significant fibrosis)
    - DCV+SOF in genotype 1 treatment naïve, treatment experienced or interferon ineligible or intolerant
    - DCV+SOF in genotype 3 interferon ineligible or intolerant
    - DCV+SOF in genotype 4 treatment experienced or interferon ineligible or intolerant.
- F4 subpopulation (cirrhotic)
    - DCV+SOF in genotype 1 treatment experienced
    - DCV+SOF in genotype 3 interferon ineligible or intolerant
    - DCV+PR in genotype 4 treatment experienced
    - DCV+SOF in genotype 4 interferon ineligible or intolerant

Table 39 Cost-effective treatment regimen at £20-30,000 per QALY gained for F3 and F4 subpopulations

Genotype	Treatment status	F3	F4
1	Treatment naïve	SOF+PR ***(DCV+SOF at £30,000)***	SOF+PR
	Treatment experienced	**DCV+SOF**	**DCV+SOF**
	Interferon ineligible or intolerant	**DCV+SOF**	SMV+SOF
3	Treatment naïve	PR	SOF+RBV
	Treatment experienced	SOF+PR	SOF+PR
	Interferon ineligible or intolerant	**DCV+SOF**	**DCV+SOF**

4	Treatment naïve	SOF+PR	SMV+PR
	Treatment experienced	**DCV+SOF**	**DCV+PR**
	Interferon ineligible or intolerant	**DCV+SOF**	**DCV+SOF**

BOC: boceprevir; DCV: daclatasvir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir.

Cost-effective DCV-containing regimens are highlighted in bold.

Table 40 Cost-effectiveness results for the F3 subpopulations (adapted from Tables 36-38 p97-99 from the manufacturer's response to the ERG's points for clarification)

Population	Treatment regimen	Total cost (£)	Total QALYs	Incremental results		
				Costs (£)	QALY	ICER (£)
Genotype 1						
Treatment-naive	PR	32,183	9.8	-	-	-
	No treatment	40,394	8.1	-	-	-
	SMV+PR	41,051	11.1	8,867	1.3	6,945
	TVR+PR	44,991	10.7	-	-	-
	SOF+PR	**46,314**	**11.7**	**5,264**	**0.6**	**8,692**
	BOC+PR	49,470	9.9	-	-	-
	DCV+SOF	**63,156**	**12.4**	**16,842**	**0.7**	**25,454**
Treatment-experienced	No treatment	40,394	8.09	-	-	-
	DCV+SOF	**61,188**	**12.62**	**20,794**	**4.5**	**4,587**
Interferon-ineligible /intolerant	No treatment	40,394	8.1	-	-	-
	DCV+SOF	**61,188**	**12.6**	**20,794**	**4.5**	**4,587**
	SMV+SOF	61,883	12.3	-	-	-
	SOF+RBV	82,390	11.1	-	-	-
Genotype 3						
Treatment-naive	**PR**	**16952**	**11.13**	-	-	-
	No treatment	40654	7.61	-	-	-
	DCV+SOF	69983	11.51	-	-	-
	SOF+RBV	75094	12.26	58,142	1.1	51,247
Treatment-experienced	PR	29,246	10.18	-	-	-
	No treatment	40,654	7.61	-	-	-
	SOF+PR	**43,552**	**11.76**	**14,306**	**1.6**	**9,043**
	DCV+SOF	72,518	11.18	-	-	-
	SOF+RBV	78,462	11.84	34,909	0.1	439,757
Interferon-ineligible /intolerant	No treatment	40,654	7.61	-	-	-
	DCV+SOF	**69,983**	**11.51**	**29,329**	**3.9**	**7,523**
	SOF+RBV	85,244	10.99	-	-	-
Genotype 4						
Treatment-naive	PR	31,922	9.79	-	-	-
	SMV+PR	35,826	11.72	3,904	1.9	2,016
	SOF+PR	**38,760**	**12.59**	**2,934**	**0.9**	**3,375**
	No treatment	42,556	7.65	-	-	-
	DCV+PR	59,257	11.57	-	-	-
	DCV+SOF	61,188	12.62	22,428	0.0	868,019
Treatment-experienced	No treatment	£42,556	7.65	-	-	-
	PR	£45,481	8.38	-	-	-
	SMV+PR	£56,820	9.74	-	-	-

Population	Treatment regimen	Total cost (£)	Total QALYs	Incremental results		
				Costs (£)	QALY	ICER (£)
	DCV+PR	£59,257	11.57	-	-	-
	DCV+SOF	**£61,188**	**12.62**	**1,931**	**5.0**	**3,750**
Interferon-ineligible /intolerant	No treatment	42,556	7.65	-	-	-
	DCV+SOF	**61,188**	**12.62**	**18,632**	**5.0**	**3,750**
[(1)]SOF+PR was not presented in the fully incremental comparison in Table 37 but was included in the pairwise comparison in Table 30, hence it is included here.						

Table 41 Cost-effectiveness results for the F4 subpopulations (adapted from Tables 39-41 p100-102 from the manufacturer's response to the ERG's points for clarification)

Population	Treatment regimen	Total cost (£)	Total QALYs	Incremental results		
				Costs (£)	QALY	ICER (£)
Genotype 1						
Treatment-naive	PR	36,091	8.9	-	-	-
	No treatment	46,723	6.6	-	-	-
	SMV+PR	47,209	10.2	-	-	-
	TVR+PR	47,625	10.2	-	-	-
	SOF+PR	**48,237**	**11.4**	**12,146**	**2.4**	**4,964**
	BOC+PR	49,405	9.6	-	-	-
	DCV+SOF	121,215	12.6	72,977	1.2	61,484
Treatment-experienced	No treatment	46,723	6.6	-	-	-
	DCV+SOF	**121,215**	**12.6**	**74,492**	**6.0**	**12,443**
Interferon-ineligible /intolerant	No treatment	46,723	6.6	-	-	-
	SMV+SOF	**62,722**	**12.2**	**15,999**	**5.6**	**2,857**
	DCV+SOF	98,849	8.7	-	-	-
	SOF+RBV	121,215	12.6	58,493	0.4	151,547
Genotype 3						
Treatment-naive	PR	37,041	8.1	-	-	-
	No treatment	45,262	6.3	-	-	-
	SOF+RBV	**76,317**	**12.1**	**39,276**	**3.9**	**9,957**
	DCV+SOF+RBV[(1)]	119,111	12.5	42,794	0.5	89,126
Treatment-experienced	PR	31,595	9.5	-	-	-
	SOF+PR	**44,676**	**11.5**	**13,081**	**2.0**	**6,543**
	No treatment	45,262	6.3	-	-	-
	SOF+RBV	90,464	10.0	-	-	-
	DCV+SOF+RBV[(1)]	119,111	12.5	74,435	1.0	72,662
Interferon-ineligible /intolerant	No treatment	45,262	6.3	-	-	-
	SOF+RBV	107,594	7.6	-	-	-
	DCV+SOF+RBV[(1)]	**119,111**	**12.5**	**73,849**	**6.3**	**11,781**
Genotype 4						
Treatment-naive	**SMV+PR**	**36,890**	**11.51**	**-**	**-**	**-**
	PR	43,457	7.97	-	-	-
	No treatment	46,723	6.57	-	-	-
	DCV+PR	61,750	11.12	-	-	-
	SOF+PR	61,816	9.55	-	-	-
	DCV+SOF	121,215	12.55	84,324	1.0	80,548
	No treatment	46,723	6.57	-	-	-

Population	Treatment regimen	Total cost (£)	Total QALYs	Incremental results		
				Costs (£)	QALY	ICER (£)
Treatment-experienced	PR	49,012	7.46	2,289	0.9	2,557
	SMV+PR	59,340	9.10	-	-	-
	DCV+PR	**61,750**	**11.12**	**12,739**	**3.7**	**3,481**
	DCV+SOF	121,215	12.55	59,464	1.4	41,522
Interferon-ineligible /intolerant	No treatment	46,723	6.57	-	-	-
	DCV+SOF	**121,215**	**12.55**	**74,492**	**6.0**	**12,443**

BOC: boceprevir; DCV: daclatasvir; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; PI: protease inhibitor; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir.
(1) Table 40 p101 presented the DCV-containing regimen as DCV+SOF but it should ready DCV+SOF+RBV as per Table 33 p81.

The manufacturer also presented results for the F0-F4 patient population, these are presented in Tables 43-45 (p142-144) of the manufacturer response to the ERG's points for clarification. The results are not presented in the main body of text because the ERG considered that it is inappropriate to evaluate the cost-effectiveness of DCV in the entire patient population given the heterogeneity between the different subgroups.

In response to the ERG's points for clarification, the manufacturer presented results for the F0-F2 subgroup population. The analyses were incomplete for some subpopulations as the manufacturer only included comparators against which DCV-containing regimens were cost-effective based on pairwise comparisons in the F0-F4 population. Table 42 shows the cost-effectiveness results presented by the manufacturer. The results presented by the manufacturer for the F0-F2 subpopulation are reported in more detail in the manufacturer's response to the ERG's points for clarification (Tables 46-48 p108-110). DCV+SOF is the cost-effective regimen at a threshold of £20,000 per QALY for the F0-F2 subpopulation who are interferon ineligible or intolerant irrespective of genotype and for genotype 1 treatment experienced patients. DCV+SOF is the cost-effective regimen for genotype 4 treatment experienced patients at a threshold of £30,000 per QALY gained.

Table 42 Cost-effectiveness results for the F0-F2 subpopulations (calculated from Tables 46-48 p108-110 from the manufacturer's response to the ERG's points for clarification)

Population	Treatment regimen	Total cost (£)	Total QALYs	Incremental results		
				Costs (£)	QALY	ICER (£)
Genotype 1						
Treatment-experienced	No treatment	£19,984	11.49			
	DCV+SOF	**£60,610**	**14.12**	**£40,626**	**2.64**	**£15,398**
Interferon-ineligible /intolerant	No treatment	£19,984	11.49	-	-	-
	SMV+SOF	£59,937	13.93	-	-	-
	DCV+SOF	**£60,610**	**14.12**	**40,626**	**2.64**	**£15,398**
	SOF+RBV	£75,386	13.25	-	-	-
Genotype 3						
Interferon-ineligible /intolerant	No treatment	£23,368	10.92	-	-	-
	DCV+SOF	**£60,976**	**14.07**	**37,609**	**3.15**	**11,930**
	SOF+RBV	£79,320	13.07	-	-	-

Population	Treatment regimen	Total cost (£)	Total QALYs	Incremental results		
				Costs (£)	QALY	ICER (£)
Genotype 4						
Treatment-experienced	PR	£19,571	12.52	-	-	-
	No treatment	£20,463	11.41	-	-	-
	SMV+PR	£41,613	12.86	-	-	-
	DCV+PR	£54,551	13.52	-	-	-
	DCV+SOF	**£60,610**	**14.12**	**41,039**	**1.60**	**25,580**
Interferon-ineligible /intolerant	No treatment	£20,463	11.41	-	-	-
	DCV+SOF	**£60,610**	**14.12**	**40,146**	**2.72**	**14,774**

5.2.11.1 Sensitivity analysis results

In the original submission, the manufacturer presented results for the PSA, scenario, threshold and univariate sensitivity analyses for the analyses described in Section 5.2.8 Sensitivity Analysis. All results were presented as pairwise comparisons between the DCV-containing regimen indicated for the subpopulation and each included comparator. The results can be found in Tables 113-136 p198-220 in the MS. The ERG does not present these results because they refer to the model without the corrections incorporated in the manufacturer's response to the points of clarification and because the presentation of cost-effectiveness ratios for pairwise comparisons rather than a full incremental analysis is not appropriate.

In response to the ERG's points for clarification, the manufacturer updated the PSA results based on the updated model with the corrections discussed in Section 5.2.10 Modifications to the model in response to the ERG's points for clarification. The manufacturer presented scatterplots and cost-effectiveness curves for pairwise comparisons between DCV-containing regimens and each included comparator (Figures 13-28 p83-91 of the manufacturer's response to the ERG's points for clarification). The probability that the DCV-containing regimen is cost-effective at a threshold of £20,000 per QALY gained was also presented for each pairwise comparison for the F3 and F4 subgroups (Table 35 p92 of the manufacturer's response to the ERG's points for clarification). In addition, the manufacturer presented a threshold analysis on the lowest SVR that DCV-containing regimens would need to achieve to be cost-effective for each pairwise comparison for all subpopulations (Figures 1 p10 and Table 6 p12). The ERG does not present these results because they refer to pairwise comparisons rather than a full incremental analysis.

The manufacturer concluded that the results were robust to the changes explored in the sensitivity analysis. Specifically, the DCV-containing regimens which were cost-effective in the base-case remained cost-effective in the sensitivity analysis. Results were sensitive to the time horizon (less favourable cost-effectiveness for shorter time horizons), age of the patients' cohort (more favourable cost-effectiveness for younger patients) and discount rate (more favourable cost-effectiveness for 0% discount rate).

5.3 ERG's critique of the manufacturer's submitted economic evaluation

5.3.1 The manufacturer's economic evaluation compared with the NICE reference case checklist

Table 43 summarises the economic submission and the ERG's assessment of whether the *de novo* evaluation meets NICE's reference case and other methodological recommendations.

Table 43 The NICE reference case checklist

Attribute	Reference Case	Included in MS	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Comparator(s)	Alternative therapies in the NHS, including those currently regarded as current best practice	Partially	The comparators mostly agree with those included in the NICE scope.[47] However, there were comparisons that were excluded due to lack of comparative effectiveness data: • SOF+PR in genotypes 1and 4 treatment experienced. • SOF+PR in genotype 3 treatment naïve F3, F4. • SOF+RBV and SMV+SOF in genotype 4 interferon ineligible or intolerant. A watchful waiting strategy was included in the NICE scope but it was not included as a comparator. The F0-F2 analysis excluded comparators based on a pairwise assessment of cost-effectiveness in the F0-F4 population. Treatment sequencing was not explored in the model. This was not specified in the NICE scope but is relevant to any treatment being appraised for both first and second line use.
Type of economic evaluation	Cost-effectiveness analysis with full incremental analysis	Partially	The manufacturer conducted a cost-effectiveness analysis. Full incremental results were presented in the manufacturer's response to the ERG's points for clarification for the F3 and F4 sub-populations. Results for the F0-F2 sub-population, F0-F4 population, and sensitivity analyses were presented as pairwise comparisons.
Perspective - costs	NHS and Personal Social Services	Yes	NHS only.
Perspective - benefits	All health effects on individuals	Partially	Anticipated health effects of treatment on treated individuals are captured. Health benefits to other non-treated patients that result from reduced onward transmission of Hepatitis C are not captured in the main model though were quantified to some extent separately.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	The economic model followed a life-time horizon (80 years).
Synthesis of evidence on outcomes	Systematic review	Partially	Data for DCV-containing regimens were obtained from trials identified by a systematic review. It is unclear how the studies for comparators were identified. No evidence synthesis was conducted in the F0-F2, F3 or F4 subpopulations. Response rates were obtained from individual trial arms or subgroup analyses of individual trial arms.
Outcome measure	QALYs	Yes	Each model state was associated with a specific HRQoL weight; achieving SVR is associated with a higher HRQoL. HRQoL decrements were applied for the time in treatment to reflect the impact of adverse events.

Health states for QALY measurement	Described using a standardised and validated instrument	Yes	HRQoL weights for the health states were obtained from published studies [49] using EQ-5D reported directly by patients. Most of the HRQoL decrements for the comparator regimens were obtained from published studies using EQ-5D reported directly by patients with the exception of SOF+PR, SOF+RBV and DCV-containing regimens.[63 81 91 92] The HRQoL decrement for SOF+PR was obtained from a study which mapped SF-36 to EQ-5D; the decrements for SOF+RBV and for DCV-containing regimens were calculated by the manufacturer by multiplying the incidence rate of a selection of adverse events by the HRQoL decrement for each adverse event obtained from a time trade-off study conducted by the manufacturer in the UK.
Benefit valuation	Time Trade Off or Standard Gamble	Yes	The EQ-5D tariff used in the source studies for HRQoL weights was estimated with time trade-off. Non-EQ-5D data was also used the time trade-off method to value health state descriptions.
Source of preference data	Representative sample of the public	Yes	The EQ-5D tariff used in the source studies for HRQoL weights was estimated from a representative sample of the UK public. A sample from the UK public was also used for the time trade-off study conducted by the manufacturer to value adverse event health states.
Discount rate	3.5% for costs and benefits	Yes	Alternative discount rates (0% and 6%) were tested in the scenario analysis.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	No equity weighting was used.
Sensitivity analysis	Probabilistic sensitivity analysis	Partially	A probabilistic sensitivity analysis was conducted but the base-case results are based on the deterministic analysis. The probabilistic results are reported as pairwise comparisons between the relevant DCV-containing regimen and each of the included comparators. Expected costs and QALYs were not presented for the probabilistic analysis with the exception of a graphical presentation in the manufacturer response to the ERG points for clarification.
ERG: evidence review group. HRQoL: health-related quality of life. QALY: quality-adjusted life year. DCV: Daclatasvir. SOF: Sofobuvir. PR: pegylated interferon with ribavirin.			

5.3.2 Model structure

The model structure is generally appropriate and is similar to the model structures used in previous hepatitis C appraisals. Three concerns regarding the model are:

- The health states used to model HCV chronic progression;
- The assumption of zero disease progression amongst patients with SVR;
- Modelling of long term treatment pathways; and
- No incorporation of relapse and reinfection in treated patients.

5.3.2.1 Health states used to model HCV chronic progression

The use of METAVIR fibrosis scores is clinically appropriate although differs from a number of previous models including those used in NICE appraisals.[49 50 63 91 92] The primary concern regarding use of health states defined by METAVIR fibrosis scores is the extent to which the available literature describing SVR response, disease progression, costs and utilities relates to this

description of disease severity. The manufacturer acknowledges that the clinical trials providing data on SVR for the comparators do not typically stratify SVRs by METAVIR score but instead tend to stratify according to presence of cirrhosis. Where SVRs are presented by METAVIR these tend to be for the group F3-F4 rather than for the F3 and F4 groups separately. Therefore, and as described in Section 4.4.2, the manufacturer often had to extrapolate estimates from other patient groups in order to model outcomes in the F3 subpopulation. Similarly, health state cost and utility data used in the model were estimated for patients with mild (ISHAK fibrosis 0-2), moderate (ISHAK fibrosis 3-5) and severe disease (ISHAK fibrosis 6).[49] These were extrapolated to the health states in the manufacturers model by assuming that mild patients are equivalent to those with METAVIR score F0-1, moderate patients to those with METAVIR score F2-3 and severe patients to those with METAVIR score F4. Only the disease progression parameters were available by METAVIR score. Nonetheless, had the manufacturer chosen the standard model structure dividing chronic hepatitis C by severity (mild, moderate and cirrhotic disease), other relevant data could have been used instead. The ERG therefore has a general concern that the model structure may have resulted in sub-optimal use or exclusion of relevant data.

5.3.2.2 Assumption of zero progression following SVR

The manufacturer does not provide evidence to support the assumption that patients with SVR experience no disease progression. Evidence suggests that SVR patients experience disease progression albeit at a much lower rate than patients without SVR. The submission for SMV, for example,[63] used data from Cardoso to estimate the probability of progression from compensated cirrhosis to HCC.[105] The Cardoso study suggests that, amongst those with bridging fibrosis or cirrhosis, SVR reduced risk of HCC by an hazard ratio of 0.23 (95% CI: 0.09-0.55). Other studies in patients with moderate to severe disease but without decompensated cirrhosis report risk reductions of 0.14-0.39.[106-110] Studies reporting on the impact of SVR status on decompensated cirrhosis indicated risk reductions of 0-0.09.[106-110] Using the manufacturer's estimates of the probability of progression to HCC and decompensated cirrhosis (1.4% and 3.9% per annum respectively) therefore suggests that the risk of these events in patients with SVR may be in the range and 0.20-0.55% and 0-0.35% respectively. These clearly exceed general population risks of HCC (5-year age band incidence does not exceed 0.05% in any age or gender strata).[111]

5.3.2.3 Modelling long term treatment pathways

The model considers only the cost-effectiveness of alternative single courses of treatment used immediately. In practice, patients who do not achieve SVR may be re-treated and patients who receive no treatment may receive treatment later down the line once their liver disease worsens. This issue is discussed in more detail in 5.3.4.1 Comparators included by the manufacturer.

5.3.2.4 No incorporation of relapse and reinfection in treated patients

The model assumes that patients with SVR do not get re-infected nor relapse. This is likely to overestimate the benefits of regimens with high SVR rates, such as DCV+SOF. However, the impact on the results will depend on the extent to which the re-infection and relapse rates in SVR patients differ from the infection rates in the general population.

5.3.3 Population

The populations considered by the manufacturer generally capture key distinct subpopulations who differ with respect to available treatments and outcomes. The exclusion of patients co-infected with HIV and of those pre- or post-liver transplant from this appraisal appears reasonable given the imminent trial results.

The ERG has a number of concerns with the manufacturers approach:

- The absence of full analyses for patients with milder disease;
- The scope of the previously treated subgroup in genotype 1;
- Heterogeneity amongst the previously treated sub-population; and
- Heterogeneity amongst the interferon ineligible or intolerant subgroup.

5.3.3.1 Analyses for the milder sub-population

The ERG believes that the analysis of the F0-F4 population is not informative for decision making given the differences in licensed and NICE recommended comparators, details of licensed regimens (such as licensed treatment duration), SVR rates and long term prognosis between those with milder disease (METAVIR score F0-F2), those with significant fibrosis (METAVIR score F3) and those with compensated cirrhosis (METAVIR score F4). Therefore, as part of the points for clarification, the ERG requested analyses for the F0-F2 subpopulation. These were provided by the manufacturer for pairwise comparisons in which the DCV-containing regimen was found to be cost-effective in the overall (F0-F4) population. This resulted in comparators being omitted for the majority of subgroups. Very little information was provided on the SVR rates for the comparators that were included, and very few of the estimates seem to have been taken from F0-F2 subgroup analyses. Furthermore, watchful waiting (no treatment at baseline with further treatment considered at disease progression), which was included in the NICE scope, was not included in the manufacturer's submission. The ERG considers that omission of watchful waiting renders the F0-F2 analysis incomplete, as waiting to treat these patients at a more severe disease stage (F3 or F4) is a relevant treatment alternative.

5.3.3.2 Scope of previously treated subpopulation

The treatment experienced subpopulation reflects current first line treatment practice (with genotype 1 patients receiving a protease inhibitor in combination with PR and other genotypes receiving PR). There will however be a group of prevalent genotype 1 patients treated with PR historically for whom

no cost-effectiveness evidence is presented. The manufacturer indicates that these patients are expected to represent a very small subgroup of patients. The ERG clinical advisors estimate that approximately half the prevalent treatment experienced genotype 1 population will have failed PR but not a protease inhibitor.

5.3.3.3 Heterogeneity amongst previously treated subpopulation

The manufacturer considers all treatment failures as a single group. Patients who fail in different ways (initial null response, partial response or relapse following response) are known to experience different SVRs on some therapies and for some therapies these subpopulations are indicated for different treatment durations. An approach that considered these patients' as distinct subpopulations may therefore result in different decisions regarding the cost-effectiveness of different treatments than the approach taken by the manufacturer that pools all treatment failures.

5.3.4 Interventions and comparators

The comparators considered by the manufacturer as relevant are in line with the appraisal scope and the licensed indications for the treatments. The ERG has a number of concerns relating to the choice and modelling of comparators:

- Omission of relevant licensed comparators on the basis of a lack of relevant data (and inclusion of comparators not recommended by NICE);
- Treatment durations used in the analysis;
- The modelling of early stopping rules; and
- The modelling of generic comparators.

5.3.4.1 Comparators included by the manufacturer

The ERG has major concerns regarding the omission of relevant licensed comparators on the basis of a lack of relevant data. During the preparation of this report, NICE guidance was issued on SMV+PR and SOF-containing regimens.[23 25]The NICE recommendations on SMV+SOF were postponed since more data is expected in the near future. The following comparators were omitted from the MS but have been recommended by NICE or recommendations are pending in the case of SMV+SOF (all were included in the final scope for daclatasvir):

- SOF+PR in genotype 1 treatment experienced patients F3
- SOF+PR in genotype 1 treatment experienced patients F4
- SOF+PR in genotype 3 treatment naïve F4
- SOF+PR in genotype 4 treatment experienced F4
- SMV+SOF for genotype 4 interferon ineligible or intolerant F3
- SMV+SOF for genotype 4 interferon ineligible or intolerant F4

The ERG therefore considers these comparators as relevant to the current appraisal and should be included in any cost-effectiveness analyses.

The following comparators were included in the MS but have not subsequently been recommended by NICE:

- SOF+PR in genotype 4 treatment naive F3
- SOF+RBV in genotype 1 interferon-ineligible or intolerant patients F3
- SOF+RBV in genotype 1 interferon-ineligible or intolerant patients F4
- SOF+RBV in genotype 3 treatment naïve F3
- SOF+RBV in genotype 3 treatment naïve F4
- SOF+RBV in genotype 3 treatment experienced F3
- SOF+RBV in genotype 3 treatment experienced F4
- SOF+RBV in genotype 3 interferon-ineligible or intolerant patients F3

The ERG therefore considers that these comparators are not relevant to the current appraisal.

The exclusion of PR and the protease inhibitors in combination with PR (i.e. BOC+PR, TVR+PR and SMV+PR) for patients whom have already received BOC+PR or TVR+PR by the manufacturer is in line with clinical guidelines and was confirmed as reflecting UK practice by the clinical advisors to the ERG.

Omission of watchful waiting and treatment sequencing

The ERG has concerns that one comparator mentioned in the scope, watchful waiting, and other possible treatment pathways, such as treatment sequences, have not been evaluated.

Watchful waiting comprises an initial period of no active treatment followed by treatment at a later date dependent on the occurrence of biological changes. Watchful waiting is likely to be particularly relevant in this appraisal for F0-F2 and F3 patients where treatment initiation at more severe disease stages such as F3 or F4 are relevant treatment options.

In addition, as DCV-based regimens are being considered for use in treatment experienced (or "second-line") patients a relevant question is whether treatment should be used in treatment naïve ("first line") patients or whether it should be reserved for use in treatment failures.

The ERG considers that omission of both watchful waiting and treatment sequencing are likely to reduce the reliability of any decisions based on the manufacturer's model. This is explored further in the ERG exploratory analyses (see Section 6.3.4 ERG's exploratory analysis).

5.3.4.2 Durations of treatment

DCV+SOF was assumed to be used for a duration of 12 weeks for non-cirrhotic patients and 24 weeks for cirrhotic regardless of other patient's characteristics. DCV's marketing authorisation allows for an extension from 12 to 24 weeks in non-cirrhotic patients with genotype 1 who have previously received a protease inhibitor and a reduction from 24 to 12 weeks in treatment naïve cirrhotic patients with characteristics associated with good prognosis (e.g. IL28B CC genotype and /or low baseline viral load). These different regimens are explored in the sensitivity analyses conducted by the manufacturer and will be re-analysed in the ERG's sensitivity analysis (see Section 6.3.2 Scenario 2: Alternative treatment durations).

SOF+PR is assumed to be given for 12 weeks in all populations. SOF's marketing authorisation states that consideration should be given to extending the duration of therapy to 24 weeks in patients with characteristics that are predictive of low response to interferon-based therapies e.g. advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype, or prior null response to PR. The cost of this comparator may therefore be underestimated in these subpopulations. This is explored in the ERG's sensitivity analysis (see Section 6.3.2 Scenario 2: Alternative treatment durations).

The PR component of SMV+PR is assumed to be given for 48 weeks in previously treated genotype 4 patients. The license states that 48 weeks of treatment should be given to partial and null responders but that prior relapse patients should receive 24 weeks of treatment. The cost of this comparator may therefore be overestimated in this subpopulation. The ERG therefore explores this in a sensitivity analysis (see Section 6.3.2 Scenario 2: Alternative treatment durations).

5.3.4.3 Early stopping rules

The ERG has a number of concerns with the modelling of early stopping rules. Firstly, it is unclear why ADVANCE and not also the ILLUMINATE study was used to inform the eRVR rate for TVR+PR in F3 patients.[13 56] Patients in ILLUMINATE experienced a slightly higher rate of eRVR (65%)[56] than those in ADVANCE (58%)[13]. Hence, the use of the ADVANCE study may therefore marginally overestimate the cost of TVR+PR. Moreover, there is a greater source of uncertainty in the use of eRVR rates from the overall population of individual trials to model outcomes in patients who are F3 or F4. It seems likely that the eRVR rates in F3 or F4 patients would be lower than those in the broader trial populations, and that the costs of BOC+PR, TVR+PR and DCV+PR may therefore be underestimated. However, the ERG is not aware of any data on which to base estimates for the F3 or F4 subgroup.

5.3.4.4 RBV and IFN products and dosing

The manufacturer assumes that all patients receiving PR receive Pegasys® and Rebetol®. Other formulations of PR are available with different costs (see Section 5.3.8.4 Acquisition costs of

peginterferon and RBV for a discussion). The dose of RBV is assumed to be fixed across patients in the model. Although dosing varies between 800mg and 1,400mg depending on patient weight, the use of 1,000mg dosing by the manufacturer seems to be a reasonable approximation given the relatively low cost of RBV (£67 per week).

Patients receiving PR are assumed to receive 48 weeks of treatment in all subpopulations with the exception of genotype 3 treatment naïve patients. Shorter durations of PR are allowed for within the SPC for patients with certain characteristics who experience early response. However, the advisors to the ERG indicated that, for the F3 and F4 subpopulations, shorter durations would only be likely in genotype 4 treatment naïve patients. A duration of 24 weeks could be administered in this subpopulation if early response is observed (HCV RNA undetectable at week 4 and 24). A relatively low proportion of patients experienced eRVR (HCV RNA undetectable at weeks 4 and 12, 12%)[112] in the 042 study used to inform SVR rates for PR in this subgroup. In addition, the SVR rates used in the model reflect outcomes following 48 weeks of treatment. The ERG therefore considers that inclusion of a PR comparator with early stopping rules would be unlikely to have a marked impact on the cost-effectiveness results.

RBV may be given alongside SMV+SOF on the basis of an individual assessment of clinical need and alongside DCV+SOF for patients with genotype 1 and 4 with compensated cirrhosis. The ERG do not expect exclusion of RBV costs in these patient groups to have a major impact on the results of the model, Therefore, this is not explored further. It should be noted that the data for DCV+SOF in genotype 1 and 4 patients includes some patients who received RBV (although this was not found to impact on outcomes). The data for SMV+SOF was restricted to patients who did not receive RBV.

5.3.5 Perspective, time horizon and discounting

The ERG considered the perspective, time horizon and discounting to be appropriate.

5.3.6 Treatment effectiveness and extrapolation

5.3.6.1 SVR rates

The manufacturer's approach to estimating SVR rates for the model is subject to a number of forms of bias. Firstly, it is unclear whether a systematic review underpinned the selection of trials for the comparators. Therefore, whether the identified list of trials is complete and representative of the totality of the available evidence. Secondly, all comparisons of trial arms in the F0-F2, F3 and F4 populations are at high risk of bias as they were not randomised and are not adjusted for imbalances in baseline characteristics. This is of particular concern since trial data was rarely available for the specific subpopulation of interest. In many cases, trial data for DCV and for comparators was extrapolated across genotypes, between patients with different METAVIR scores and between patients with different treatment histories. In addition, the necessary extrapolations often differed

according to the comparator study, increasing further the potential for bias. The difference in SVR rates across comparators is therefore subject to high levels of uncertainty. Ideally, efforts would have been made to compare the baseline characteristics of the patients informing each SVR rate within each subpopulation in order to assess the potential for bias. However, this could not be done in any comprehensive way as baseline characteristics are not generally reported for trial subpopulations (e.g. for the F3-F4 subgroup of a trial). Efforts to adjust the observed SVR rates would also have been limited by the reporting of baseline characteristics and lack of access to individual patient data.

The ERG reviewed the manufacturer's base case inputs for each comparator and subpopulation. The ERG considers that the manufacturer has broadly selected appropriate SVR rates given the available data with a number of exceptions. These issues are discussed in detail in Section 4.4.2 and are summarised here:

DCV+SOF in genotype 1 treatment naïve F3 (non-cirrhotic) patients: the source of the 95% SVR presented by the manufacturer for this subgroup is unclear and appears to have been subject to some sort of adjustment from the raw data.

SOF+RBV in genotype 3 ineligible or intolerant F4 (cirrhotic) patients: The data used by the manufacturer was taken from the POSITRON study. The POSITRON data used was from the relevant population, however the 12 week treatment duration does not reflect the licensed duration of 24 weeks. This is likely to underestimate the SVR rate in this subgroup since treatment duration has been shown to be a strong predictor of outcomes for patients receiving SOF+RBV. Data from a treatment naïve cirrhotic subgroup of the VALENCE study, which administered treatment for 24 weeks, are likely to be more appropriate. The VALENCE study did not interferon intolerant or ineligible patients. However, it provides SVR rates for treatment naïve patients for the same treatment duration as the product licence. Since the SVR rate for DCV+SOF in interferon ineligible or intolerant patients was extrapolated from treatment naïve patients, extrapolating the VALENCE data from treatment naïve to interferon ineligible or intolerant is likely to be more appropriate than using POSITRON.

SOF+PR in genotype 4 treatment naïve F4 (cirrhotic) patients: the manufacturer uses data from NEUTRINO, which provided results for cirrhotic treatment naïve patients with genotypes 4-6. However, the ERG was concerned that, since this subpopulation comprised only two patients, the results may be unreliable. A wider subpopulation including patients with genotypes 1, 4, 5 and 6 who are cirrhotic and treatment naïve may be more robust.

A number of other areas of uncertainty were identified. Firstly, in F4 (cirrhotic) genotype 3 patients, the manufacturer used an SVR rate of 100% from the AI444-040 trial for both treatment naïve and treatment experienced patients. This data appears to have been selected by the manufacturer on the

basis that the 24 week duration reflects the license more closely than the 12 week duration observed in ALLY-3. However AI444-040 contains no genotype 3 treatment experienced patients and only two genotype 3 patients with METAVIR score F4. The ALLY-3 data more closely reflects the population of interest and includes a larger sample of patients. For SOF+PR in genotype 1 treatment naïve F3 patients, the manufacturer uses data from cirrhotic patients from the NEUTRINO trial. However, the ERG anticipates that the true response rate for this comparator in F3 patients is likely to lie between the response rate reported for cirrhotic and non-cirrhotic patients.

5.3.6.2 Treatment discontinuation

The manufacturer includes discontinuations due to a lack to adverse events in the model. The ERG has two concerns regarding the approach taken to modelling discontinuations. Firstly, discontinuations may occur for other reasons than adverse events. For example, SPCs for BOC+PR, DCV+PR, SMV+PR, TVR+PR and PR include futility rules, whereby patients receiving these drugs who fail to exhibit sufficient treatment response are discontinued. Discontinuations may also occur for other reasons such as general adherence issues. Secondly, the source of the adverse event rates presented by the manufacturer is unclear in many cases and appears to be capturing discontinuations for reasons other than adverse events. For example, the manufacturer uses discontinuations from DCV+PR and PR in genotype 4 patients of 18.3% and 38.1% respectively (from study AI444-042) whereas the clinical section reports AEs leading to discontinuation of study drugs in 3.7% and 7.1% of patients respectively. The source of the figures used is unclear and could not therefore be checked. Nonetheless, the ERG believes that, where discontinuation data is reported as having been sourced from the MAIC report, the figures relate to discontinuations due to adverse events. Where the data is reported as having been sourced from individual trials, total discontinuation rates seem to have been used. MAIC data is used in F3 genotype 1 treatment naïve patients only. Alternative discontinuation rates for this subpopulation are therefore explored as a sensitivity analysis (see Section 6.3.3 Scenario 3: Alternative discontinuation rates).

5.3.6.3 Transition probabilities

Concerns with the transition probabilities fall in to three categories:

- Whether the transitions between fibrosis stages have been based on the best available data;
- Estimation of outcomes in patients with genotype 3 and 4; and
- Whether the transitions experienced by patients following cirrhosis are reflective of the experience of current UK patients.

Data used to estimate progression between fibrosis stages

The manufacturer uses data from Thein et al. to estimate transitions between fibrosis stages.[54] Thein et al. estimated transition probabilities based on aggregate data. The methods used have been

subject to validation.[74] However, the method and validation appears to have assumed that all patients experience the average disease duration in their cohort. It is unclear whether this method performs well when disease duration varies across patients, as in the studies included by Thein. Mapping from non-METAVIR fibrosis staging methods also introduces uncertainty, as does the disaggregation of collapsed METAVIR fibrosis stages using a 50%/50% rule. In addition, the use of study level covariates to adjust for differences between studies suffers from the standard concerns with meta-regression. Specifically, relationships between trial-level characteristics and transition rates may be confounded by trial-level characteristics that were not controlled for and the power of these analyses is very limited (20 variables were investigated using 111 data points). This means that the coefficient estimates may be unreliable, and important determinants of transition rates may have been missed. Furthermore, some variables, such as country, were not explored. This may be important if countries differ in the way they diagnose and care for hepatitis C patients. Finally, the model includes disease duration as a covariate which is equivalent to using study follow-up as a covariate. This implies that either studies with longer follow-up included patients with a different prognosis or that there is some time dependency in the transition rates. The latter seems to be more likely. In any case, using baseline disease duration to inform the transition rate regressions does not seem appropriate. For these reasons, the estimates from the Thein study should be considered with caution.

UK data on disease progress estimated from individual patient data are available and do not suffer from these limitations, given the concerns with the Thein et al. study these alternative data sources are therefore explored as a sensitivity analysis (Section 6.3.5 Scenario 5: Alternative parameter inputs for the natural history of the disease).

Estimation of outcomes in patients with genotype 3 and 4

The approach and data used to inflate transition rates in genotype 3 patients seems reasonable. It is possible that other transitions (e.g. from cirrhosis to decompensated cirrhosis) would also occur more rapidly in genotype 3 patients and that the overall rate of disease progression in these genotypes may therefore be underestimated. However, the ERG is not aware of any data on this.

Patients with genotype 4 are assigned the transition probabilities associated with non-genotype 1 patients in Thein et al. Thein et al provides no information on the genotype distribution of non-genotype 1 patients. However, in the countries in which the studies in Thein were predominantly carried out (in Europe and the USA), non-genotype 1 comprises almost entirely genotype 2 and 3 patients.[113] Genotype 2 patients are at lower risk of fibrosis progression and HCC whereas genotype 3 patients are at a higher risk.[70] Outcomes in genotype 4 patients are more difficult to ascertain due to the low prevalence of this genotype in Europe and the USA. Data from Kanwal suggest no difference in progression rates between genotype 4 and genotype 1 patients. Use of

genotype 1 data in this population would therefore seem more appropriate than using the non-genotype 1 data from Thein et al. (Section 6.2.3 Issue 3: Natural history of genotype 4 patients).

Transitions following cirrhosis

There are two concerns with the data informing the transitions following compensated cirrhosis (F4). The first of these concerns is that no progression from the SVR F4 state to decompensated cirrhosis or HCC is assumed. This has been discussed in detail in Section 5.3.2.2 Assumption of zero progression following SVR, and will be explored in the ERG analysis (Section 6.2.4 Issue 4: Progression of cirrhotic patients with SVR). A second concern is that the transitions from F4 onwards may not be representative of current UK practice given the dates and locations in which the studies were carried out and the patients included in these studies (which include all patients, not just patients who failed to achieve SVR).

More recent data which are specific to patients who failed to achieve SVR are available. A study by van de Meer[109] analysed outcomes in 405 patients who had not responded to a course of interferon based-treatment received in the period 1990-2003 and whom were followed up for a median of 8.4 years. Amongst patients without SVR all-cause mortality was 26% (95% CI: 20.2-28.4%) at 10 years compared to 21% in Fattovich.[71] Although this difference appears small, it is surprising given that patients enrolled in van de Meer had less severe fibrosis (ISHAK 4-6) compared to those in the Fattovich study who were all cirrhotic (ISHAK 6). It seems quite plausible that patients without SVR are enriched for poor prognostic factors and would therefore be associated with poorer outcomes than those in Fattovich who represent an all-comers cirrhotic cohort (treatment history is not reported). The ERG therefore explore alternative sources of data on progression beyond the F4 state as a sensitivity analysis (see Section 6.3.5 Scenario 5: Alternative parameter inputs for the natural history of the disease).

The data on transplant rates and outcomes are very dated. However comparison of these data to current UK data suggests that the values used in the model are reasonable. UK data suggests that 58 patients received transplant for a hepatitis C indication in the year 2011-12 [114] and that 2,050 people were living with decompensated cirrhosis or HCC in 2010.[52] A 3% annual transplant rate may therefore be reasonable, and may even be an underestimate if some patients with disease caused by Hepatitis C are classified as having a cancer indication for transplant. The survival estimates for transplant recipients aligns with 8 year survival data reported for all first adult elective heart beating liver only transplants in patients with chronic hepatitis C in the period 1994-2005.[115]

5.3.7 Health related quality of life

The ERG considered the approach taken by the manufacturer to be generally appropriate. The mapping between METAVIR stages and severity of chronic hepatitis C was agreed as generally

appropriate by the ERG clinical advisors. The ERG considered it reasonable to assume that the HRQoL decrement associated with adverse events from treatment is experienced throughout the treatment regimen. The sources of HRQoL data were mostly appropriate and met the NICE reference case criteria with the exception of some of the HRQoL decrements (more details below).

The ERG has concerns regarding:

- The assumption that cirrhotic patients with SVR experience a greater increase in HRQoL compared with patients with mild or moderate disease;
- The assumption that the HRQoL improvement associated with achieving SVR is experienced immediately following treatment cessation;
- Using the same HRQoL for mild patients across the METAVIR stage F0-F1 and for moderate across the METAVIR score F2-F3; and
- Some of the HRQoL decrements associated with the adverse effects from treatment used in the model.

5.3.7.1 HRQoL improvement in cirrhotic patients with SVR

The ERG considered the assumption that cirrhotic patients with SVR experience a greater increase in HRQoL compared with patients with mild or moderate disease to be subject to uncertainty. In the model, cirrhotic patients with SVR experience an increase in HRQoL of 0.17 (compared to 0.06 in patients with mild disease and 0.05 in patients with moderate disease) and reach the same absolute HRQoL as patients with moderate disease (F2-F3) with SVR. This assumption was also noted as of concern in the Scottish Medicine Consortium (SMC) recommendation on DCV.[116] As a result, the manufacturer was requested by the SMC to present an analysis with a lower HRQoL improvement of 0.05. The manufacturer submissions to NICE for the comparator regimens TVR, BOC, SMV and SOF did not make this assumption. Instead, these submissions assumed the same increment in HRQoL for achieving SVR for cirrhotic patients as in mild or in moderate disease patients.[63 91 92]

A recent study by Vera-Llonch et al found that the age- and gender-adjusted mean EQ-5D was 0.04 higher in patients with SVR compared with patients without SVR.[117] This study analysed EQ-5D data from the ADVANCE trial in treatment naïve genotype 1 patients. The study included patients with and without bridging fibrosis and cirrhosis, however the analyses presented do not separately analyse the HRQoL benefits of SVR according to fibrosis severity.

The ERG considers that, although cirrhotic patients with SVR are likely to experience improvements in HRQoL, those improvements are likely to be in the same order of magnitude as those experienced by patients with moderate or mild disease. Therefore, the HRQoL improvement in cirrhotic patients

following SVR is tested in the ERG analysis (see Section 6.2.5 Issue 5: HRQoL Improvement of cirrhotic patients with SVR).

5.3.7.2 Immediate improvement in HRQoL for patients with SVR at treatment cessation

The manufacturer's model assumes that patients who achieve SVR experience the HRQoL improvement immediately at treatment cessation rather than from SVR at 24 weeks after the end of the treatment. There are two reasons to believe that there may be some delay in experiencing the benefits of SVR. At the end of treatment, patients are not yet aware of their SVR status and hence may still be anxious about their condition. Secondly, time may be required for the liver to restore its function. Therefore, the benefit of SVR may have been overestimated. Nonetheless, the overestimation of the benefit is expected to be small (as the benefit of SVR is small and the 24 week duration is short relative to the model duration). This is therefore unlikely to have an impact on the overall results.

5.3.7.3 HRQoL in F0-F1 and F2-F3 patients

The HRQoL associated with the chronic hepatitis C disease states was obtained from Wright et al assuming that mild disease is equivalent to F0-F1 and moderate disease is equivalent to F2-F3. The ERG agrees that this mapping is appropriate. However, for the F3 subgroup applying the F2-F3 HRQoL score which will reflect an average of F2 and F3 HRQoL will overestimate the true HRQoL in F3 patients. This will bias in favour of treatments with high SVRs, such as DCV-containing regimens, since the benefits remaining at F3 are exaggerated. However, this is not explored further since the ERG is not aware of alternative appropriate data sources to inform the model.

5.3.7.4 HRQoL decrement associated with adverse effects from treatment

The estimates of HRQoL decrement associated with adverse events were mostly appropriate with the exception of HRQoL decrement associated with BOC+PR and SMV+PR at 0.0671 and 0.0798 respectively. PR-containing regimens are typically associated with larger decrements in HRQoL in line with other HRQoL decrements used in this submission at 0.102-0.148. In addition, the source of HRQoL decrement for BOC+PR is unclear since the ERG was unable to find the value used in the MS (0.0671) in the quoted source.[92] However, since these decrements are applied for a short period, it is unlikely that changes will have a large impact on the results.

The method used by the manufacturer to estimate the HRQoL decrement associated with the DCV-containing regimens was considered to be reasonable. The method used assumes that the effects of adverse events are additive; that adverse events influence HRQoL for the duration of treatment and that adverse events are the only driver of treatment related changes in HRQoL. These assumptions are likely to represent a very rough approximation to reality. Nonetheless, and as discussed above, since

these decrements are applied for a short period, it is unlikely that changes will have a large impact on the results.

5.3.7.5 The systematic review on HRQoL

As described in Section 5.2.6.1 Systematic review of HRQoL in chronic hepatitis C, the manufacturer conducted a systematic review of the published literature on HRQoL in chronic hepatitis C but did not use the studies identified to inform the submission. The systematic review did not identify more appropriate estimates for the HRQoL associated with health states than the study used by the manufacturer.[49] However, the systematic review did identify a relevant study to inform the HRQoL decrement associated with SOF-containing regimens.[80] Using this study for the HRQoL decrement associated with SOF+RBV would have avoided the second best alternative of calculating a weighted average of incidence of adverse events by their HRQoL decrement. Nonetheless, The HRQoL decrements used in the MS are similar to those reported in Stepanova et al, hence the impact on the results is likely to be minimal.

5.3.8 Resources and costs

The ERG considers the approach to identify, measure and value resource use and costs to be mostly appropriate. The costs associated with each health state and the monitoring costs were obtained from studies published more than 10 years ago. Hence there is the risk that some costs, although inflated to the appropriate price base, may be out-of-date. However, the ERG clinical advisors considered the costs to be broadly appropriate.

The ERG some concerns regarding the following aspects of the approach to costing:

- Exclusion of lifetime monitoring costs for cirrhotic patients with SVR;
- Exclusion of costs of adverse events;
- Exclusion of costs of determining SVR status;
- Costs for peg-interferon and RBV;
- Wastage associated with discontinuation;
- The mapping of the costs between health states; and
- Costs of monitoring during treatment for oral regimens.

5.3.8.1 Lifetime monitoring costs for cirrhotic patients with SVR

The manufacturer assumed that the cost of the health states post-SVR only applied for the first year after treatment discontinuation. This was justified with reference to the Janssen submission to NICE on TVR.[91] However, in this submission, the mild and moderate SVR states post-SVR are monitored for one year and cirrhotic patients with SVR are assumed to require life-long monitoring consisting of 6-monthly ultrasounds and monitoring of alpha-fetoprotein. In the MSD submission to NICE on BOC,

the cost of health states post-SVR was applied in the first year following treatment for METAVIR F0-F3 patients but for five years after treatment for F4 cirrhotic patients.[92 98] The cost for cirrhosis (F4) post-SVR was assumed to be half the cost of cirrhosis (F4) pre-SVR. The ERG clinical advisors agreed that cirrhotic patients with SVR are likely monitored throughout their lifetime given the risk of decompensation and HCC. The monitoring consists of screening for HCC with liver ultrasound scans every 6 months. For this reason, the ERG will test the impact of assuming lifetime monitoring costs in cirrhotic patients with SVR (see Section 6.2.6 Issue 6: Lifetime monitoring costs of cirrhotic patients with SVR).

5.3.8.2 Costs associated with adverse events

The costs associated with adverse events were not included in the base-case. This is inconsistent with the approach taken for the impact of adverse events on HRQoL. However, the ERG clinical advisors considered these costs to be small. The ERG does not consider the omission of costs due to adverse events to have a large impact on the model results.

5.3.8.3 Costs associated with determining SVR status

The manufacture did not include the costs associated with determining SVR status. These were estimated in the Shepherd et al study as £108.21 (inflated to the 2012-13 price base). Given the small magnitude of costs, and that it is a one-off cost, it is unlikely to have an impact on the results.

5.3.8.4 Acquisition costs of peginterferon and RBV

There is some uncertainty around the acquisition costs of peginterferon and RBV. The manufacturer chose peginterferon alfa-2a with RBV to cost the PR regimen. The recommended dose of peginterferon alfa-2a is 180mcg prefilled syringe per week in combination with oral RBV or as monotherapy. Although there are other options available (e.g. peginterferon alfa-2b in combination with RBV capsules and RBV generic), the ERG considers that any difference in the costs of products that can be used to deliver PR would be unlikely to impact markedly on the results.

5.3.8.5 Wastage associated with treatment discontinuation

As discussed in Section 5.2.5.2. Treatment discontinuation, patients may discontinue treatment due to adverse events. The manufacturer incorporated treatment discontinuation in the model as a reduction in costs. However, there may be some wastage if patients are provided with the drugs to take home and discontinue treatment before finishing their stock. The trials suggest that discontinuation rates are generally low for DCV- and SOF-containing regimens (<5%). However, PR-containing regimens are associated with larger discontinuation rates, such as PR in genotype 1 patients at 26%[57 58], PR in genotype 3 at 22%[28], DCV+PR in genotype 4 at 18% and PR in genotype 4 at 38% (observed in AI444-042). Therefore, the costs of these treatments may be underestimated if patients discontinue treatment whilst having in their possession surplus drugs. The impact of wastage in the cost-

effectiveness results depends on the amount of drugs dispensed to patients and the proportion of patients who discontinue treatment in clinical practice. This is likely to have a small impact on PR due to its low cost.

5.3.8.6 Costs in F0-F1 and F2-F3 patients

As with HRQoL, the costs associated with the chronic hepatitis C disease states were obtained from Wright et al assuming that mild disease is equivalent to F0-F1 and moderate disease is equivalent to F2-F3. The ERG agrees that this mapping is appropriate. However, and similarly to the issue raised in the HRQoL section (see Section 5.3.7.3 HRQoL in F0-F1 and F2-F3 patients), the ERG thinks that this is likely to bias in favour of treatments with higher SVRs in the F3 subpopulations.

5.3.8.7 Costs of monitoring during treatment for oral regimens

The costs of monitoring during treatment may be lower for oral regimens then injectable regimens such as PR The manufacturer explored the impact on excluding monitoring costs for DCV+SOF but not for the other oral comparators (see Section 5.2.8 Sensitivity analysis). If the monitoring costs for oral regimens are lower, their total cost may be overestimated. However, it is unlikely to have an impact on the results given the relatively small cost of monitoring compared with the acquisition costs of oral drugs.

5.3.8.8 Systematic review on costs in chronic hepatitis C

The manufacturer conducted a systematic review on costs related to chronic hepatitis C. However, the results of this review did not inform the model. Nonetheless, and given the results of the systematic review, the ERG considers that the manufacturer generally used the most appropriate estimates (with the caveats discussed above). The systematic review identified one UK study reporting costs following treatment, the Backx et al study.[99] The Backx et al results are difficult to incorporate into the model since as costs are stratified according to baseline disease severity and will therefore capture the costs associated with downstream events (e.g. decompensated cirrhosis and HCC in patients with cirrhosis at baseline). Nonetheless, the Backx et al study indicates that cirrhotic patients with SVR incur long-term costs.

5.3.9 Sensitivity analysis

The manufacturer presented a wide range of sensitivity analyses, including scenario, univariate, threshold and probabilistic sensitivity analysis. A major limitation of the sensitivity analysis is that all results were presented as pairwise comparisons between each DCV-containing regimen and each included comparator. Pairwise comparisons are not informative for decision making since relevant comparators are excluded.

In addition, the following additional weaknesses were identified with respect to the non-probabilistic analyses: use of the AI0444-040 clinical data is not considered appropriate in non-cirrhotic patients

even as a scenario analysis

[redacted]; no justification was provided for the ranges used in the univariate sensitivity analyses and some potentially important inputs and assumptions were not tested (e.g. HRQoL following SVR in cirrhotic patients).

The probabilistic sensitivity analysis inappropriately assigned distributions to baseline characteristics. More fundamentally, the manufacturer did not provide ICERs based on the probabilistic results (with the exception of some graphical presentations) and these could not be calculated from the information provided by the manufacturer in the report or model. Thus any potential impact of non-linearity on the expected ICERs could not be assessed using the manufacturer model.

5.3.10 Model validation and face validity check

5.3.10.1 Model validation

The electronic model is coded in Microsoft Excel and is fully executable. While it is well presented, the reliance on forms and macros written in visual basic and the use of hidden sheets and private sub routines in visual basic mean that the operation of the model is not transparent. The large quantity of sheets and visual basic coding prohibit a comprehensive evaluation of the model. It is the opinion of the ERG that the basic model structure is simple but that the means by which it has been coded is overly complex.

A major limitation of the manufacturer's model is that it is only designed to conduct pairwise comparisons between each of the DCV-containing regimens and a single comparator. Hence, cost-effectiveness estimates for each of the comparators needs to be run separately. In addition, incremental cost-effectiveness results for the all the relevant comparators and interventions required calculation by hand rather than this being conducted automatically in the model, which is time consuming and more prone to errors (particularly given the large number of subpopulations under consideration and the use of macros that automatically revert to default settings and hide sheets following certain operations).

The ERG took a pragmatic approach to validation. The ERG checked that the parameter inputs in the electronic model included in the original submission matched those described in the report. There were small discrepancies identified; these are summarised in Appendix 2 and were corrected in Section 6.1 ERG corrections and adjustments to the manufacturer's base-case model. The ERG ran the model included in the original submission and confirmed results for the base-case analyses for the all F3 population subgroups (Tables 104-106 p189-191 of MS) and for a selection of subgroups with F4 and F0-F4 disease. Any discrepancies were queried in the response to the points for clarification. The ERG ran the updated model submitted with the manufacturer's responses to the points for

clarification and confirmed results for a selection of comparators and subpopulations. All results were as expected. The elements of the visual basic code corresponding to the basic decision tree and Markov model structure were inspected and found to be reasonable. Although the model structure is the same for both the treatment and comparator arm, many of the macros separately estimate the same functions for each. This increases the possibility that differences may arise between arms due to errors in coding.

Fundamental calculations for the on therapy and Markov trace components of the model were spot checked for specific comparators. In addition, the ERG conducted a number of validation tests, namely:

- Setting all costs inputs to zero. The expected result is that costs for both treatments are equal to zero.
- Setting all HRQoL for health states as one and HRQoL decrements as zero. The expected result is for the QALYs to equal the life years.
- Set the discount rate to zero. The expected result is for the discounted costs and QALYs to be equal to the undiscounted results.
- Run probabilistic model with all parameters' standard errors set to zero. The expected result is to obtain probabilistic results identical to the deterministic results.
- Set the model parameters for the DCV-containing regimen equal to the comparator regimen for two comparators in genotype 1. The expected result is that mean costs and QALYs are identical for both treatments.

All results were as expected with the exception of setting all HRQoL for health states as one and HRQoL decrements as zero. In this test, QALYs greater than LYs by 0.000135 per patient for all treatments irrespective of genotype and discount rates, this small discrepancy could not be resolved.

5.3.10.2 Face validity check

The ERG compared a selection of the model outputs with the natural history in some published studies.[105 109 118] Appendix 4 details the methods and the results of the face validity check. The baseline characteristics of the cohort in the model were defined as per the baseline characteristics of the cohort in each of the studies. The model time horizon was set to reflect the median follow-up period of each study. Across the three studies, the model appears to underestimate the event rates in patients with and without SVRs. For example, the van der Meer study reports that all-cause mortality over a median follow-up of 8.4 years is 1.01% (95% CI 0.46 to 1.56) for patients with SVR and 2.93 (95% CI 2.36 to 3.51) for patients without SVR. The model predicts that a mortality rate of 0.32% for patients with SVR and 1.65% for patients without SVR. The direction of bias is unclear since both patient groups (with and without SVR) are affected. The ERG will therefore explore alternative

sources of parameter inputs on the natural history of the disease in its exploratory analysis (Section 6.3.5 Scenario 5: Alternative parameter inputs to the natural history of the disease).

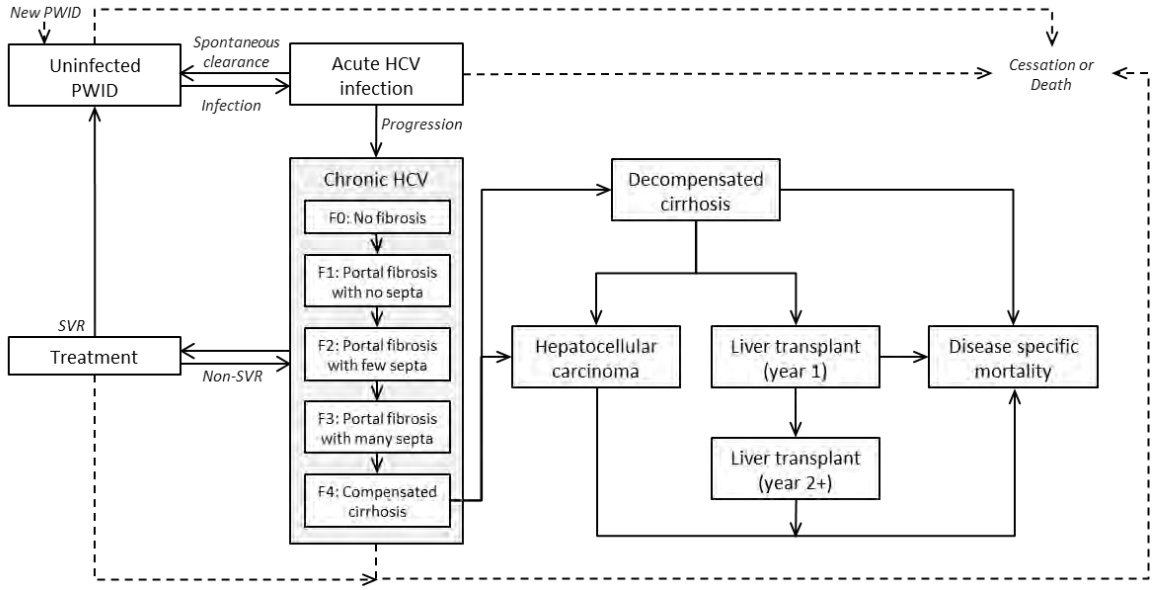
5.3.11 Transmission model of hepatitis C infection

5.3.11.1 Description of transmission model

Section 4.2 of the manufacturer's submission attempts to quantify the additional health benefits of treating chronic hepatitis C in terms of the reduction in future rates of infection (i.e. the reduction in onward transmission). The manufacturer refers to two published economic evaluations by Martin et al. (2011, 2013),[42 119] which assess the impact of treatment on future prevalence of chronic hepatitis C.

The manufacturer presents a *de novo* disease transmission model that characterises hepatitis C transmission in a population of people who inject drugs. Figure 3 shows the model structure, which expands on the chronic disease model described in Section 5.2.1 Model Structure to incorporate acute infection and disease transmission.

Figure 3 Structure of the manufacturer's disease transmission model



The manufacturer utilised inputs from Martin et. al 2013 to populate the disease transmission model (see Table 10, p36 of the manufacturer's submission).[119] The manufacturer does not describe in detail how the disease transmission model works and refers to an abstract for additional information.

The manufacturer assumes that the prevalence of hepatitis C is 25% among people who inject drugs. The model estimates the impact of treating all people who inject drugs and that are infected with hepatitis C within a one-year period on the downstream costs and health gains associated with new

hepatitis C infections over a 50 year period. The treatments considered are DCV+SOF, TVR+PR and no treatment for patients with genotype 1 disease.

The inputs specified in the submission suggest that the disease transmission model characterises a population of 4,240 people who inject drugs in which 25% have chronic hepatitis C, with 53% infected with genotype 1 disease and the remaining 47% infected with other genotypes (unspecified).

In the model, patients who are at risk of infection include prevalent people who inject drugs that are not infected with hepatitis C, new people who inject drugs (i.e. new entrants to the population), and those cured from hepatitis C either due to spontaneous clearance of acute infection (26%) or by successful treatment. The rate of transmission depends on the prevalence of hepatitis C as well as the proportion of the population assumed to be on opiate substitute therapy and those considered at high risk of transmission.

Patients are assumed to be offered only one line of therapy. After the first year, it is assumed that amongst new infections 50% of genotype 1 patients will be treated with TVR or BOC triple therapy, for which an SVR rate of 63% is used. The remaining patients are assumed to be treated with PR, with an SVR of 37% for genotype 1 and 67% for genotypes 2 and 3. The ERG notes that these SVR rates do not correspond to the SVR rates applied in the static model. The proportion of patients assumed to have genotypes 2 and 3 disease is not specified.

The results are provided in Tables 11 and 12 (p37) of the manufacturer's submission, and suggest that treating all patients with DCV+SOF instead of TVR+PR within a one year period would avoid £8,803 costs and 1.42 QALY losses from future hepatitis C infections per successfully treated genotype 1 patient. Treating all patients within a one year period with DCV+SOF instead of no treatment is estimated to avoid £18,236 costs and 2.92 QALY losses per successfully treated genotype 1 patient. The manufacturer states that they also estimated a more feasible clinical scenario in which the treatment rate is 8 per 1000 people who inject drugs (this equates to a treatment rate of 8 per 250 or 3.2% of those infected with chronic hepatitis C). The manufacturer only provides adjusted ICERs for this scenario, stating that the ICER for DCV+SOF compared to TVR+PR would fall from £9,867 to £8,156 and the ICER for DCV+SOF compared to no treatment would fall from £4,263 to £3,250.

5.3.11.1 Critique of transmission model

The manufacturer has not provided a full description of how the disease transmission model operates and the abstract does not provide further information. In the time provided for this appraisal, it was not possible for the ERG to fully interrogate the model. Spot checks revealed that the treatment arm of the model estimates fewer infections than the control arm even when efficacy rates are set to 100% for both comparators.

The costs, QALYs and numbers of liver disease related events associated with each new infection appear to be estimated within the static model presented in Section 5.2.1 Model Structure. It appears that these values are calculated per every new infection, which the ERG notes will double count events for patients who become re-infected with chronic hepatitis C following successful treatment. While the abstract describes a scenario in which the treatment rate among people who inject drugs is assumed to increase over time it appears that the model applies a constant treatment rate in the population of people who inject drugs. The ERG notes that this implies an increasing uptake of treatment among those infected with chronic hepatitis C for any scenario where the prevalence of hepatitis C in the population of people who inject drugs falls. The manufacturer does not provide estimates of the change in prevalence in hepatitis C for any scenario.

The base case ICERs provided by the manufacturer in Tables 11 and 12 of the MS correspond to the subpopulation with genotype 1 disease who are F3. The ERG notes a typographical error whereby the total QALYs for DCV+SOF in Table 11 correspond to the analysis comparing DCV+SOF with BOC+PR (13.68) instead of with TVR+PR (13.43) but the quoted ICER is correct. Adding the cost and QALY differences to the base case ICER, as the manufacturer has done in Tables 11 and 12, implies that all treated hepatitis C infections among people who inject drugs are of genotype 1 and have F3 (non-cirrhotic) disease. The default prevalence setting in the model is 27.5% and the default treatment rate is 8/1000 people who inject drugs. While this represents a treatment rate of 2.9% of people who inject drugs and who are infected with chronic hepatitis C, it would represent a much higher treatment rate if the population were restricted further to those with just F3 (non-cirrhotic) disease. Using the distribution of patients across METAVIR stages provided by the manufacturer it would be expected that 16.8% of the prevalent population have F3 disease, which would imply a treatment rate of 8/42 (19%) among these patients in the disease transmission model. The ERG notes that such high treatment rates may represent an unrealistic scenario, especially among people who inject drugs.

It was not possible to recreate the manufacturer's results using the model provided. Running the model for the default setting and selecting the treatment and comparator arms corresponding to the F3 (non-cirrhotic) population produces the results shown in Table 44.

Table 44 Comparing future infections and complications and associated cost/QALY

	DCV+SOF	TVR+PR	Difference
Patients treated in 2015	33.92	33.92	-
New chronic infections up to 2065	3864	5100	-1237
Complications of new infections			
DC	292	321	-30
HCC	123	135	-12

Liver transplant	46	50	-4
Liver related deaths	294	318	-25
Discounted results up to 2065			
Costs	20,305,943	22,507,913	-2,201,970
QALYs lost	5083	2689	-606

Treating all patients instead of 8/1000 people who inject drugs results in a total cost difference of £3,228,057 and a total QALY difference of -837. These figures produce a smaller difference per person treated (-£3,228 and 0.837) compared to the manufacturer's estimate in Table 13 (-£8,803 and 1.42).

The ERG believes that reducing onward transmission is an important benefit associated with successful treatment of hepatitis C. However the analysis provided by the manufacturer is insufficient to characterise this benefit. Given the lack of detail provided in the submission and the fact that the results could not be reproduced, the estimates provided by the manufacturer should be interpreted with caution. The base-case ICERs provided by the manufacturer relate to subgroups of the population defined by genotype, METAVIR stage and treatment experience or eligibility and relate only to the treatment of patients who inject drugs. In order to combine the results from a disease transmission model with these base-case ICERs additional information is required. For each subpopulations, it would be necessary to know the proportion at risk of transmitting disease (e.g. the number that are current injecting drug users) and the rate of treatment uptake among those at risk of transmitting disease (to be used alongside the appropriate SVR rate for the relevant comparators in each group). It would then be necessary to combine the groups in order to estimate the added benefit of switching to a treatment with a higher SVR rate for some or all of the groups.

5.4 Conclusions of the cost effectiveness section

The manufacturers' model represents the most relevant source of existing evidence on the cost-effectiveness of daclatasvir-based regimens for the treatment of chronic hepatitis C. The manufacturer presented results for four different disease severity groups: patients with METAVIR fibrosis scores F0-F4, F0-F2, F3 and F4. Within each of these disease severity categorisations the manufacturer presented separate results according to genotype (1, 3 and 4) and treatment history (treatment naïve, treatment experienced and ineligible for or intolerant to interferon-based therapies).

Given the heterogeneity across METAVIR fibrosis states in terms of SVR rates, natural history, therapy durations (and therefore costs) and NICE recommended treatments, the ERG do not consider the F0-F4 analysis to be informative. The F0-F2 analysis omits the possibility of watchful waiting (i.e. a no treatment option that allows for subsequent treatment if and when a patient reaches F3 or F4) and excludes relevant comparators in most subgroups. Again, the ERG considers insufficient evidence has been presented for the F0-F2 subpopulation.

The ERG therefore considers the manufacturer to have presented informative evidence for only those patients who are F3 or F4 (compensated cirrhotic), and even this is subject to uncertainty and potential bias. At a cost-effectiveness threshold of £20,000 per QALY, amongst F3 patients the manufacturers' analysis found DCV+SOF to be cost-effective in genotype 1 treatment experienced or interferon ineligible or intolerant patients, in genotype 3 interferon ineligible or intolerant patients, and in genotype 4 treatment experienced or interferon ineligible or intolerant patients. Amongst F4 patients, the manufacturers' analysis found DCV+SOF to be cost-effective in genotype 1 treatment experienced patients, in genotype 3 interferon ineligible or intolerant patients, and genotype 4 interferon ineligible or intolerant patients and DCV+PR to be cost-effective in genotype 4 treatment experienced patients.

However, the ERG considers the analysis presented for the F3 and F4 to be subject to considerable uncertainty and potential bias. In particular the ERG would like to highlight the following major concerns with the analysis presented.

***Comparator choice*:** The ERG believes that the manufacturer has omitted important comparators both in terms of specific drugs and treatment strategies. Specific drugs recently recommended by NICE in the SOF and SMV appraisals have been omitted from the current analysis on the basis of a lack of data. This is not an adequate justification for excluding comparators that are expected to be used in the NHS within the next year and which were included within the DCV final scope. The strategy described in the final scope as "Best supportive care (watchful waiting)" has been interpreted as a no treatment option. In practice, a true watchful waiting strategy whereby patients are monitored and treated if and when their disease worsens is a relevant comparator which has not been considered by the manufacturer. Finally, the analysis presented by the manufacturer does not consider the possibility that it may be cost-effective to hold DCV back for use in treatment failures rather than to use it in treatment naïve patients. This is relevant here as DCV is being considered for use as a first line and second line treatment option.

SVR data: The SVR data used in the model have been obtained from individual trial arms. They therefore represent an unadjusted or "naïve" indirect comparison and are associated with a high degree of uncertainty. This uncertainty is compounded by extrapolating between populations with different disease severities, treatment histories and sometimes genotypes. This is of particular concern for the F3 patients as data is almost never reported specifically for F3 patients.

Modelling of treatment experienced patients: Modelling of treatment experienced patients considered this group as a single entity. There is strong evidence that type of prior treatment experience (which may involve an initial response followed by failure, a partial response or no response at all) is predictive of SVR rates. Consideration of treatment experienced patients as a single group is therefore

likely to mask heterogeneity in costs and outcomes. Furthermore, the treatment experienced subpopulation in genotype 1 comprises only individuals who have failed treatment with a protease inhibitor plus PR. This omits a large group of prevalent genotype 1 patients who will have failed PR and for whom no evidence is presented. Appraisal of DCV in this group would require an understanding of any difference in outcomes amongst PR only experienced genotype 1 patients, and inclusion of additional comparators (namely the protease inhibitors).

Experience of F4 patients who achieve SVR: The manufacturer assumes that patients who achieve SVR from F4 receive a large boost to utility, do not face further risks of disease progression and do not require long term monitoring. These assumptions do not appear to reflect the available evidence and will exaggerate the benefit of achieving SVR in F4 patients.

***Natural history model*:** The ERG has concerns that the rates of disease progression used in the model do not reflect the natural history of patients with chronic hepatitis C in the UK.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 ERG corrections and adjustments to the manufacturer's base case model

The ERG found a number of anomalies in the manufacturer's model. Appendix 2 details the anomalies and the ERG's corrections. Briefly, these anomalies included that transition rates were implemented as transition probabilities, data entry errors, that monitoring costs in SVR patients applied for the first year of the model rather than the first year following SVR, that all-cause mortality was assumed to be lower than the general population in SVR patients, that the F3 subgroup contained F4 patients at baseline and inclusion of baseline patient characteristics in the probabilistic sensitivity analysis.

Table 45-46 summarises the updated cost-effectiveness results following the corrections. Appendix 4 presents the full incremental results for the F3 and F4 subpopulations. All results are deterministic. The results of the manufacturer's base-case are similar to the results after the ERG's corrections. The corrections did not change the cost-effective intervention at the £20,000 and £30,000 per QALY gained threshold.

Table 45 Comparison of the cost-effectiveness results from the manufacturer's model and after the ERG's corrections for the F3 population

Genotype	Treatment status	Manufacturer's model		ERG's corrections	
		Cost-effective intervention	ICER £/QALY	Cost-effective intervention	ICER £/QALY
1	TN	SOF+PR[1]	8,692	SOF+PR[2]	10,330
	TE	**DCV+SOF**	**4,587**	**DCV+SOF**	**5,906**
	III	**DCV+SOF**	4,587	**DCV+SOF**	**5,906**
3	TN	PR	NA	PR	NA
	TE	SOF+PR	9,043	SOF+PR	10,349
	III	**DCV+SOF**	**7,523**	**DCV+SOF**	**9,607**
4	TN	SOF+PR	**3,375**	SOF+PR	4,010
	TE	**DCV+SOF**	**3,750**	**DCV+SOF**	**4,655**
	III	**DCV+SOF**	**3,750**	**DCV+SOF**	**4,655**

(1) The cost-effective comparator at £30,000 per QALY gained is DCV+SOF with an ICER of £25,454.
(2) The cost-effective comparator at £30,000 per QALY gained is DCV+SOF with an ICER of £29,631.
TN: Treatment naïve. TE: Treatment experienced. III: Interferon intolerant or ineligible.
BOC: boceprevir; DCV: daclatasvir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir. NA: not applicable (the cost-effective intervention is the cheapest comparator).
Cost-effective daclatasvir-containing comparators are highlighted in bold.

Table 46 Comparison of the cost-effectiveness results from the manufacturer's model and after the ERG's corrections for the F4 population

Genotype	Treatment status	Manufacturer's model		ERG's corrections	
		Cost-effective intervention	ICER £/QALY	Cost-effective intervention	ICER £/QALY

1	TN	SOF+PR	4,964	SOF+PR	4,912
	TE	**DCV+SOF**	**12,443**	**DCV+SOF**	**12,704**
	III	SMV+SOF	2,857	SMV+SOF	2,956
3	TN	SOF+RBV	9,957	SOF+RBV	10,177
	TE	SOF+PR	6,543	SOF+PR	6,398
	III	**DCV+SOF+RBV**	**11,781**	**DCV+SOF+RBV**	**12,042**
4	TN	SMV+PR	N/A	SMV+PR	N/A
	TE	**DCV+PR**	**3,481**	**DCV+PR**	**3,781**
	III	**DCV+SOF**	**12,443**	**DCV+SOF**	**12,704**

TN: Treatment naïve. TE: Treatment experienced. III: Interferon intolerant or ineligible.
BOC: boceprevir; DCV: daclatasvir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir. NA: not applicable (the cost-effective intervention is the cheapest comparator).
Cost-effective daclatasvir-containing comparators are highlighted in bold.

6.2 The ERG's base-case

The ERG conducted a number of changes to the manufacturer's model that together constitute the ERG's base-case. The rationale and methodology used to implement each change are discussed below in turn.

6.2.1 Issue 1: Relevant comparators

The first key issue is that the manufacturers' analysis did not include all the relevant comparators (Section 5.3.4.1 Comparators included by the manufacturer). This occurred for two reasons. Firstly, the manufacturer removed from the analysis potentially relevant comparators where they did not consider there to be reliable evidence on SVR rates. Secondly, after the manufacturer presented the submission and during the ERG review, NICE issued separate guidance on SMV and on SOF for chronic hepatitis C. This guidance recommended some comparators excluded by the manufacturer. These are therefore considered relevant and are included by the ERG. Some comparators were not recommended by NICE but were included by the manufacturer; these are not considered relevant and are therefore excluded by the ERG. NICE delayed recommendations on SMV+SOF since additional evidence on this comparator is expected to report in the near future and will inform separate guidance for this comparator. SMV+SOF comparators have therefore been retained in the analysis. Table 47 shows the final set of comparators considered relevant by the ERG.

Table 47 Interventions and comparators included in the ERG's base-case

	Treatment-naive	Treatment-experienced	Interferon-ineligible/intolerant
Genotype 1	**DCV+SOF** SOF+PR SMV+PR TVR+PR BOC+PR PR No treatment	**DCV+SOF** *SOF+PR* No treatment	**DCV+SOF** ~~SOF+RBV~~ SMV+SOF No treatment
Genotype 3	**DCV+SOF(+RBV for cirrhotic)** ~~*SOF+PR*~~ for F3 *SOF+PR* for F4 ~~SOF+RBV~~ PR No treatment	**DCV+SOF(+RBV for cirrhotic)** SOF+PR ~~SOF+RBV~~ PR No treatment	**DCV+SOF(+RBV for cirrhotic)** ~~SOF+RBV~~ for F3 SOF+RBV for F4 No treatment
Genotype 4	**DCV+SOF** **DCV+PR** ~~SOF+PR~~ for F3 SOF+PR for F4 SMV+PR PR No treatment	**DCV+SOF** **DCV+PR** ~~*SOF+PR*~~ for F3 *SOF+PR* for F4 SMV+PR PR No treatment	**DCV+SOF** ~~*SOF+RBV*~~ *SMV+SOF* No treatment

BOC: boceprevir; DCV=daclatasvir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir.
Bold indicates daclatasvir-containing comparators.
Italic+underlined indicates comparators considered by the manufacturer as relevant but not included in the economic evaluation for some or all subgroups due to lack of data. These have been included in the ERG analysis.
Strikethrough indicates comparators removed from the manufacturers' analysis by the ERG because they were not recommended by NICE.

SVR rates, discontinuation rates and on treatment HRQoL decrements were not available from the manufacturer submission for the additional comparators. SVR rates were therefore obtained from previous appraisals. For patients with genotype 4 who are treatment experienced and F4, no data was available from the SOF appraisal. For this group, the ERG applied the same data used in the ERG base-case (see Section 5.2.5.1 SVR rates) for treatment naïve genotype 4 F4 patients and assumed that there is a decrement associated with being treatment experienced. This decrement is assumed equal to the decrement assumed by the FDA for genotype 1 patients. The SVR rates used are presented in Table 48. The on treatment HRQoL decrements were as per the manufacturer base-case. The proportions of patients discontinuing treatment was assumed to be zero as both SOF+PR and SMV+SOF were associated with very small proportions of discontinuation in the manufacturer base-case. The changes to comparators were applied in all ERG analyses.

Table 48 SVR estimates for comparators included by the ERG

Subpopulation	Comparator	SVR rate	Source and rationale
Genotype 1 TE F3	SOF+PR	78%	FDA data used in the NICE appraisal of SOF (extracted from SOF FAD p36)[25]
Genotype 1 TE F4	SOF+PR	As above	As above
Genotype 3 TN F4	SOF+PR	83.3%	LONESTAR-2 (genotype 3 TE, 83.3% response observed both in 12 cirrhotic and 12 non-cirrhotic patients), assumed as TE, as in the NICE appraisal of SOF[25]

Subpopulation	Comparator	SVR rate	Source and rationale
Genotype 4 TE F4	SOF+PR	68.6%	TN data for SOF+PR from NEUTRINO (79.6%, genotypes 1,4,5,6 TN and cirrhotic), minus the decrement assumed by the FDA for TE in genotype 1 (i.e. -11%) extracted from the sofosbuvir FAD p36[25]
Genotype 4 III F3	SMV+SOF	89.5%	COSMOS (genotype 1 TN, F3-F4) as per the NICE appraisal of SMV[23]
Genotype 4 III F4	SMV+SOF	As above	As above
TN: Treatment naïve. TE: Treatment experienced. III: Interferon intolerant or ineligible. SOF: sofosbuvir. PR: peginterferon with ribavirin. SMV: simeprevir. FDA: Food and Drug Administration.			

6.2.2 Issue 2: Appropriate SVR estimates

As discussed in Section 5.3.6.1 SVR rates, the ERG has some concerns regarding the SVR data used for a number of comparators. Specifically, the SVR estimates for DCV+SOF for genotype 1 treatment naïve F3, SOF+RBV for genotype 3 interferon ineligible or intolerant F4 and SOF+PR for genotype 4 treatment naïve F4.

Table 7 shows the preferred SVR estimates for these comparators, together with the source. The rationale for these choices is presented in detail in Section 49. In brief, the source of the DCV+SOF data in genotype 1 treatment naïve F3 patients is unclear and appears to have been adjusted in some way. The ERG therefore uses the raw data. Data for SOF+RBV in genotype 3 interferon ineligible or intolerant F4 does not reflect the licensed dosage whereas alternative data is available that does. For SOF+PR in genotype 4 treatment naïve F4 patients, the available estimate of SVR was based on one response in two individuals and was therefore replaced by a larger subgroup analysis (albeit one that also includes genotypes 1, 5 and 6).

Table 49 ERG's preferred SVR estimates

Subpopulation	Comparator	Manufacturer's base-case	ERG's base-case	Source and rationale
Genotype 1 TN F3	DCV+SOF	95.0%	100.0%	Ai444-040 trial. Source of 95% is unclear.
Genotype 3 III F4	SOF+RBV	21.4%	92.3%	VALENCE (G3 TN cirrhotic)[19 120]. Manufacturer used POSITRON data which used a 12 week rather than the 24 week license duration of therapy. Response for this comparator has been shown to be associated with treatment duration.
Genotype 4 TN F4	SOF+PR	50.0%	79.6%	NEUTRINO (G1, 4, 5 or 6 TN cirrhotic)[14 20]. Manufacturer used an SVR based on a sample size of 2, extend to genotypes 1, 4, 5, 6 TN cirrhotic subpopulation to increase sample size to 54.
TN: Treatment naïve. TE: Treatment experienced. III: Interferon intolerant or ineligible. RBV: ribavirin. SPC: summary of product characteristics.				

6.2.3 Issue 3: Natural history of genotype 4 patients

As discussed in Section 5.3.6.3 Transition probabilities, the manufacturer used transition probabilities estimated from a meta-analysis by Thein et al to estimate the transitions between METAVIR score states.[54] In Thein et al, genotype is a binary variable that can take the value of 1 for genotype 1 patients and 0 for non-genotype 1 patients. The manufacturer assumed that genotype 4 patients experience the transition probabilities of non-genotype 1 patients in Thein et al. However, and as discussed in Section 5.2.5.3 Transition probabilities, the non-genotype 1 patients in Thein et al are likely comprise almost entirely of genotype 2 and 3. In addition, data from Kanwal et al suggests no difference in transition probabilities between genotype 1 and genotype 4 patients.[70] For these reasons, the ERG considers it more appropriate to use the Thein et al genotype 1 data to simulate the progression of genotype 4 patients. This change was therefore implemented for the ERG's base-case.

6.2.4 Issue 4: Progression of cirrhotic patients with SVR

The manufacturer assumed that cirrhotic patients who achieved SVR did not progress to decompensated cirrhosis or HCC. As discussed in Section 5.3.2.2 Assumption of zero progression following SVR, the ERG considers this to be an assumption which has little evidence base. Therefore, for the ERG's base-case, cirrhotic patients with SVR are at risk of progression albeit at a much smaller risk than that faced by cirrhotic patients without SVR.

The ERG identified a number of studies that report the reduction in risk of progression for cirrhotic patients with SVR.[106-110] The relative risk associated with SVR (vs. non-SVR) for progression to decompensated cirrhosis ranges from 0 to 0.09 while the relative risk for progression to HCC ranges from 0.14 to 0.39. Given the uncertainty in the appropriate estimate, the ERG took the relative risk for progression as the half-way point within these ranges. Therefore, in the ERG's base-case, cirrhotic patients with SVR are at risk of progression to decompensated cirrhosis and HCC. The relative risk is 0.045 for the transition from F4 (cirrhosis) to decompensated cirrhosis and 0.265 for the transition from F4 (cirrhosis) to HCC. As the results were not particularly sensitive to inclusion of these parameters, alternative values were not explored further.

6.2.5 Issue 5: HRQoL Improvement of cirrhotic patients with SVR

As discussed in Section 5.3.7.1 HRQoL improvement in cirrhotic patients with SVR, the manufacturer assumed that cirrhotic patients with SVR experience an increase in HRQoL almost three times greater than non-cirrhotic patients (0.17 vs 0.05-0.06). This assumption was not appropriately justified. The ERG found no evidence to suggest that cirrhotic patients experience a greater improvement in HRQoL than non-cirrhotic patients. For this reason, the ERG assumes in its base-case that cirrhotic patients with SVR have the same improvement in HRQoL as patients with moderate disease at 0.05.

6.2.6 Issue 6: Lifetime monitoring costs of cirrhotic patients with SVR

The ERG clinical advisors agreed that cirrhotic patients with SVR are monitored throughout their lifetime due to the risk of HCC. The ERG clinical advisors indicated that monitoring typically consists of 6-monthly ultrasound scans of the liver. The manufacturer assumed that cirrhotic patients with SVR incur monitoring costs only in the first year after SVR at £1,464 (the same cost assigned to cirrhotic patients without SVR). Therefore, in its base-case, the ERG assumes that cirrhotic patients with SVR also incur the lifetime monitoring costs associated with the 6-monthly ultrasound scan. These costs are applied from year 3 onwards (as patients already receive some follow-up costs in year 2).

The cost of the ultrasound scan to the liver was obtained from the NHS reference costs for 2012-13.[121] The NHS reference costs include two potentially relevant items, RA23Z for ultrasound scan less than 20 minutes at £64, and RA24Z for ultrasound scan more than 20 minutes at £63. Hence, the yearly monitoring costs of cirrhotic patients with SVR are assumed to be £127.

Note that Issues 4-6 impact only on the F4 subpopulations as F3 patients never enter the F4 SVR state.

6.2.7 Use of deterministic results

Due to the large number of populations and comparators and the relatively long model run-times, the ERG was not able to calculate probabilistic ICERs. The ERG did however explore the potential for non-linearity in the model to generate differences between the deterministic and probabilistic results. The difference between the probabilistic and deterministic results was found to be small. In genotype 4 treatment naïve patients differences in costs and QALYs for two comparators (PR, DCV+PR) were found to be less than £100 (costs) and 0.02 (QALYs) and are therefore likely to have only very small impacts on the ICERs.

6.2.8 The ERG's base-case

6.2.8.1 Cost-effectiveness results

Tables 50-51 summarise the cost-effectiveness results for each individual change and for the combined changes that make up the ERG base-case. The Tables show the cost-effective comparator for each subpopulation at a threshold of £20,000 per QALY. The subpopulations for whom DCV-containing comparators are cost-effective are in bold. When the cost-effective comparator at the threshold of £30,000 per QALY is different, it is presented as a numbered footnote to the Table. The cells in grey mark the subpopulations in which changes occurred from the manufacturer's base-case after the ERG's corrections. All results are deterministic and fully incremental. Appendix 4 reports the full results.

The difference in results between the manufacturer's base-case after the corrections by the ERG and the ERG's base-case is mostly driven by (i) the addition of relevant comparators and removal of comparators not recommended by NICE, and (ii) by the use of alternative SVR estimates.

In F3 (non-cirrhotic) patients, there were two major differences between the manufacturer's corrected results and the ERG's base-case. Firstly, SMV+PR became the cost-effective comparator in genotype 4 treatment naïve patients when SOF+PR was removed from the comparators. Secondly, DCV+SOF became the cost-effective comparator at a cost-effectiveness threshold of £20,000 per QALY rather than SOF+PR in genotype 1 treatment naïve patients when using the SVR estimate considered by the ERG to be more appropriate for DCV+SOF (95% in the manufacturer vs. 100% in the ERG's base-case). In both the manufacturer and ERG base-case analysis DCV+SOF is cost-effective at a £30,000 per QALY base-case.

In the F4 (cirrhotic) patients, DCV-containing comparators were originally cost-effective in genotype 1 treatment experienced, genotype 3 interferon ineligible or intolerant and in genotype 4 treatment experienced or interferon ineligible or intolerant. Inclusion of SOF+PR resulted in this comparator rather than DCV+SOF becoming cost-effective in genotype 1 and 4 treatment experienced patients at a threshold of £20,000 per QALY (in genotype 4 treatment experienced patients DCV+PR is cost-effective at a threshold of £30,000 per QALY with an ICER or £20,508). Inclusion of SMV+SOF resulted in this comparator rather than DCV+SOF becoming cost-effective in genotype 4 interferon intolerant or ineligible patients. The change in SVR estimates for SOF+RBV in genotype 3 interferon ineligible or intolerant patients, from 21.4% in the manufacturer's base-case to 92.3% in the ERG's base-case, changed the cost-effective comparator from DCV+SOF+RBV to SOF+RBV.

In summary, in the ERG's base-case, DCV-containing regimens are cost-effective for the following subpopulations:

- F3 (non-cirrhotic):
    - Genotype 1 treatment naïve, treatment experienced and interferon ineligible or intolerant
    - Genotype 3 interferon intolerant or ineligible
    - Genotype 4 treatment experienced or interferon ineligible or intolerant
- F4 (cirrhotic): DCV-containing comparators are not cost-effective in any of the populations.

Table 50 Comparison of cost-effectiveness results for the manufacturer's base-case with ERG's corrections, each change by the ERG and the ERG base-case for the F3 subpopulation

Genotype		1			3			4		
Subpopulation		TN	TE	III	TN	TE	III	TN	TE	III
ERG's corrections to manufacturer	Cost-effective comparator	SOF+PR[1]	**DCV+SOF**	**DCV+SOF**	PR	SOF+PR	**DCV+SOF**	SOF+PR	**DCV+SOF**	**DCV+SOF**
	ICER £/QALY	10,330	**5,906**	**5,906**	NA	10,349	**9,607**	4,010	**4,655**	**4,655**
Issue 1: Relevant comparators	Cost-effective comparator	SOF+PR[1]	**DCV+SOF**	**DCV+SOF**	PR	SOF+PR	**DCV+SOF**	SMV+PR	**DCV+SOF**	**DCV+SOF**
	ICER £/QALY	10,330	**15,687**	**5,906**	NA	10,349	**9,607**	2,639	**4,655**	**4,655**
Issue 2: Appropriate SVR estimates	Cost-effective comparator	**DCV+SOF**	Not applicable to these subpopulations.		Not applicable to these subpopulations.			Not applicable to these subpopulations.		
	ICER £/QALY	**19,739**								
Issue 3: Natural history genotype 4	Cost-effective comparator	No impact in the non-genotype 4 subpopulations.						SMV+PR	**DCV+SOF**	**DCV+SOF**
	ICER £/QALY							3,598	**5,906**	**5,906**
ERG's base-case	Cost-effective comparator	**DCV+SOF**	**DCV+SOF**	**DCV+SOF**	PR	SOF+PR	**DCV+SOF**	SMV+PR	**DCV+SOF**	**DCV+SOF**
	ICER £/QALY	**19,739**	**15,687**	**5,906**	NA	10,349	**9,607**	3,598	**5,906**	**5,906**

(1) DCV+SOF is cost-effective at £30,000 per QALY gained; ICER=£29,631 per QALY gained.

TN: Treatment naïve. TE: Treatment experienced. III: Interferon intolerant or ineligible. ERG: Evidence review group. QALY: quality-adjusted life year. Cost-effective intervention at £20,000 per QALY. ICER: Incremental cost-effectiveness ratio £/QALY gained. BOC: boceprevir; DCV: daclatasvir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir. NA: not applicable. Cost-effective daclatavir-containing comparators are highlighted in bold.

Grey shadowing highlights analyses in which the cost-effective intervention at £20,000 or 30,000 per QALY switches from the ERG's corrections to the manufacturer's base-case analysis.

Table 51 Comparison of cost-effectiveness results for the manufacturer's base-case with ERG's corrections, each change by the ERG and the ERG base-case for the F4 subpopulation

Genotype		1			3			4		
Subpopulation		TN	TE	III	TN	TE	III	TN	TE	III
ERG's corrections to manufacturer	**Cost-effective comparator**	SOF+PR	**DCV+SOF**	SMV+SOF	SOF+RBV	SOF+PR	**DCV+SOF+RBV**	SMV+PR	**DCV+PR**	**DCV+SOF**
	ICER £/QALY	4,912	**12,704**	2,956	10,177	6,398	**12,042**	N/A	**3,781**	**12,704**
Issue 1: Relevant comparators	**Cost-effective comparator**	SOF+PR	SOF+PR	SMV+SOF	SOF+PR	SOF+PR	**DCV+SOF+RBV**	SMV+PR	SOF+PR(1)	SMV+SOF
	ICER £/QALY	4,912	654	2,956	2,924	6,398	**12,042**	N/A	1,778	3,366
Issue 2: Appropriate SVR estimates	**Cost-effective comparator**	Not applicable to these subpopulations.					SOF+RBV	SMV+PR	Not applicable to these subpopulations	
	ICER £/QALY						5,546	N/A		
Issue 4: Progression of F4 SVR	**Cost-effective comparator**	SOF+PR	SOF+PR	SMV+SOF	SOF+PR	SOF+PR	**DCV+SOF+RBV**	SMV+PR	SOF+PR(2)	SMV+SOF
	ICER £/QALY	6,180	1,432	4,030	4,184	8,091	**14,857**	N/A	2,704	4,493
Issue 5: HRQoL of F4 SVR	**Cost-effective comparator**	SOF+PR	SOF+PR	SMV+SOF	SOF+PR	SOF+PR	**DCV+SOF+RBV**	SMV+PR	SOF+PR	SMV+SOF
	ICER £/QALY	7,612	1,040	4,690	4,497	9,502	**18,695**	N/A	2,830	5,341
Issue 6: Lifetime costs of F4 SVR	**Cost-effective comparator**	SOF+PR	SOF+PR	SMV+SOF	SOF+PR	SOF+PR	**DCV+SOF+RBV**	SMV+PR	SOF+PR(3)	SMV+SOF
	ICER £/QALY	5,268	1,026	3,327	3,274	6,726	**12,399**	N/A	2,151	3,737
ERG's base-case	**Cost-effective comparator**	SOF+PR	SOF+PR	SMV+SOF	SOF+PR	SOF+PR	SOF+RBV	SMV+PR	SOF+PR	SMV+SOF
	ICER £/QALY	10,399	2,983	7,216	7,228	12,813	12,282	N/A	5,072	7,974

(1) DCV+PR is the cost-effective comparator at £30,000/QALY gained; ICER=£20,508/QALY gained.
(2) DCV+PR is the cost-effective comparator at £30,000/QALY gained; ICER=£24,955/QALY gained.
(3) DCV+PR is the cost-effective comparator at £30,000/QALY gained; ICER=£20,982/QALY gained.

TN: Treatment naïve. TE: Treatment experienced. III: Interferon intolerant or ineligible. ERG: Evidence review group. QALY: quality-adjusted life year. Cost-effective intervention at £20,000 per QALY. ICER: Incremental cost-effectiveness ratio £/QALY gained. BOC: boceprevir; DCV: daclatasvir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir. NA: not applicable. Cost-effective daclatavir-containing comparators are highlighted in bold.

Grey shadowing highlights analyses in which the cost-effective intervention at £20,000 or 30,000 per QALY switches from the ERG's corrections to the manufacturer's base-case analysis.

6.3 Sensitivity analysis to the ERG's base-case

The ERG conducted a number of sensitivity analysis to its base-case in order to explore the impact of uncertainties in the evidence on the results. Each scenario is discussed in turn.

6.3.1 Scenario 1: Exclusion of comparators subject to uncertainty

There is uncertainty regarding the relevance of two comparator comparators, SMV+PR in genotype 1 patients and SMV+SOF in interferon ineligible or intolerant with genotype 1 or 4 (F4 and F3 patients).

- **Scenario 1.1. Exclusion of SMV+PR in genotype 1 patients**
  The marketing authorisation for SMV recommends that alternatives to SMV+PR should be considered for patients infected with HCV genotype 1a with the NS3 Q80K polymorphism or when testing is not accessible since its efficacy is substantially reduced in patients with the Q80K polymorphism.[15] Therefore, the ERG tests the impact of excluding SMV+PR from the analysis for genotype 1 treatment naïve patients.

- **Scenario 1.2. Exclusion of SMV+SOF**
  As discussed in Section 5.3.4.1 Comparators included by the manufacturer, the comparator SMV+SOF will be subject to future NICE guidance given the expectation of additional evidence in the short term. Hence, there is uncertainty regarding whether this treatment comparator will be recommended by NICE. For this reason, the ERG tested the exclusion of SMV+SOF from the relevant subgroups (genotype 1 and 4 interferon ineligible or intolerant, F3 or F4).

6.3.2 Scenario 2: Alternative treatment durations

The marketing authorisations for DCV, SOF and SMV allow alterations to the licensed treatment durations for specific subpopulations. The impact of these changes on the cost-effectiveness results is approximated in Scenarios 2.1-2.3 by reducing or increasing the total costs per patient by the relevant amount. The monitoring costs were unchanged. This will underestimate the difference in costs. However, since the monitoring costs are relatively small compared with the drug acquisition costs, this difference is likely not to impact on the results of these scenarios.

- **Scenario 2.1. Treatment duration of DCV+SOF**
  The treatment duration of DCV+SOF can be increased to 24 weeks (from 12 weeks) for genotype 1 treatment experienced F3 (non-cirrhotic) patients.[46] Hence, for this scenario, the costs of DCV+SOF were increased by the weekly costs of DCV+SOF over an additional 12 weeks (an increase of £4,958 x 12 weeks = £59,501).

The treatment duration of DCV+SOF can be reduced to 12 weeks (from 24 weeks) for genotype 1 or 4 treatment naïve F4 (cirrhotic) patients with positive prognostic factors.[46] Hence, for this scenario, the costs of DCV+SOF were reduced by the weekly costs of DCV+SOF over an additional 12 weeks (a decrease of £4,958 x 12 weeks = £59,501).

- **Scenario 2.2. Treatment duration of SMV+PR**

  The treatment duration of the PR component of SMV+PR should be reduced from 48 to 24 weeks in genotype 4 treatment experienced patients.[15] The marketing authorisation specifies that partial and null responders should receive 48 weeks of PR but prior relapse patients should receive 24 weeks of treatment. In the RESTORE study, from which the SVR rates for the SMV+PR comparator were derived, 26% of treatment experienced patients (19/72) were prior relapse patients.[63] Hence, for these patients, the PR component should be reduced from 48 to 24 weeks. This represents a cost-saving of £1,182 (the weekly cost of PR at £191.35 x 24 weeks x 26% x (100-1% of discontinuations). It should be noted that the different recommendations by partial response, null response and relapse patients indicate that these patients are likely to have different SVRs and hence should have been analysed separately by the manufacturer.

- **Scenario 2.3. Treatment duration of SOF+PR**

  Treatment duration of SOF+PR can be extended to 24 weeks, especially for patients with characteristics which are predictive of low response e.g. advanced fibrosis/cirrhosis, high baseline viral concentrations, previous unresponsiveness to PR, non-CC genotype IL28B polymorphism, or people of African or Caribbean family origin.[15] Hence, for this scenario, the model was re-run assuming that SOF+PR is given for 24 weeks rather than 12 weeks adding an additional £37,279 to the cost of this comparator.

6.3.3 Scenario 3: Alternative discontinuation rates

As discussed in Section 5.3.6.2 Treatment discontinuation, the ERG has some concerns regarding the discontinuation rates used for the genotype 1 treatment naïve F3 subpopulation; namely, that the discontinuation rates related to discontinuations due to adverse events only. Therefore, it tested the impact of using the discontinuation rates of the genotype 1 treatment naïve F4 subpopulation in this subgroup. Table 52 summarises the changes.

Table 52 Scenario 3: Alternative discontinuation rates for genotype 1 treatment naïve F3 subpopulation

Comparator	F3 subpopulation		F4 subpopulation	
	Discontinuation rate (SE)	Source	Discontinuation rate (SE)	Source

DCV+SOF (vs TVR)	0.005 (0.006)	MAIC	0	AI444-040 clinical trial report
TVR+PR	0.145 (0.012)	MAIC	0.262 (0.023)	ADVANCE[13]
BOC+PR	0.122 (0.017)	MAIC	0.413 (0.026)	SPRINT-2[12]
SOF+PR	0.015 (0.007)	MAIC	0.021 (0.008)	NEUTRINO[14 20]
SMV+PR	0.023 (0.007)	MAIC	0.002 (0.006)	QUEST 1 and QUEST 2[15 67 68]
PR	0.264 (0.021)	NV15942	0.264 (0.021)	NV15942[57 58]
No treatment	0	Assumption	0	Assumption
MAIC: Matching-adjusted indirect comparison. BOC: boceprevir; DCV: daclatasvir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir.				

6.3.4 Scenario 4: Alternative SVR estimates

As discussed in Section 5.3.6.1 SVR rates, the ERG finds the SVR estimates for some subpopulations to be subject to uncertainty:

- For SOF+PR for genotype 1 treatment naïve F3, the manufacturer chose the SVR achieved in cirrhotic patients to inform the estimate for the F3 subpopulation rather the estimate from non-cirrhotic patients. The ERG acknowledges that the F3 subpopulation is more severe than the overall non-cirrhotic population and hence is likely to achieve lower SVR. However, the SVR estimate from cirrhotic patients is likely to underestimate the SVR in F3 patients, who have less severe disease. Therefore, the ERG tested the impact of using the mid-point between the SVR achieved in patients with compensated cirrhosis and those without cirrhosis. It should be noted that the SVR rate in F3 patients is not known and use of the mid-point may over or underestimate the true value.
- For genotype 3 F4 patients, the manufacturer chose the SVR achieved in the AI0444-040 trial where DCV+SOF+RBV was received for 24 weeks in F3-F4 patients. Therefore, the SVR rate may be an overestimate for F4 patients, who are more severe. ALLY-3 offers an alternative source of SVR estimates in the correct population, but it tests the comparator DCV+SOF over 12 weeks. Although it may be an underestimate of the SVR achieved with the DCV+SOF+RBV comparator over 24 weeks, it is a plausible alternative SVR estimate in this population. Therefore, the ERG tests the impact of this SVR estimate in the genotype 3 treatment naïve, treatment experienced and interferon ineligible or intolerant F4 subpopulation.
- The ERG also tests the impact of reverting to the manufacturer's preferred estimates for SOF+RBV for the genotype 3 interferon or intolerant F4 subpopulation and for SOF+PR for the genotype 4 treatment naïve F4 subpopulation. The ERG tests the manufacturers' preferred values for SOF+RBV because, although they do not reflect the licensed treatment duration, they were obtained from the target population. The ERG tests the manufacturer's preferred

value for SOF+PR because, although they were obtained from a very small subgroup (two patients), the values used by the manufacturer were specific to solely genotype 4 patients.

The alternative SVR rates explored by the ERG in the sensitivity analysis are presented as Table 53.

Table 53 Scenario 4: Alternative SVR estimates

Subpopulation	Comparator	ERG's Base-case	Scenario	Source and rationale
Genotype 1 TN F3	SOF+PR	81.0%	86.5%	NEUTRINO. Mid-point of non-cirrhotic 92% and cirrhotic 81%. Cirrhotic results may be an underestimate for F3-F4. [14 20]
Genotype 3 TN F4	DCV+SOF+RBV	100%	[redacted]	ALLY-3. ALLY-3 tested DCV+SOF over 12 weeks in the F3-F4 subpopulations whereas AI0444-040 tested DCV+SOF+RBV over 24 weeks in a F3-F4 subpopulation. ALLY-3 provides a conservative SVR estimate whilst AI0444-040 provides an optimistic estimate for the cirrhotic population. Data taken from manufacturer points for clarification.
Genotype 3 TE F4	DCV+SOF+RBV	100%	[redacted]	ALLY-3. ALLY-3 tested DCV+SOF over 12 weeks in the F3-F4 subpopulations whereas AI0444-040 tested DCV+SOF+RBV over 24 weeks in a F3-F4 subpopulation. ALLY-3 provides a conservative SVR estimate whilst AI0444-040 provides an optimistic estimate for the cirrhotic population. Data taken from manufacturer points for clarification.
Genotype 3 III F4	DCV+SOF+RBV	100%	[redacted]	Extrapolated from genotype 3 TN F4.
Genotype 3 III F4	SOF+RBV	92.3%	21.4%	Revert to manufacturer value in sensitivity analysis given that this is for the correct population but with the incorrect treatment duration. [69]
Genotype 4 TN F4	SOF+PR	79.6%	50.0%	Revert to manufacturer value in sensitivity analysis given use of extrapolation across genotypes in base-case. [20]

TN: Treatment naïve. TE: Treatment experienced. III: Interferon ineligible or intolerant.
SOF: Sofobuvir. PR: pegylated interferon and ribavirin. DCV: Daclatasvir. RBV: Ribavirin.

6.3.4.2 Exploratory analysis: Impact of SVR on QALYs

As discussed in Section 4.4.3 Conclusions from the uncontrolled indirect comparisons, the SVR estimates are highly uncertainty. This uncertainty is due to relying on unadjusted (or naïve) direct comparisons between individual trial arms for estimates of effectiveness rather than randomised or indirect comparisons. For this reason, the ERG explored the difference in lifetime QALYs associated with 5% change in SVR estimates in the F3 and F4 subpopulation.

In this analysis, the ERG changed the SVR rate of DVC+SOF in 5% decrements in genotype 1 and genotype 3 treatment naïve F3 and F4 subpopulations. The results suggest that a 5% change in SVR rate is associated with 0.14-0.15 QALY difference in the genotype 1 F3 subpopulation and 0.16 QALY difference in the F4 subpopulation. In genotype 3, a 5% change in SVR is associated with 0.16-0.17 QALY difference in both the F3 and the F4 populations. In other words, if the SVR rate of

DCV+SOF in genotype 1 patients is 95% rather than 100%, the total lifetime QALYs per patient reduce from 12.84 to 12.70 (reduction of 0.14 QALYs).

6.3.5 Scenario 5: Alternative parameter inputs for the natural history of the disease

This set of three scenarios explore the impact of alternative parameter inputs on the progression of chronic hepatitis C, namely progression from F3 to F4 (cirrhosis) in scenario 5.1. and 5.2 and progression from F4 (cirrhosis) to decompensated cirrhosis and HCC in scenario 5.3. Table 54 compares the parameter inputs used in the base-case with those tested in this scenario. Each scenario is discussed in turn.

Table 54 Scenario 5: parameter inputs

Subpopulation	1-year transition probability		Source
	ERG's Base-case	Scenario	
Scenario 5.1. Progression from F3 to F4 (cirrhosis) – non-tertiary centres			
Genotypes 1 and 4	0.110	0.048	Grishchenko et al 2009[40]
Genotype 3	0.141	0.062	
Scenario 5.2. Faster progression from F3 to F4 (cirrhosis) – tertiary centres			
Genotypes 1 and 4	0.110	0.066	Sweeting et al 2006 [122]
Genotype 3	0.141	0.086	
Scenario 5.3. Progression from F4 (cirrhosis) to decompensated cirrhosis and hepatocellular cancer			
From F4 (cirrhosis) to decompensated cirrhosis	0.039	0.036	Van der Meer et al 2012 [109]
Genotype 1 and 4: from F4 (cirrhosis) to hepatocellular cancer	0.014	0.026	
Genotype 3: from F4 (cirrhosis) to hepatocellular cancer	0.020	0.038	

- **Scenario 5.1. Progression from F3 (significant fibrosis) to F4 cirrhosis – non-tertiary centres**

  As discussed in Section 5.3.6.3 Transition probabilities, the ERG has concerns about the robustness of the analysis used by the manufacturer to inform transitions from F3 to F4 (cirrhosis) and the relevance of this analysis to the UK. In this scenario, this transition probability is estimated from a UK patient cohort aged 50 years with genotype 1 (obtained from Grishchenko et al).[40] This transition probability was estimated from the Trent database which includes patients referred for secondary care. The Trent cohort includes patients who attend non-tertiary referral centres, and has therefore been argued to be more representative of the care provided in the UK. The analyses do not suffer from the limitations of the Thein et al. study as they were estimated from individual patient data. The sample size used in the analysis is unclear although previous analyses of these data included 398

patients.[122] The transition probability from moderate disease to cirrhosis is used to approximate the transition probability from F3 to F4. Genotype 3 patients experience faster progression, which is incorporated via the Kanwal et al multiplier as per the manufacturer model and ERG base-case.[70] Note that this scenario is only applicable to the F3 subpopulation.

- **Scenario 5.2. Progression from F3 (significant fibrosis) to F4 cirrhosis – tertiary centres**
  Patients receiving care in tertiary centres may have more severe disease and hence progress more quickly than those receiving secondary care. Sweeting et al compared the transition rates of three UK observational cohorts of patients with chronic hepatitis C: the Trent HCV cohort, the HCV national register cohort and the St. Mary's hospital cohort, which is a tertiary referral centre in London.[122] The authors found that patients at the tertiary centre progressed faster than individuals in the Trent cohort, after adjusting for confounders. The hazard ratio for progression is 1.39 (95% CI: 1.10-1.74). In the model, the hazard ratio for progression is applied to the Grishchenko et al transition data. Again, genotype 3 patients are assumed to progress more quickly as in the manufacturer model and ERG base-case. Note that this scenario is only applicable to the F3 subpopulation.

- **Scenario 5.3. Transitions following cirrhosis**
  As discussed in Section 5.3.6.3 Transition probabilities the ERG has concerns that the data informing the transitions from cirrhosis is not representative of current UK patients. Van der Meer et al present more recent data on progression which is specific to patients who fail to achieve SVR.[109] Van der Meer et al evaluated the association between SVR and a range of patient outcomes in 530 patients with chronic HCV infection and advanced fibrosis. Patient outcomes include all-cause mortality, decompensated cirrhosis (liver failure), HCC, liver-related mortality and liver transplantation. The limitations of the van der Meer data are (i) that the patient cohort is a mix of patients with Ishak 4 to 6, 54% of which have Ishak=6 (cirrhosis) rather than cirrhotic patients only, and (ii) is a multicentre study outside the UK. The transition rates from van der Meer are converted into transition probabilities and applied in the model. For genotype 3, the Kanwal et al multiplier is applied as in the manufacturer and ERG base-case.[70]

6.3.6 Results of the ERG's sensitivity analysis to the ERG's base-case

Tables 55-56 summarise the cost-effectiveness results for the sensitivity analysis for the F3 and F4 subpopulations separately. The Tables show the cost-effective comparator for each subpopulation at a threshold of £20,000 per QALY. When the cost-effective comparator at the threshold of £30,000 per QALY is different, it is presented as a numbered footnote to the Table. All results are deterministic

and fully incremental. The subpopulations for whom DCV-containing comparators are cost-effective are in bold. The cells in grey mark the subpopulations in which changes occurred from the ERG base-case. Appendix 4 reports the full results.

The results for the F3 subpopulation are generally robust to the sensitivity analysis except for longer treatment durations for DCV+SOF (Scenario 2.1), longer treatment duration for SOF+PR (Scenario 2.3), use of an alternative SVR estimate (Scenario 4), and slower progression of the disease (Scenario 5.1-5.2). Specifically:

- The cost-effective comparator changes in Scenario 2.1, where the treatment duration of DCV+SOF is increased from 12 to 24 weeks, from DCV+SOF to SOF+PR in genotype 1 treatment experienced patients.
- The cost-effective comparator changes in scenario 2.3, where the treatment duration of SOF+PR is increased from 12 to 24 weeks, from SOF+PR to PR in the genotype 3 treatment experienced subpopulation.
- The cost-effective comparator changes in Scenario 4, where higher SVR estimates for SOF+PR are applied (81% in the base-case vs 86.5% in the sensitivity analysis), from DCV+SOF in the base-case to SOF+PR in the genotype 1 treatment naïve subpopulation.
- The cost-effective comparator changes in Scenarios 5.1 and 5.2, where slower progression between F3 and F4 is assumed. Use of non-tertiary data (Scenario 5.1) changes the cost-effective comparator from DCV+SOF to SOF+PR at a threshold of £20,000 but not £30,000 per QALY in treatment naïve and treatment experienced genotype 1 patients. When the tertiary data (Scenario 5.2) is used, the cost-effective comparator in treatment naïve patients changes from DCV+SOF to SOF+PR but again only when a £20,000 per QALY threshold is used.

The results for the F4 subpopulation were robust to all sensitivity analysis except for exclusion of SMV+SOF (Scenario 1.2); the treatment duration of SOF+PR (Scenario 2.3) and SVR estimates (Scenario 4).

- The cost-effective comparator changes in scenario 1.2, where SMV+SOF is excluded as a comparator, to no treatment becoming cost-effective rather than SMV+SOF at a cost-effectiveness threshold of £20,000 per QALY in genotype 1 and 4 interferon ineligible or intolerant patients. In this analysis DCV+SOF is now cost-effective at a threshold of £30,000 per QALY.
- In Scenario 2.3 the treatment duration of SOF+PR is assumed to increase from 12 to 24 weeks. The cost-effective comparator changes from SOF+PR to SMV+PR in genotype 1 treatment naïve patients, to PR in genotype 3 treatment naïve patients (although SOF+PR is

cost-effective at the £30,000 per QALY gained threshold), to PR in genotype 3 treatment experienced patients and to DCV+PR in genotype 4 treatment experienced patients.

- In scenario 4, use of a reduced response rate for SOF+RBV in genotype 3 interferon ineligible or intolerant patients results in this comparator no longer being cost-effective. The no treatment option becomes cost-effective at a threshold of £20,000 per QALY and DCV+SOF+RBV is cost-effective at a threshold of £30,000 per QALY.

Table 55 Sensitivity analysis to the ERG's base-case for the F3 subpopulation

Genotype		1			3			4		
Subpopulation		TN	TE	III	TN	TE	III	TN	TE	III
ERG's base-case	CE	**DCV+SOF**	**DCV+SOF**	**DCV+SOF**	PR	SOF+PR	**DCV+SOF**	SMV+PR	**DCV+SOF**	**DCV+SOF**
	ICER	**19,739**	**15,687**	**5,906**	NA	10,349	**9,607**	3,598	**5,906**	**5,906**
1.1. Exclusion of SMV+PR	CE	**DCV+SOF**	Not applicable to these subpopulations.							
	ICER	**19,739**								
1.2. Exclusion of SMV+SOF	CE	Not applicable to these subpopulations.		**DCV+SOF**	Not applicable to these subpopulations.					**DCV+SOF**
	ICER			**5,906**						**5,906**
2.1 Treatment duration of DCV+SOF	CE		SOF+PR	Not applicable to these subpopulations.						
	ICER		3,033							
2.2. Treatment duration of SMV+PR	CE	Not applicable to these subpopulations.							**DCV+SOF**	
	ICER								**5,906**	
2.3. Treatment duration of SOF+PR	CE	**DCV+SOF**	**DCV+SOF**	Not applicable to these subpopulations.		PR	Not applicable to these subpopulations.			
	ICER	**15,943**	**5,906**			N/A				
3. Discontinuation rates (F3)	CE	**DCV+SOF**	Not applicable to these subpopulations.							
	ICER	**19,838**								
4. SVR estimates	CE	SOF+PR	Not applicable to these subpopulations.							
	ICER	6,897								
5.1. Progression F3 to F4 (UK non-tertiary)	CE	SOF+PR[(1)]	SOF+PR[(2)]	**DCV+SOF**	PR	SOF+PR	**DCV+SOF**	SMV+PR	**DCV+SOF**	**DCV+SOF**
	ICER	16,015	6,337	**10,196**	N/A	14,855	**14,354**	6,912	**10,196**	**10,196**
5.2. Progression F3 to F4 (UK tertiary)	CE	SOF+PR[(3)]	**DCV+SOF**	**DCV+SOF**	PR	SOF+PR	**DCV+SOF**	SMV+PR	**DCV+SOF**	**DCV+SOF**
	ICER	13,398	**19,736**	**8,199**	N/A	12,746	**12,102**	5,370	**8,199**	**8,199**
5.3. Transition following cirrhosis	CE	**DCV+SOF**	**DCV+SOF**	**DCV+SOF**	PR	SOF+PR	**DCV+SOF**	SMV+PR	**DCV+SOF**	**DCV+SOF**
	ICER	**18,901**	**15,091**	**5,901**	N/A	9,951	**9,238**	3,733	**5,901**	**5,901**

(1) DCV+SOF is cost-effective at £30,000 per QALY gained; ICER=£28,542 per QALY gained.

(2) DCV+SOF is cost-effective at £30,000 per QALY gained; ICER=£23,152 per QALY gained.

(3) DCV+SOF is cost-effective at £30,000 per QALY gained; ICER=£24,525 per QALY gained.

CE: cost-effective intervention at £20,000 per QALY. ICER: Incremental cost-effectiveness ratio £/QALY gained. BOC: boceprevir; DCV: daclatasvir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir. NA: not applicable. Cost-effective DCV-containing comparators are highlighted in bold. Grey shadowing highlights different results from the ERG base-case.

Table 56 Sensitivity analysis to the ERG's base-case for the F4 subpopulation

Genotype		1			3			4		
Subpopulation		TN	TE	III	TN	TE	III	TN	TE	III
ERG's base-case	CE	SOF+PR	SOF+PR	SMV+SOF	SOF+PR	SOF+PR	SOF+RBV	SMV+PR	SOF+PR	SMV+SOF
	ICER	10,399	2,983	7,216	7,228	12,813	12,282	N/A	5,072	7,974
1.1 Exclusion of SMV+PR	CE	SOF+PR	Not applicable to these subpopulations.							
	ICER	10,399								
1.2. Exclusion of SMV+SOF	CE	Not applicable to these subpopulations.		NT(1)	Not applicable to these subpopulations.					NT(1)
	ICER			N/A						N/A
2.1 Treatment duration of DCV+SOF	CE	SOF+PR(2)	Not applicable to these subpopulations.					SMV+PR	Not applicable to these subpopulations.	
	ICER	10,399						N/A		
2.2. Treatment duration of SMV+PR	CE	Not applicable to these subpopulations.							SOF+PR	
	ICER								5,072	
2.3. Treatment duration of SOF+PR	CE	SMV+PR	SOF+PR	Not applicable	PR(4)	PR	Not applicable	SMV+PR	**DCV+PR**	Not applicable
	ICER	17,409	17,873		N/A	N/A		N/A	**8,775**	
4. SVR estimates	CE	Not applicable to these subpopulations.			SOF+PR	SOF+PR	NT(3)	SMV+PR	Not applicable to these subpopulations.	
	ICER				7,228	12,813	N/A	N/A		
5.3. Transition following cirrhosis	CE	SOF+PR	SOF+PR	SMV+SOF	SOF+PR	SOF+PR	SOF+RBV	SMV+PR	SOF+PR	SMV+SOF
	ICER	11,004	3,929	7,990	8,127	13,395	12,979	N/A	5,938	8,718

(1) DCV+SOF is cost-effective at £30,000 per QALY gained; ICER=£25,349 per QALY gained.

(2) DCV+SOF is cost-effective at £30,000 per QALY gained; ICER=£24,074 per QALY gained.

(3) This is the result when the SVR estimate of SOF+RBV is changed from 92.3% to 21.4%. Here, DCV+SOF+RBV is cost-effective at £30,000 per QALY gained; ICER=£24,477 per QALY gained. Changing the SVR estimate of DCV+SOF+RBV from 100% to 57.9% (and keeping the SVR estimate of SOF+RBV at 92.3%) results in DCV+SOF+RBV to be dominated by SOF+RBV.

(4) SOF+PR is cost-effective at £30,000 per QALY gained; ICER=£27,724 per QALY gained.

CE: cost-effective intervention at £20,000 per QALY. ICER: Incremental cost-effectiveness ratio £/QALY gained. BOC: boceprevir; DCV: daclatasvir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir. NA: not applicable. Cost-effective DCV-containing comparators are highlighted in bold. Grey shadowing highlights different results from the ERG base-case.

6.3.7 ERG's exploratory analysis

6.3.7.1 Watchful waiting

The ERG is concerned that the watchful waiting comparator described by NICE may be a more relevant alternative than no treatment because patients may receive treatment at a later date, possibly upon disease worsening. As an illustrative analysis, the ERG therefore explored the impact of watchful waiting strategies in the genotype 1 treatment naïve F3 subpopulation.

In the watchful waiting strategy, patients are followed up without treatment until they reach F4. Patients are then treated with one of the currently available options for this subpopulation: PR, SMV+PR or SOF+PR. SMV+PR is used as representative of the protease inhibitors in this exploratory analysis as TVR+PR and BOC+PR are dominated options in genotype 1 treatment naïve F4 patients.

This approach was implemented in the model by modifying the no treatment arm. In the watchful waiting analysis, all patients in the no treatment arm who transition from F3 to F4 are immediately treated (with PR, SMV+PR or SOF+PR depending on the watchful waiting comparator). They may either experience response and move to the SVR F4 state or fail to respond and move to the F4 state. The proportion of patients responding is taken from the ERG base-case rates of response to PR, SMV+PR or SOF+PR in genotype 1 treatment naïve F4 patients.

The results of this analysis are presented in Table 57. In this subpopulation, all watchful waiting comparators are dominated by PR and do not impact upon the cost-effectiveness of DCV-containing regimens. It should be noted that this analysis makes the assumptions that transition to F4 is identified immediately and treatment is initiated immediately for all patients who transition to F4.

Table 57 Results of analysis including watchful waiting comparators in ERG base-case analysis for genotype 1 treatment naïve F3 patients

Intervention	Cost	QALYs	ICER (£/QALY)
PR	£31,003	10.41	Reference
NT→PR	£32,641	9.41	Dominated
NT	£37,903	8.88	Dominated
SMV+PR	£40,455	11.53	8,428
NT→SMV+PR	£42,330	9.83	Dominated
TVR+PR	£44,387	11.14	Dominated
NT→SOF+PR	£44,532	10.22	Dominated
SOF+PR	£45,915	12.06	10,330
BOC+PR	£48,290	10.44	Dominated

Intervention	Cost	QALYs	ICER (£/QALY)
DCV+SOF	£61,339	12.84	19,739

BOC: boceprevir; DCV: daclatasvir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir. NT: no treatment. ICER=incremental cost-effectiveness ratio. QALY=quality adjusted life year.

Watchful waiting strategies are described as NT followed by (→) comparator received at F4.

This analysis suggests that watchful waiting may not be a cost-effective strategy in F3 patients (though further analysis would be required to demonstrate this in other F3 subpopulations). This is perhaps unsurprising as treatment of patients in F3 avoids (for the SVR patients) transition to F4 or F4 SVR, both of which are associated with reduced HRQoL. It should however be noted that the watchful waiting strategy using PR on transition to F4 dominates the no treatment comparator. This suggests that the costs and QALYs associated with no treatment may be underestimated for all comparisons in which watchful waiting is considered appropriate.

6.3.7.2 Treatment sequencing: using DCV as second line following non-response

DCV+SOF was found in both the ERG base-case analysis and the manufacturer base-case analysis to be cost-effective in treatment naïve and treatment experienced F3 genotype 1 patients. This raises the question of whether it is optimal to use DCV in genotype 1 F3 patients who are treatment naïve or to use a comparator in treatment naïve patients (first line) followed by DCV+SOF (or in fact any other second line treatment) for patients who fail first line treatment. The ERG therefore explored the cost-effectiveness of using each available first-line option followed by each available second-line option in genotype 1 treatment naïve F3 patients. For first line treatments, the ERG focused on PR and SMV+PR (as the only non-dominated protease inhibitor-based treatment). For second line treatments, the ERG considered both possible second-line treatment options (SOF+PR, DCV+SOF). The ERG did not consider SOF+PR followed by SOF+PR or DCV+SOF as it unclear whether patients would receive two lines of SOF-containing treatment. The additional comparators considered in genotype 1 treatment naïve F3 patients were therefore:

- PR followed by SOF+PR in patients who fail to reach SVR
- PR followed by DCV+SOF in patients who fail to reach SVR
- SMV+PR followed by SOF+PR in patients who fail to reach SVR
- SMV+PR followed by DCV+SOF in patients who fail to reach SVR

This approach was implemented by modifying the PR and SMV+PR arms of the existing model to include an additional year of treatment for all patients who fail to achieve SVR with first line therapy. During this year patients who achieve SVR from first line treatment experience no further treatment and the HRQoL and risk of all-cause death as per the ERG base-case. All patients without SVR receive second line treatment (with the associated short term cost and HRQoL implications) and the possibility of experiencing response (a transition to SVR F3). Patients who do not experience an SVR

in year 2 are assumed to face the risk of progression from F3 to F4. Patients who experience an SVR in year 2 are assumed to face no risk of progression. For simplicity, all patients are assumed to experience health state costs throughout the first two years of the model.

Table 58 shows the results of this analysis. The cost-effective treatment option for genotype 1 treatment naïve F3 patients is to offer PR first line and then DCV+SOF for treatment failures. Compared to this option, DCV+SOF is associated with an ICER of £89,106 per QALY.

Table 58 Results of analysis including treatment sequencing comparators in ERG base-case analysis for genotype 1 treatment naïve F3 patients

Intervention	Cost	QALYs	ICER (£/QALY)
PR	£31,003	10.41	
PR→SOF+PR	£35,781	12.12	2,791
NT	£37,903	8.88	Dominated
SMV+PR	£40,455	11.53	Dominated
SMV+PR→SOF+PR	£42,560	12.11	Dominated
PR→DCV+SOF	£43,760	12.65	15,284
TVR+PR	£44,387	11.14	Dominated
SOF+PR	£45,915	12.06	Dominated
SMV+PR→DCV+SOF	£46,888	12.40	Dominated
BOC+PR	£48,290	10.44	Dominated
DCV+SOF	£61,339	12.84	89,106

BOC: boceprevir; DCV: daclatasvir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir. NT: no treatment. ICER=incremental cost-effectiveness ratio. ICER=incremental cost-effectiveness ratio. QALY=quality adjusted life year.

Treatment sequencing strategies are described as first-line comparator followed by (→) second-line comparator.

6.4 Conclusions from ERG analyses

6.4.1 Summary of cost-effectiveness of DCV-containing regimens

Table 59 presents a summary of the ERG base-case ICERs for DCV-based regimens in each subpopulations. These results are discussed in detail in the following two sub-sections.

Table 59 Summary of ERG base case ICERs for DCV- containing regimens

Genotype	Treatment status	F3 subpopulations, ICER (£/QALY)	F4 subpopulations, ICER (£/QALY)
		ERG base-case	ERG base-case
1	TN	19,739	118,636
	TE	15,687	105,972
	III	5,906	311,193

3	TN	254,711	139,045
	TE	Dominated	143,489
	III	9,607	172,219
4 – DCV+SOF	TN	36,203	150,076
	TE	5,906	73,768
	III	5,906	190,379
4 – DCV+PR	TN	Dominated	Dominated
	TE	Extendedly dominated	52,459
	III	NA	NA

TN: Treatment naïve. TE: Treatment experienced. III: Interferon intolerant or ineligible.

6.4.1.1 Patients with METAVIR fibrosis score F3

Both the manufacturers' and the ERG base-case found DCV+SOF to be cost-effective in the following populations at a threshold of £20-30,000 per QALY:

- Genotype 1 treatment naïve
- Genotype 1 treatment experienced
- Genotype 1 interferon ineligible or intolerant
- Genotype 3 interferon ineligible or intolerant
- Genotype 4 treatment experienced
- Genotype 4 interferon ineligible or intolerant

The robustness of each of these findings with respect to the sensitivity analysis conducted by the ERG is discussed below. Where appropriate, the ERG also discusses where extrapolation of SVR rates across clinical populations is likely to have introduced additional uncertainty or bias.

Genotype 1 treatment naïve: The ERG base-case ICER for DCV+SOF in this subpopulation was £19,739 per QALY (vs. SOF+PR). This result was found to be sensitive to using alternative SVR estimates for SOF+PR. Using a midway point between the cirrhotic and non-cirrhotic patients resulted in SOF+PR becoming cost-effective. The ICERs for DCV+SOF also went beyond a £20,000 per QALY cost-effectiveness threshold when UK estimates of progression from F3 to F4 were used (ICERs of £28,542 and £24,525 vs. SOF+PR when non-tertiary and tertiary data were used respectively).[40 122] The SVR rates used (with the exception of SOF+PR) do not seem to obviously bias in favour or against DCV+SOF in this subpopulation.

The ERG conducted exploratory analysis to assess the impact of incorporating treatment sequences in the model. These analysis suggest that it is likely to be much more cost-effective to treat patients with PR followed by DCV+SOF if they fail to achieve SVR with PR than to use DCV+SOF in all patients

as a first line treatment. In this more complete analysis, it therefore seems highly unlikely that DCV+SOF is cost-effective for first-line (treatment naïve) use.

Genotype 1 treatment experienced: The ERG base-case ICER for DCV+SOF in this subpopulation was £15,687 per QALY (vs. SOF+PR). This result was found to be sensitive to extending the duration of DCV+SOF treatment to 24 weeks for all patients and to using UK-based estimates of progression from F3 to F4, all of which resulted in SOF+PR becoming cost-effective (though when tertiary centre progression rates were used DCV+SOF remained cost-effective at a threshold of £30,000 with an ICER of £23,152 vs. SOF+PR).[122] The ERG considers that the SOF+PR SVR rates in this subpopulation are associated with considerable additional uncertainty as they are based on an extrapolation from treatment naïve to treatment experienced patients conducted by the FDA. The DCV+SOF data in this population relate to a 24 week treatment duration and may therefore overestimate SVR rates for the 12 week licensed duration.

Genotype 1 interferon ineligible or intolerant: DCV+SOF remained cost-effective in all ERG sensitivity analyses with ICERs ranging from £5,906 to £10,196 per QALY (vs. no treatment). In all sensitivity analyses DCV+SOF dominated SMV+SOF. The ERG does not consider the SVR rates to be biased in favour or against DCV+SOF in the comparison of these treatments. The comparison with no treatment may be biased in favour of both active treatments due to the use of treatment naïve data in the interferon ineligible or intolerant population.

Genotype 3 interferon ineligible or intolerant: DCV+SOF remained cost-effective in all ERG sensitivity analyses with ICERs ranging from £9,238 to £14,354 per QALY (vs. no treatment). No active comparators are included in this subpopulation. Again, this ICER may be biased due to the extrapolation of treatment naïve data to interferon ineligible or intolerant patients.

Genotype 4 treatment experienced: DCV+SOF remained cost-effective in all ERG sensitivity analyses (ICERs £5,906 to £10,196 per QALY vs. no treatment). Results for this subgroup are subject to uncertainty due to the extrapolation of genotype 1 data to genotype 4 patients for DCV+SOF.

Genotype 4 interferon ineligible or intolerant: DCV+SOF remained cost-effective in all ERG sensitivity analyses with ICERs ranging from £5,906 to £10,196 per QALY (vs. no treatment). In all sensitivity analyses, DCV+SOF dominated SMV+SOF. The ERG does not consider the SVR rates to be biased in favour of DCV+SOF in the comparison of the active treatments. However, the comparison with no treatment may be biased in favour of both active treatments due to the use of treatment naïve data in the interferon ineligible or intolerant population. Uncertainty is also increased due to the extrapolation of genotype 1 data to genotype 4 patients for both comparators.

In all other subgroups (genotype 3 treatment naïve or treatment experienced, genotype 4 treatment naïve), DCV-containing regimens were not cost-effective in the manufacturer base-case or any of the ERG sensitivity analyses. In genotype 3 treatment naïve patients, DCV+SOF was associated with an ICER of £254,711 compared to PR (incremental costs £54,136 and incremental QALYs 0.21). In genotype 3 treatment experienced patients, DCV+SOF is dominated by SOF+PR (incremental costs £28,771 and incremental QALYs -0.51). In genotype 4 treatment naïve patients, DCV+SOF is associated with an ICER of £36,203 per QALY compared to SMV+PR (incremental costs £26,064, incremental QALYs 0.72). DCV+PR is dominated in this subgroup. The finding that DCV+SOF is not cost-effective in genotype 3 treatment naïve or experienced patients is likely to be robust given the high ICERs. For genotype 4 treatment naïve patients, relatively small changes to the SVR rates could plausibly result in DCV+SOF becoming cost-effective. However, and although not explored by the ERG, it seems possible that a more cost-effective strategy in this subpopulation would be to use SMV+PR as a first-line treatment and DCV+SOF as a second-line treatment.

6.4.1.2 Patients with METAVIR fibrosis score F4

In the ERG's base-case, none of the DCV-containing regimens were found to be cost-effective at in the F4 population at cost-effectiveness thresholds of £20 to £30,000. The ERG's findings are in contrast to the manufacturers' findings in four of the nine F4 subpopulations. The reasons for these differences are summarised below:

Genotype 1 treatment experienced: DCV+SOF was found to be cost-effective by the manufacturer. However, the ERG's base-case, which included SOF+PR, found this comparator to be cost-effective. The comparison of DCV+SOF to SOF+PR in the ERG analysis found DCV+SOF to be associated with an ICER of £105,972 per QALY (incremental costs £73,601, incremental QALYs 0.69).

Genotype 3 interferon ineligible or intolerant: DCV+SOF+RBV was found to be cost-effective by the manufacturer but SOF+RBV was found to be cost-effective by the ERG following adjustment of the SVR rates to reflect the licensed duration of SOF+RBV in this subpopulation. The comparison of DCV+SOF+RBV to SOF+RBV in the ERG analysis found DCV+SOF to be associated with an ICER of £172,219 per QALY (incremental costs £43,397 and incremental QALYs 0.25).

Genotype 4 treatment experienced: DCV+PR was found to be cost-effective by the manufacturer but the ERG's base-case which included SOF+PR found this comparator to be cost-effective. The comparison of DCV+PR to SOF+PR in the ERG analysis found DCV+PR to be associated with an ICER of £52,459 per QALY (incremental costs £9,534 and incremental QALYs 0.18).

Genotype 4 interferon ineligible or intolerant: DCV+SOF was found to be cost-effective by the manufacturer. However, the ERG's base-case, which included SMV+SOF, found this comparator to

be cost-effective. The comparison of DCV+SOF to SMV+SOF found DCV+SOF to be associated with an ICER of £190,379 per QALY (incremental costs £57,998 and incremental QALYs 0.30).

In the other F4 subpopulations the ERG base-case analyses found DCV-containing regimens to be associated with ICERs of £118,636-311,913 per QALY or to be dominated.

Further sensitivity analyses around the ERG's base-case resulted in DCV-containing regimens becoming cost-effective in the following cases:

- DCV+SOF becomes cost-effective at a threshold of £30,000 per QALY in genotype 1 treatment naïve patients when the treatment duration of DCV+SOF is reduced to 12 weeks for all patients (ICER: 24,074 per QALY vs. SOF+PR).
- DCV+SOF becomes cost-effective at a threshold of £30,000 per QALY in interferon ineligible and intolerant patients with genotype 1 and 4 (ICERs is £25,349 vs. no treatment for both groups) when SMV+SOF is excluded as a comparator.
- DCV+SOF+RBV becomes cost-effective in genotype 3 interferon ineligible or intolerant patients at a threshold of £30,000 per QALY (ICER £24,477 per QALY vs. no treatment when the SVR estimate for SOF+RBV from the manufacturer submission is used (which reflects the effectiveness of a shorter duration of SOF+RBV than licensed).
- DCV+PR becomes cost-effective (ICER £8,775 per QALY vs. PR) in genotype 4 treatment experienced patients when the duration of therapy with SOF+PR is extended to 24 weeks for all patients.

7 End of life

The manufacturer's submission states that life expectancy for patients with chronic HCV is generally at least 20 years, including for patients with the most advanced fibrosis or compensated cirrhosis. Daclatasvir-based regimens and other treatments which offer SVR may offer extensions to average survival time by delaying the onset of decompensated liver disease and hepatocellular cancer; however this has not been demonstrated to date. Daclatasvir is indicated for a relatively large patient population. The ERG therefore concludes that end of life criteria do not apply in this case.

8 Overall conclusions

8.1 Clinical effectiveness

The manufacturer's submission presented data on daclatasvir in combination with different treatments, across genotypes 1,3 and 4, for patients with and without prior treatment experience, and at a range of disease severities. A summary of the SVR rates found in the four submitted trials of daclatasvir –based regimens is given in Table 60.

Table 60: Summary of submitted trials on clinical effectiveness of daclatasvir

	Treatment naïve	Treatment experienced	Data source
All patients (METAVIR F0 – F4)			
Genotype 1			
DCV+SOF (12-24 weeks)	100% (70/70)	100% (21/21)	AI444-040
DCV+SOF+RBV (12-24 weeks)	98% (55/56)	100% (20/20)	AI444-040
DCV+PR (12 weeks)	60% (88/146)	No data	AI444-010
Genotype 3			
DCV+SOF+RBV (24 weeks)	100% (5/5)	No data	AI444-040
DCV+SOF (24 weeks)	85% (11/13)	No data	AI444-040
DCV+SOF (12 weeks)	90% (91/101)	86% (44/51)	ALLY-3
Genotype 4			
DCV+SOF	No data		
DCV+PR (24 weeks)	82% (67/82)	No data	AI444-042
DCV+PR (12 weeks)	100% (12/12)	No data	AI444-010
Compensated cirrhosis (METAVIR 4)			
Genotype 1			
DCV+SOF (12-24 weeks)	[redacted]	[redacted]	AI444-040
DCV+SOF+RBV (12-24 weeks)	[redacted]	[redacted]	AI444-040
DCV+PR (12 weeks)	[redacted]	[redacted]	AI444-010
Genotype 3			
DCV+SOF+RBV (24 weeks)	[redacted]	[redacted]	AI444-040
DCV+SOF (24 weeks)	[redacted]	[redacted]	AI444-040
DCV+SOF (12 weeks)	58% (11/19)	69% (9/13)	ALLY-3
Genotype 4			
DCV+SOF	No data		
DCV+PR (24 weeks)	[redacted]	[redacted]	AI444-042
DCV+PR (12 weeks)	[redacted]	[redacted]	AI444-010

BOC: boceprevir; DCV: daclatasvir; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir. NT: no treatment.

In general the ERG concurs with the manufacturer in concluding that daclatasvir, either in combination with sofosbuvir or PR, has a high SVR rate, potentially approaching 100% in some categories (e.g. genotype 1 patients without advanced fibrosis). This effect appears to be consistent across genotypes 1 and 3, and potentially for genotype 4 also, although no data on daclatasvir

combined with sofosbuvir were available in genotype 4 patients. Daclatasvir in combination with sofosbuvir appears similarly effective in patients with and without prior treatment experience, although numbers of patients with treatment experience were small.

The ERG disagrees with the manufacturer's conclusion that daclatasvir-based treatment was equally effective in patients with advanced fibrosis or compensated cirrhosis as in patients without them. This conclusion was based on the high SVR rates among a very few patients in the AI444-040 trials with cirrhosis. In the ALLY-3 trial SVR rates were rather lower in patients with compensated cirrhosis. These patients received a shorter course of treatment, without ribavirin, and this may partially explain the lower SVR rates. However, based on the limited evidence presented ERG notes that the efficacy of daclatasvir may be lower in patients with compensated cirrhosis: but that it is not has not been demonstrated adequately.

The manufacturers reported no specific conclusions on the relative effectiveness of daclatasvir when compared to other treatments. Evidence was limited by the fact that the key daclatasvir plus sofosbuvir trials had no control arms, so most treatment comparisons were indirect and observational in nature, and not randomised, and so prone to bias. The randomised trials provided good evidence that daclatasvir combined with PR gives superior SVR rates than PR alone. For genotype 1, treatment-naïve patients, the benchmarking and MAIC analyses presented good evidence that daclatasvir with sofosbuvir has superior SVR rates than PR, boceprevir or telaprevir. Daclatasvir plus sofosbuvir also appeared to have similar or higher SVR rates than simeprevir with PR and sofosbuvir with PR, although data on these two treatment combinations were limited. In genotype 3 patients daclatasvir with sofosbuvir was not found to be clearly superior to any other treatments. For treatment-experienced patients or patients with advanced fibrosis/compensated cirrhosis data were too limited to draw any firm conclusions.

The ERG concurs with the manufacturer's conclusion that daclatasvir has a good adverse event profile. Evidence from the two randomised trials showed that daclatasvir with PR had a broadly similar rate of adverse events as PR alone. Evidence from MAIC analyses suggested that daclatasvir with sofosbuvir had similar or lower rates of adverse events than other treatments (boceprevir, telaprevir, sofosbuvir and simeprevir, each in combination with PR) in both genotype 1 and genotype 3 patients.

8.2 Cost-effectiveness

The ERG undertook a number of exploratory and sensitivity analyses to the manufacturer's model. The corrections of the anomalies found in the manufacturer's model had a minor impact on the results. The ERG changed a range of parameters in the model that together constitute the ERG's base-case. Those changes include (i) the inclusion of all relevant comparators and exclusion of the

regimens not recommended by NICE in the recent appraisals of sofosbuvir and simeprevir, (ii) alternative SVR estimates for a number of regimens, (iii) alternative progression rates for genotype 4, (iv) allowing cirrhotic patients to progress to decompensated cirrhosis and HCC, (v) reducing their HRQoL improvement in line with F2 and F3 patients and (vi) assigning cirrhotic patients lifetime monitoring costs. In the ERG's base-case, for the F3 subpopulations, daclatasvir + sofosbuvir is cost-effective in genotype 1 treatment naïve, treatment experienced and interferon ineligible or intolerant, in genotype 3 interferon ineligible or intolerant, and in genotype 4 treatment experienced and interferon ineligible or intolerant. In F4 (cirrhotic) patients, daclatasvir-containing regimens are not cost-effective in any of the subpopulations. The difference in results between the ERG's and the manufacturer's base-case is driven by the addition of relevant comparators and removal of comparators not recommended by NICE, and by the use of alternative SVR estimates.

The ERG conducted a number of sensitivity analysis to its base-case in order to explore the impact of uncertainties in the evidence on the results. The results were sensitive to changes in treatment duration and to alternative SVR estimates. Specifically, at the £30,000 per QALY threshold, in the F3 (non-cirrhotic) genotype 1 treatment naïve subpopulation, using a higher estimate of SVR for sofosbuvir+PR to reflect that F3 patients may experience better outcomes than cirrhotic patients resulted in sofosbuvir+PR comparator becoming cost-effective instead of daclatasvir +sofosbuvir. In addition, in the F3 (non-cirrhotic) genotype 1 treatment experienced subpopulation, assuming a 24 week treatment duration for daclatasvir +sofosbuvir resulted in sofosbuvir+PR becoming cost-effective. At a cost-effectiveness threshold of £20,000 per QALY the results are also sensitive to the use of alternative rates of progression from F3 to F4 in treatment naïve and experienced genotype 1 patients. In the F4 (cirrhotic) subpopulation, daclatasvir-containing regimens became cost-effective at a threshold of £30,000 per QALY in genotype 1 treatment naïve patients when a 12 week treatment duration for daclatasvir +sofosbuvir was used and in genotype 3 interferon ineligible or intolerant patients when an alternative SVR rate was used for sofosbuvir+RBV. Daclatasvir+PR also became cost-effective at a cost-effectiveness threshold of £20,000 when the duration of sofosbuvir+PR was extended to 24 weeks in genotype 4 treatment experienced patients.

The ERG conducted two exploratory analyses in the genotype 1 treatment naïve F3 patients, one including watchful waiting strategies and the other including treatment sequence strategies. The results were robust to the inclusion of watchful waiting strategies. The treatment sequences strategies consist of trying patients on cheaper less effective regimens and reserving the more expensive regimens, such as daclatasvir +sofosbuvir or sofosbuvir+PR, as second line for patients who do not achieve SVR. The results suggest that the cost-effective regimen for this subpopulation is to offer PR as a first line then daclatasvir +sofosbuvir as second line for treatment failures.

8.3 Strengths, weaknesses and areas of uncertainty

8.3.1 Strengths

The manufacturer's submitted evidence on clinical effectiveness broadly covered the final scope set out by NICE. The review of daclatasvir trials included all relevant trials in which daclatasvir had been used. Reviews for other treatments were likely to have identified the majority of trials of other relevant treatments. The submission covers the key clinical outcomes, including SVR rates, adverse events and mortality.

The manufacturers' cost-effectiveness analysis generally follows the NICE reference case and the NICE scope, with the exceptions discussed above. The populations considered generally capture key distinct subpopulations that differ with respect to available treatments and outcomes. The model simulates the costs and benefits over the patients' lifetime. Its structure is appropriate and similar to other models used in previous hepatitis C appraisals. The ERG considers that the manufacturer's model captures most important health outcomes associated with the treatment and natural history of chronic hepatitis C. The ERG considers the selection of data on quality of life and resource use and costs in the model to be generally appropriate.

8.3.2 Weaknesses and areas of uncertainty

Some caution is warranted regarding the clinical efficacy of daclatasvir due to the following concerns:

- The two studies that evaluated combinations of daclatasvir and sofosbuvir did not have a control group, and may therefore be at high risk of bias. Despite the objective endpoints employed in the trials the lack of a control group means that the true efficacy of daclatasvir +sofosbuvir is uncertain.
- All trials of daclatasvir had small sample sizes, reducing confidence in the reliability of their results.
- SVR12-24 results in patients with METAVIR score F3 or F4, or with a diagnosis of compensated cirrhosis or with prior treatment experience were all based on small subgroups and their reliability is limited. Therefore there is great uncertainty around the efficacy of daclatasvir in these important subgroups of patients.
- Evidence was unavailable for daclatasvir based comparators in some patient subgroups in which daclatasvir is licensed:
    - DCV+SOF in genotype 1 treatment-experienced patients. All evidence comes from the 040 trial which used a 24 week treatment duration in these patients whereas the license for non-cirrhotic patients is 12 weeks (with allowance for a 24 week duration).
    - No evidence is available for DCV+SOF in genotype 4 patients.
    - No evidence is available for DCV+SOF in interferon ineligible or intolerant patients across genotypes.

  - No evidence is available for DCV+SOF±RBV in genotype 3 patients with compensated cirrhosis and/or treatment experience for the 24 week treatment duration. These patient groups are currently licensed to receive 24 weeks of treatment, [redacted]
  - No evidence is available for DCV+PR in genotype 4 treatment experienced patients.
- All comparisons of daclatasvir with other treatments were based on indirect comparisons. These are neither randomised nor controlled comparisons and so may be prone to error and bias, particularly if trial conditions or patient populations varied across trials

The major weaknesses in the cost-effectiveness submission consist of: (i) the inappropriate analysis of the F0-F2 population, (ii) heterogeneity in the treatment experienced subpopulations, (iii) exclusion of relevant comparators, (iv) quality of the SVR data, (v) experience of the F4 (cirrhotic) patients who achieve SVR and (vi) progression of patients with chronic hepatitis C in the natural history model. In addition, the model did not quantify the benefits of reduced onward transmission of hepatitis C in a way that could robustly inform decision making.

8.3.3 Areas of uncertainty

The clinical effectiveness of daclatasvir remains uncertain in a number of areas. As the key daclatasvir (plus sofosbuvir) trials were not randomised controlled trials some uncertainty remains over the accuracy of estimates of SVR in these trials given their potential for bias. Considerable uncertainty remains over the effectiveness of daclatasvir combined with sofosbuvir in patients with advanced fibrosis or compensated cirrhosis. This arises because of the inconsistency in SVR rates in compensated cirrhosis patients between the AI444-040 and ALLY-3 trials. Because patients in ALLY-3 received a shorter course of treatment without ribavirin it is unclear whether the poorer SVR rates in that trial are due to treatment differences, differences between genotypes, or are genuine difference in effectiveness in patients with compensated cirrhosis. Limited or absent data mean the effectiveness of daclatasvir-based regimens is also uncertain or unknown in a number of additional key patient subgroups including: patients with treatment experience (particularly in genotypes 1 and 4), patients intolerant of or ineligible for interferon, patients of genotype 4, patients co-infected with HIV and patients post liver transplant.

A key area of uncertainty is the relative effectiveness of daclatasvir when compared to other treatments (e.g. telaprevir, boceprevir, sofosbuvir, simeprevir). As the key daclatasvir trials did not contain a comparator arm all treatment comparisons are indirect and uncontrolled and hence have the potential for bias. While the submission made some attempts to compensate for such bias it is not certain if this was sufficient. As such it is not possible to reliably determine whether daclatasvir (in

combination with sofosbuvir or PR) is more or less effective than other potential newer treatments for HCV (particularly sofosbuvir and simeprevir).

For the assessment of cost-effectiveness the major area of uncertainty is the treatment effectiveness, i.e. SVR rates, of daclatasvir-containing regimens and its comparators across the different subpopulations. As discussed above, SVR is a key cost-effectiveness driver in that it is associated with a halt in disease progression, increase in quality of life and zero long-term costs. However, SVR rates used in the model were obtained from individual trial arms rather than randomised comparisons or a mixed treatment comparison. They represent an unadjusted non-randomised comparison. SVR rates may be biased if the individual trial arms are not comparable in all factors that affect outcomes. The high risk of bias makes the SVR rates very uncertain. In addition, the SVR rates were frequently extrapolated between subpopulations with different disease severities, treatment histories and sometimes genotypes. This extrapolation compounds the uncertainty in the SVR rates.

Another important area of uncertainty is treatment duration. For two treatments, daclatasvir +sofosbuvir and SOF+PR, the marketing authorisations allow for alterations to the licensed treatment durations for specific subpopulations. daclatasvir +sofosbuvir can be increased from 12 to 24 weeks in genotype 1 treatment experienced non-cirrhotic patients and reduced from 24 to 12 weeks in genotype 1 or 4 treatment naïve cirrhotic patients with positive prognostic factors. sofosbuvir+PR can be extended to 24 weeks in patients with characteristics predictive of low response. The proportion of patients which will require these modifications in practice is a significant source of uncertainty regarding the total cost of these comparators. No evidence has been provided by the manufacturer regarding these proportions.

8.4 Implications for research

As neither of the two key daclatasvir trials presented in the submission were randomised controlled trials, there is a particular need to test the efficacy of daclatasvir combined with sofosbuvir (with or without ribavirin) in randomised controlled trials. Ideally these trials should compare daclatasvir based treatment to other treatments likely to be highly effective (e.g. sofosbuvir, or sofosbuvir combined with simeprevir). Such trials should seek to recruit patients across the full spectrum of genotypes, disease severities and prior treatment experience.

There is a particular need to accurately determine the SVR rate using daclatasvir combined with sofosbuvir (with or without ribavirin) in patients with advanced fibrosis and/or compensated cirrhosis (METAVIR F3 and F4), across all genotypes. Ideally this should be obtained from randomised controlled trials as above, but single-arm trials focusing on patients with advanced disease may also be beneficial. Similarly, further trials are needed to focus on other small subgroups where data is

currently limited, including: genotype 4 patients, patients with treatment experience, patients ineligible/intolerant to interferon, patients with HIV co-infection and patients post liver transplant.

There are a number of new treatments for chronic HCV that have recently undergone, or are undergoing assessment including daclatasvir. Hence there is a need to formally compare the efficacy of these new treatments to determine their relative efficacy and to find which are most effective and cost-effective.

More research is required on the HRQoL benefit of achieving SVR, particularly in cirrhotic patients. This analysis could be conducted using the currently available individual patient data generated in the clinical trials of treatments for chronic hepatitis C. This research also has the potential to improve the evidence base on how disease severity and other patient characteristics can affect HRQoL in chronic hepatitis C.

A key area of research that emerges from this appraisal is in the development of improved methods and methodological guidance for synthesising disconnected networks of evidence including evidence from single arm trials. Although the literature is well developed for indirect comparisons between randomised controlled trials with common comparators, it is much less so when only evidence from single arm trials or trials without common comparators is available.

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10 Appendices

10.1 Appendix 1 SVR estimate

Appendix table 1. Compiled SVR rates based upon best available evidence: significant fibrosis (F3 to F4 non-cirrhotic) population

HCV genotype	Treatment experience/ Eligibility	Treatment regimen	SVR n/N (%)	SVR 12 or 24	Source	Manufacturer comments	ERG comments	ERG: Preferred value n/N (%)	Rationale for preferred value
1	Naive	DCV+SOF (vs TVR)	95	SVR24	MAIC[21]	*F3 to F4 subgroup analyses*	Source unclear; may have pooled F3-F4 across regimens	[redacted]	Includes [redacted] patients with F3 to F4 only from arm G (12 weeks treatment, no RBV, as per SPC)
		DCV+SOF (vs BOC)	100	SVR24	MAIC[21]	*F3 to F4 subgroup analyses*	Source unclear; may have pooled F3-F4 across regimens	[redacted]	Includes [redacted] patients with F3 to F4 only from arm G (12 weeks treatment, no RBV, as per SPC)
		DCV+SOF (vs SOF)	100	SVR12	MAIC[21]	*F3 to F4 subgroup analyses*	Source unclear; may have pooled F3-F4 across regimens	[redacted]	Includes [redacted] patients with F3 to F4 only from arm G (12 weeks treatment, no RBV, as per SPC)
		DCV+SOF (vs SMV)	100 40/40	SVR12	MAIC[21]	*F3 to F4 subgroup analyses*	Source unclear; may have pooled F3-F4 across regimens	[redacted])	Includes [redacted] patients with F3 to F4 only from arm G (12 weeks treatment, no RBV, as per SPC)
		DCV+SOF (vs other)	100 41/41	SVR12	AI444-040[4 5]	*F3 to F4 subgroup analyses*	Source unclear; may have pooled F3-F4 across regimens	[redacted]	Includes [redacted] patients with F3 to F4 only from arm G (12 weeks treatment, no RBV, as per SPC)
		TVR+PR	59	SVR24	MAIC[21] (ADVANCE AND ILLUMINATE pooled)	*F3 to F4 subgroup analyses*	Portal fibrosis or cirrhosis subgroup. All diagnosed with biopsy. Sample size unclear. Pooled analysis could not be replicated but results are plausible	59 [redacted]	No alternative SVR to suggest. Extracted SE from table 74 of MS
		BOC+PR	41	SVR24	MAIC[21]	*F3 to F4 subgroup analyses*	METAVIR 3 or 4 subgroup (biopsy confirmed), group 2 with BOC 24 wks+PR28-48 All diagnosed with biopsy N=34	14/34 (41.2)	No alternative SVR to suggest. Sample size extracted from METAVIR 3 or 4 subgroup in SPRINT-2 group 2 with BOC 24 wks+PR28-48
		SOF+PR	81	SVR12	MAIC[21] NEUTRINO	*F3 to F4 subgroup analyses*	This is based on data from patients with compensated cirrhosis: 42/52 (80.8%), likely to underestimate response	86.5%	NEUTRINO. Mid-point between non-cirrhotic 92% and compensated cirrhosis 81%.

							for F3-F4 without cirrhosis.		
		SMV+PR	68	SVR12	MAIC[21]	*F3 to F4 subgroup analyses*	"F3-F4" subgroup, 89/130	[redacted]	No alternative SVR to suggest. Sample size is from "F3-F4" subgroup, pooled data from QUEST-2 and QUEST-1 trials (Simeprevir SPC), which includes patients with GT1 1a Q80K. No F3-F4 data available for GT1 1a Q80K. Given the relatively small proportion of patients with Q80K, SVRs are unlikely to be significantly affected by their inclusion in this subgroup.
		PR	32/78 (41.2)	SVR24	NV15942[58] [57]	HCV genotype 1, 48 week 1000/1200 mg RBV (48-SD) arm; 'bridging fibrosis/cirrhosis' - not reported separately	'bridging fibrosis/cirrhosis' Data are from SVR 48	32/78 (41.2)	No alternative SVR to suggest.
	Experienced	DCV+SOF	20/20 (100.0)	SVR12	AI444-040[4 5]	Prior TVR+PR or BOC+PR failures (type of failure not specified), F3 to F4 subgroup analysis	Unclear which subgroup, presumably arm I?	[redacted]	Only F3-F4 patients from arm I
		SOF+PR	No data				Alternative clinically relevant data was used in SOF NICE appraisal	78%	FDA data (extracted from SOF FAD, p.36)
	Interferon ineligible/ Intolerant	DCV+SOF	41/41 (100.0)	SVR12	AI444-040[4 5]	Assumed as naïve, F3 to F4 subgroup analyses	Treatment naïve group G? If so, this includes F0 to F4	[redacted]	Includes [redacted] patients with F3 to F4 only from arm G (12 weeks treatment, no RBV, as per SPC)
		SOF+RBV	100/148 (67.6)	SVR12	QUANTUM and 11-1-0258[20 61]	Assumed as naïve in absence of data for interferon ineligible/intolerant population. "No cirrhosis group)	Combined data from SPC QUANTUM: naïve early-moderate fibrosis Fibrosis stage measured using biopsy in QUANTUM (0258 trial unclear)	100/148 (67.6)	No alternative data to suggest. Not recommended by NICE
		SMV+SOF	13/14 (92.9)	SVR12	COSMOS[15]	Assumed as naïve in absence of data for interferon ineligible/intolerant population. F3-F4 cohort.	Combined previous non-responders to PR (7) or treatment naïve (7), F3 and F4 based on liver biopsy	13/14 (92.9)	No alternative data to suggest
3	Naive	DCV+SOF+RBV	5/5 (100.0)	SVR12	AI444-040[4 5]	All genotype 3, F3 to F4 subgroup analysis	Source of data unclear. Data from arm F, subgroup with genotype 3? If so,	None	NA

							[redacted]		
		DCV+SOF	[redacted]	SVR12	ALLY-3[6]	Treatment-naïve, pooled F3 and F4 subgroup analyses	Treatment-naïve, pooled F3 and F4 subgroup analyses. Table 12 manufacturer response reports [redacted]	[redacted]	Based on data provided by manufacturer response to clarification, Table 12
		SOF+PR	No data					No data	No alternative data to suggest. Not recommended by NICE
		SOF+RBV	86/92 (93.5)	SVR12	VALENCE[19 20]	"No cirrhosis" population	"No cirrhosis", biopsy tested	86/92 (93.5)	No alternative data to suggest. Not recommended by NICE
		PR	99/139 (71.2)	SVR12	FISSION[14 20]	"No cirrhosis" population	"No cirrhosis", tested with biopsy, fibroscan or fibrotest/APRI	99/139 (71.2)	No alternative data to suggest
	Experienced	DCV+SOF+RBV	5/5 (100.0)	SVR12	AI444-040[4 5]	Assumed as naïve GT3 and GT1 PI failures, since no drop in SVR was seen for HCV genotype 1 treatment-experienced patients (who had received PI triple therapy and would be considered harder to treat than PR failures	Data source and fibrosis stage unclear	None	NA
		DCV+SOF	[redacted]	SVR12	ALLY-3[6]	Treatment-experienced, pooled F3 and F4 subgroup analyses Included patients with prior exposure to PR regimens, SOF+RBV, or investigational medicine. Included the following patient types: • Null responder • Partial responder • Relapser • Indeterminate • Intolerance • Breakthrough • HCV RNA never undetectable on treatment	Data checked	[redacted]	No alternative data to suggest (source: response to clarification, Table 12)
		SOF+PR	10/12 (83.3)	SVR12	LONESTAR-2[24]	"No cirrhosis" population	Data checked. Type of treatment experience of recruited patients not reported	10/12 (83.3)	No alternative data to suggest
		SOF+RBV	85/100	SVR12	VALENCE[19	Patients had previous	Data checked.	85/100	No alternative data to suggest

			(85.0)		20]	interferon-based treatment. Patients had discontinued prior treatment due to side effects, had no response or had relapse or breakthrough infection "No cirrhosis" population	matches SPC. Publication (Zeuzem 2014) reports 85/98 (87%))	(85.0)	(as per SOF MS) Not recommended by NICE
		PR	14/26 (53.8)	SVR72	HALT-C[123]	All patients were nonresponders to their most recent course of interferon-based therapy. Sixty-four percent had been previously treated with interferon and ribavirin. Genotype 3, all had bridging fibrosis/cirrhosis	Data checked.	14/26 (53.8)	No alternative data to suggest Genotype 3, all had bridging fibrosis/cirrhosis
	Interferon ineligible/ Intolerant	DCV+SOF+RBV	5/5 (100.0)	SVR12	AI444-040[4 5]	Assumed as naive	Arm F, subgroup with genotype 3? If so, [redacted]	[redacted]	[redacted] assumed as naive
		DCV+SOF	[redacted]	SVR12	ALLY-3[6]	Assumed as naive	Treatment-naïve, pooled F3 and F4 subgroup analyses. Table 12 manufacturer response reports [redacted]	[redacted]	As per Table 12 of manufacturer response. assumed as naive
		SOF+RBV	57/84 (67.9)	SVR12	POSITRON[20]	12-week regimen, "no cirrhosis"	12-week regimen, "no cirrhosis". There is no data on ineligible/intolerant patients for 24wks treatment, but VALENCE reports SVR rates for naïve non-cirrhotics: 93.5% (86/92) and experienced non-cirrhotics: 85.0% (85/100)	57/84 (67.9)	Not recommended by NICE
4	Naive	DCV+SOF	41/41 (100.0)	SVR12	AI444-040[4 5]	Assumed as genotype 1 naïve, F3–F4 subgroup analysis	Unadjusted arm G analysis from appendix 5b? If so, n=40, which includes all fibrosis stages	[redacted]	Includes [redacted] patients with F3 to F4 only from arm G (12 weeks treatment, no RBV, as per SPC). Assumed as GT 1
		DCV+PR	56/69 (81.2)	SVR12	AI444-042[7]	"No cirrhosis"	"No cirrhosis" subgroup. 56/69 using backward imputation (assigning later SVR to those with missing SVR12 data),	56/69 (81.2)	No alternative data to suggest.

							[redacted] Outcome definition is <LLOQ, TND or TD		
		SOF+PR	33/33 (100.0)	SVR12	NEUTRINO[14]	Pooled genotypes 4, 5 and 6, “no cirrhosis”	Pooled genotypes 4, 5 and 6, “no cirrhosis”	33/33 (100.0)	No alternative data to suggest. Not recommended by NICE
		SMV+PR	29/35 (82.9)	SVR12	RESTORE[15]	Assumed as overall population	Treatment naïve, all fibrosis stages combined	29/35 (82.9)	No alternative data to suggest
		PR	17/38 (44.7)	SVR12	AI444-042[7]	‘No cirrhosis’	No cirrhosis subgroup	17/38 (44.7)	No alternative data to suggest
	Experienced	DCV+SOF	21/21 (100.0)	SVR12	AI444-040[4 5]	Assumed as genotype 1 PI failures, F3–F4 subgroup analysis	Arm I, all fibrosis stages combined?	[redacted]	Only F3-F4 patients from arm I
		DCV+PR	56/69 (81.2)	SVR12	AI444-042[7]	Assumed as naïve, “No cirrhosis”	Assumed as naïve, no data on experienced patients	56/69 (81.2)	No alternative data to suggest.
		SOF+PR	No data						No alternative data to suggest. Not recommended by NICE
		SMV+PR	41/72 (56.9)	SVR12	RESTORE[15]	Prior relapsers, partial responders and null responders. Assumed as overall population	Prior relapsers, partial responders and null responders. All fibrosis stages combined, including 28.8% F4). Prior relapsers: 19/22 (86.4%) Partial responders: 6/10 (60.0%) Null responders: 16/40 (40.0%)	41/72 (56.9)	No alternative data to suggest
		PR	1/6 (16.7)	SVR72	HALT-C[123]	All patients were nonresponders to their most recent course of interferon-based therapy. Sixty-four percent had been previously treated with interferon and ribavirin. All had bridging fibrosis/cirrhosis, genotypes 4–6	Unclear how many of the 6 patients had genotype 4. 39% of total study sample had cirrhosis	1/6 (16.7)	No alternative data to suggest
	Interferon ineligible/ Intolerant	DCV+SOF	41/41 (100.0)	SVR12	AI444-040[4 5]	Assumed as genotype 1 naive	Treatment naïve group G, which includes F0 to F4 ?	[redacted]	Includes [redacted] patients with F3 to F4 only from arm G (12 weeks treatment, no RBV, as per SPC)
		SOF+RBV	No data						No alternative to suggest. Not recommended by NICE

		SMV+SOF	No data	Alternative clinically relevant data was used in SMV NICE appraisal	89.5%	COSMOS (genotype 1 TN, F3-F4) as per the NICE appraisal of SMV.[23]
BOC: boceprevir; DCV: daclatasvir; MAIC: matching-adjusted indirect comparison; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SOF: sofosbuvir; SVR: sustained virologic response; TVR: telaprevir						

Appendix table 2. Compiled SVR rates based upon best available evidence: compensated cirrhosis population

HCV genotype	Treatment experience/ Eligibility	Treatment regimen	SVR n/N (%)	SVR12 or 24	Source	Manufacturer comments	ERG comments	ERG: Preferred value n/N (%)	Rationale for preferred value
1	Naive	DCV+SOF	41/41 (100.0)	SVR12	AI444-040[4 5]	Groups I & J: Prior TVR+PR or BOC+PR failures (type of failure not specified), F3 to F4 subgroup analysis	Source unclear; may have pooled F3-F4 across regimens	[redacted]	Includes [redacted] patients with F4 only from arm G (12 weeks treatment, no RBV, as per licence)
		TVR+PR	13/21 (61.9)	SVR24	ADVANCE[13]	T12PR arm, 'Cirrhosis'	All cirrhosis confirmed by biopsy	13/21 (61.9)	No alternative data to suggest
		BOC+PR	22/42 (52.4)	SVR24	SPRINT-2[12]	Group 3 (appropriate regimen for cirrhotic patients); F3 or F4 subgroup analysis (not split by cirrhosis)	F3 or F4 subgroup, biopsy confirmed	22/42 (52.4)	No alternative data to suggest
		SOF+PR	43/54 (79.6)	SVR12	NEUTRINO[14]	"Cirrhosis"	Cirrhosis subgroup (confirmed by biopsy, fibroscan or-fibrotest+APRI)	43/54 (79.6)	No alternative data to suggest
		SMV+PR	29/48 (60.4)	SVR12	QUEST 1 and QUEST 2[15]	"F4"	"F4 (cirrhosis)"	29/48 (60.4)	No alternative data to suggest
		PR	32/78 (41.2)	SVR24	NV15942[58] [57]	HCV genotype 1, 48 week 1000/1200 mg RBV (48-SD) arm; 'bridging fibrosis/cirrhosis' - not reported separately	HCV genotype 1, 48 week 1000/1200 mg RBV (48-SD) arm; 'bridging fibrosis/cirrhosis'	32/78 (41.2)	No alternative data to suggest
	Experienced	DCV+SOF	20/20 (100.0)	SVR12	AI444-040[4 5]	PI failures, prior TVR+PR or BOC+PR failures (type of failure not specified) F3 to F4 subgroup analysis	Arm I? If so, [redacted]	[redacted]	Includes [redacted] patients with F4 only from arm I
		SOF+PR		No data				78%	FDA data (extracted from SOF FAD) [25]
	Interferon ineligible/intolerant	DCV+SOF	41/41 (100.0)	SVR12	AI444-040[4 5]	Assumed as naive	Source unclear; may have pooled F3-F4 across regimens	[redacted]	Assumed as naïve
		SOF+RBV	4/11 (36.4)	SVR12	QUANTUM and 11-1-0258[20 61]	Assumed as naïve in absence of data for interferon ineligible/intolerant population. "Cirrhosis"	Combined data from SPC QUANTUM "cirrhosis" group	4/11 (36.4)	Not recommended by NICE[25]
		SMV+SOF	13/14 (92.9)	SVR12	COSMOS[15]	Assumed as naïve in absence of data for interferon ineligible/intolerant	previous non-responders to PR (7/14) or treatment naïve (7/14), F3 and F4	13/14 (92.9)	No alternative data to suggest

						population.	based on a liver biopsy		
3	Naive	DCV+SOF+RBV	5/5 (100.0)	SVR12	AI444-040[4 5]	All genotype 3, F3 to F4 subgroup analysis	Is this SVR12 result from arm F, subgroup with genotype 3? If so, [redacted]	None	NA
		DCV+SOF	[redacted]	SVR12	ALLY-3[6]	Treatment-naïve, cirrhosis present	Naïve cirrhotics subgroup (diagnosed by biopsy, fibrotest or fibroscan)	[redacted]	No alternative data to suggest
		SOF+PR	No data				Alternative clinically relevant data was used in SOF NICE appraisal	10/12 (83.3%)	LONESTAR-2[24] (genotype 3 TE, 83.3% response observed both in 12 cirrhotic and 12 non-cirrhotic patients), assumed as TE, as in the NICE appraisal of SOF[25]
		SOF+RBV	12/13 (92.3)	SVR12	VALENCE[19 20]	"Cirrhosis"	Cirrhosis subgroup, biopsy tested	12/13 (92.3)	No alternative data to suggest
		PR	11/37 (29.7)	SVR12	FISSION[14 20]	FISSION used as best source of genotype- and cirrhosis-specific SVRs. 'Cirrhosis'	"cirrhosis" subgroup Tested with biopsy, fibroscan or fibrotest/APRI	11/37 (29.7)	No alternative data to suggest
	Experienced	DCV+SOF+RBV	5/5 (100.0)	SVR12	AI444-040[4 5]	Assumed as naïve GT3 and GT1 PI failures, since no drop in SVR was seen for HCV genotype 1 treatment-experienced patients (who had received PI triple therapy and would be considered harder to treat than PR failures	Arm F, subgroup with genotype 3? If so, [redacted]	None	NA
		DCV+SOF	[redacted]	SVR12	ALLY-3[6]	Treatment-experienced, cirrhosis present Included patients with prior exposure to PR regimens, SOF+RBV, or investigational medicine. Included the following patient types: • Null responder • Partial responder • Relapser • Indeterminate • Intolerance	Treatment experienced cirrhotics subgroup (diagnosed by biopsy, fibrotest or fibroscan)	[redacted]	No alternative data to suggest

						• Breakthrough • HCV RNA never undetectable on treatment			
		SOF+PR	10/12 (83.3)	SVR12	LONESTAR-2[24]	Type of treatment experience of recruited patients not reported “Cirrhosis”	“cirrhosis subgroup” (diagnostic method unknown)	10/12 (83.3)	No alternative data to suggest
		SOF+RBV	27/45 (60.0)	SVR12	VALENCE[19 20]	Patients had previous interferon-based treatment. Patients had discontinued prior treatment due to side effects, had no response or had relapse or breakthrough infection “Cirrhosis”	Previous IFN-based treatment. discontinued prior treatment due to side effects, no response or relapse or breakthrough infection “Cirrhosis subgroup”	27/45 (60.0)	Not recommended by NICE[25]
		PR	14/26 (53.8)	SVR72	HALT-C[123]	All patients were nonresponders to their most recent course of interferon-based therapy. 64% had been previously treated with interferon and ribavirin. Genotype 3, all had bridging fibrosis/cirrhosis	Data checked	14/26 (53.8)	No alternative data to suggest Genotype 3, all had bridging fibrosis/cirrhosis
	Interferon ineligible/intolerant	DCV+SOF+RBV	5/5 (100.0)	SVR12	AI444-040[4 5]	Assumed as naive	Arm F, subgroup with genotype 3? If so, [redacted]	[redacted]	[redacted] assumed as naive
		DCV+SOF	[redacted]	SVR12	ALLY-3[6]	Assumed as naive	Naïve cirrhotics subgroup (diagnosed by biopsy, fibrotest or fibroscan)	[redacted]	As per Table 12 of manufacturer response. assumed as naive
		SOF+RBV	3/14 (21.4)	SVR12	POSITRON[20]	12-week regimen, cirrhosis	Only 12 weeks treatment, whereas marketing authorisation recommends 24 weeks. There is no data on ineligible/intolerant patients for 24wks treatment, but VALENCE reports SVR rates for naïve cirrhotics: 92% (12/13)	12/13 (92%)	VALENCE (G3 TN cirrhotic). [19 20] Manufacturer used POSITRON data which used a 12 week rather than the 24 week license duration of therapy. Response for this comparator has been shown to be associated with treatment duration.
4	Naive	DCV+SOF	41/41 (100.0)	SVR12	AI444-040[4 5]	Assumed as genotype 1 naive	Source unclear; may have pooled F3-F4	[redacted]	Assumed as genotype 1 naïve. Includes[redacted] patients

							across regimens in genotype 1		with F4 only from arm G (12 weeks treatment, no RBV, as per SPC)
		DCV+PR	7/9 (77.8)	SVR12	AI444-042[7]	'Cirrhosis'	"Cirrhosis" subgroup (biopsy or fibroscan)	7/9 (77.8)	No alternative data to suggest
		SOF+PR	1/2 (50.0)	SVR12	NEUTRINO[14]	Pooled genotypes 4, 5 and 6, "cirrhosis"	Very small sample size. In NEUTRINO, 43/54 patients with cirrhosis (genotypes 1,4,5,6 combined) had SVR12, and 27/28 patients with genotype 4 (all fibrosis stages combined) HCV achieved SVR12.	43/54 (79.6%)	Manufacturer used an SVR based on a sample size of 2, extend to genotypes 1, 4, 5, 6 TN cirrhotic subpopulation to increase sample size to 54.
		SMV+PR	29/35 (82.9)	SVR12	RESTORE[15]	Assumed as overall population	Treatment naïve, all fibrosis stages combined	29/35 (82.9)	No alternative data to suggest
		PR	1/4 (25.0)	SVR12	AI444-042[7]	'Cirrhosis'	Cirrhosis, diagnosed with biopsy or fibroscan	1/4 (25.0)	No alternative data to suggest
	Experienced	DCV+SOF	20/20 (100.0)	SVR12	AI444-040[4 5]	Assumed as PI failures, prior TVR+PR or BOC+PR failures (type of failure not specified)	Arm I? If so, [redacted]	[redacted]	Assumed as PI failures, prior TVR+PR or BOC+PR failures, F4 only
		DCV+PR	7/9 (77.8)	SVR12	AI444-042[7]	Assumed as naive	Cirrhotics, assumed as naïve, no data on experienced patients	7/9 (77.8)	No alternative data to suggest
		SOF+PR	No data				ERG agrees no data are available. However, assumptions may be made to inform the economic model	68.6%	Treatment naïve data for SOF+PR (79.6% for G1-6 in NEUTRINO), minus the decrement assumed by the FDA for treatment experienced in genotype 1 (11%), as per SOF FAD p.36[25]
		SMV+PR	41/72 (56.9)	SVR12	RESTORE[15]	Prior relapsers, partial responders and null responders. Assumed as overall population	Prior relapsers, partial responders and null responders. All fibrosis stages combined. Prior relapsers: 19/22 (86.4%) Partial responders: 6/10 (60%) Null responders: 16/40 (40%)	41/72 (56.9)	No alternative data to suggest
		PR	1/6 (16.7)	SVR72	HALT-C[123]	All patients were nonresponders to their most recent course of interferon-based therapy.	Unclear how many of the 6 patients had genotype 4.	1/6 (16.7)	No alternative data to suggest

						Sixty-four percent had been previously treated with interferon and ribavirin. Bridging fibrosis or cirrhosis; cirrhosis and no cirrhosis pooled, genotypes 4–6 pooled	39% of total study sample had cirrhosis		
	Interferon ineligible/intolerant	DCV+SOF	41/41 (100.0)	SVR12	AI444-040[4 5]	Assumed as naive	Assumed as naïve genotype 1. Data are presumably from treatment naïve group G, which includes F0 to F4 ?	[redacted]	Only include F4 patients from arm G, assume as naïve with compensated cirrhosis
		SOF+RBV	No data					No data	No alternative to suggest. Not recommended by NICE
		SMV+SOF	No data				Agree no data are available. Assumptions may be made to inform the model.	89.5%	COSMOS (genotype 1 TN, F3-F4) as per the NICE appraisal of SMV[23]

BOC: boceprevir; DCV: daclatasvir; MAIC: matching-adjusted indirect comparison; PR: pegylated interferon-alfa+ribavirin; RBV: ribavirin; SOF: sofosbuvir; SVR: sustained virologic response; TVR: telaprevir

10.2 Appendix 2 Anomalies in the model and ERG's corrections

Anomaly	ERG correction
Rates from Thein et al were implemented as transition probabilities rather as transition rates.	• Transition rates were transformed into probabilities using the formula prob=1-exp(-rate*time) (p51 Briggs et al 2005) for F0-F1 to F1-F4 in sheet 'Markov' C11:D14. • Transition probabilities from Fattovich et al were transformed into rates to apply the genotype 3 multiplier from Kanwal et al then re-transformed into probabilities for F4 to HCC and DC to HCC, cells C18:D18 and C20:D20.
The half-cycle correction was incorrectly applied for costs and health state costs were not being applied for the year following SVR.	• Half-cycle corrected to average year n and year n-1 in the Markov trace in the treatment arm and the control arm in 'Markov (Half cycle correction)' cells G37:X116 and G136:X215. • SVR health state costs were given to everyone who got SVR in the year following treatment completion. Corrected in Markov (Half-cycle correction cells AP38:AT38 and AP138:AT138))
Data entry error in model for age-dependent transition probabilities, intercept for from F0 to F1 should be 2.0124 NOT 2.10400	• Corrected in Processed_Data sheet D338.
DCV+SOF for genotype 3 cirrhotic has 12 weeks treatment duration instead of 24 weeks	• Corrected in Data_G3_Treatment – duration of F4 treatment changed from 12 to 24 weeks, cells O19, R19, and U19.
Everyone in model incl. SVR is subject to mortality with Hep C mortality removed. Patients with SVR should experience the mortality of the general population (as reported in the MS).	• Created new column for unadjusted mortality in 'Lifetable' sheet in M13:M93. Cell M13=Sex*E13+(1-Sex)*F13 • Corrected in the VBA code: 'MM_MOD_MarkovProcess'
Remove baseline characteristics as probabilistic	• SE of baseline characteristics set to zero: o age, proportion male, initial disease severity in the 'Model control' sheet U32:U41. o Duration, alcohol, IDU, BT, design – in 'Data_Model' sheet (D163:D167) and in 'Processed_Data' sheet G308:G312.
The regimen DCV+SOF for interferon ineligible or intolerant genotype 4 F3-F4 does not exist in the model. However, the regimen for the same population but F0-F4 does exist and the inputs are the same.	• Made the F0-F4 DCV+SOF [AI444-040] applicable to all patients in 'Data_G4_Treatment'.
The price of DCV is £8,172.61 for 28 tablets (=2043.153 per week). However, the submission uses the price per week of £2,038.13.	• Changed in row 47 of the 'Data_G1, G3 and G4_Treatment' sheets.
SVR for genotype 3 treatment naïve and interferon ineligible or intolerant: DCV+SOF should read 75.0 (27/36).	• Corrected in 'Data_G3_Treatment' cells F9:F13 and L9:L13.
Baseline METAVIR distribution for the F3 population are being set to the values for an overall F3-F4 population.	• Cells T39:T40 in "Model Control" set to 100% and 0% respectively.
SVR: Sustained virological response. MS: Manufacturer's submission. DCV: Daclatasvir. SOF: Sofosbuvir.	

10.3 Appendix 3 Assessment of face validity of the manufacturer's model

In order to assess the face validity of the manufacturer's model, the ERG compared the event rates predicted by the model with those reported by published studies.[105 109 118] The table below details the methodology, the results and the ERG's comments to the results.

<table>
<tr><th>Comparison with</th><th>Method</th><th>Results</th><th>ERG's comment</th></tr>
<tr><td>Van der Meer et al[109]</td><td>The model cohort defined as per van der Meer at al: 48 years of age, 70% men, 54% F4, 46% F3, genotype 1 (since 68% of the van der Meer cohort had genotype 1), treatment naïve (since 90% of the cohort was treatment naïve.
The time horizon in the model was set as 8 years, similar to the 8.4 years in van der Meer et al.
Discount rate was set to 0%.
The outcomes compared were: all-cause death, liver-related death or liver transplantation, hepatocellular cancer, liver failure or decompensation.
Rates were approximated by dividing the cumulative incidence rate over the period of time (8 years) by 8.</td><td><table><tr><th rowspan="2">Outcome</th><th colspan="2">% Rate with SVR (95%CI)</th><th colspan="2">% Rate without SVR (95%CI)</th></tr><tr><th>Van der Meer</th><th>Model</th><th>Van der Meer</th><th>Model</th></tr><tr><td>Any event</td><td>1.43 (0.77-2.09)</td><td></td><td>5.79 (4.91-6.66)</td><td></td></tr><tr><td>All-cause death</td><td>1.01 (0.46-1.56)</td><td>0.32</td><td>2.93 (2.36-3.51)</td><td>1.65</td></tr><tr><td>Liver-death or liver transplantation</td><td>0.23 (<0.01-0.50)</td><td>0</td><td>3.20 (2.58-3.82)</td><td>1.41</td></tr><tr><td>Hepatocellular cancer</td><td>0.55 (0.14-0.96)</td><td>0</td><td>2.63 (1.83-2.89)</td><td>0.82</td></tr><tr><td>Liver failure or decompensation</td><td>0.31 (<0.01-0.62)</td><td>0</td><td>3.62 (2.9-4.29)</td><td>2.10</td></tr></table></td><td>The model under-predicted the event rates in both SVR and non-SVR populations.</td></tr>
<tr><td>Van der Meer et al[118]</td><td>Refers to the same cohort as per van der Meer et al 2012.[109] However, it reports cumulative 10-year overall survival with and without SVR.</td><td><table><tr><th rowspan="2">Outcome</th><th colspan="2">% Cumulative mortality (95%CI)</th><th colspan="2">% Cumulative mortality (95%CI)</th></tr><tr><th>Van der Meer</th><th>Model</th><th>Van der Meer</th><th>Model</th></tr><tr><td>All-cause death</td><td>8.9 (3.3-14.5)</td><td>3.57</td><td>26 (20.2-28.4)</td><td>18.59</td></tr></table></td><td>The model under-predicted all-cause mortality in both SVR and non-SVR populations.</td></tr>
<tr><td>Cardoso et al[105]</td><td>The model cohort was defined as per the Cardoso et al cohort: 55 years of age, 67% male, 58% F4, 42% F3, genotype 1 (since 60% of patients were genotype 1), treatment experienced patients (since patients received a median of two treatment courses).
The time horizon in the model was set as 4 years, similar to the 3.5 years in Cardoso et al.
Discount rate was set to 0%.
The outcomes compared were hepatocellular cancer, liver complications and liver-related death.
Rates were approximated by dividing the cumulative incidence rate over the period of time (4 years) by 4.</td><td><table><tr><th rowspan="2">Outcome</th><th colspan="2">% Rate with SVR (95%CI)</th><th colspan="2">% Rate without SVR (95%CI)</th></tr><tr><th>Cardoso</th><th>Model</th><th>Cardoso</th><th>Model</th></tr><tr><td>HCC</td><td>1.24 (0.28-2.20)</td><td>0</td><td>5.85 (4.23-7.47)</td><td>0.77</td></tr><tr><td>Liver complicatio</td><td>0.62 (0.00-</td><td>0</td><td>4.16 (2.73-</td><td>5.3</td></tr></table></td><td>The model under-predicted event rates for patients with SVR.</td></tr>
</table>

		ns	1.28)		5.59)		
		Liver death	0.61 (0.00-1.29)	0	3.76 (2.47-5.05)	0.63	

10.4 Appendix 4 Full incremental results

TN: Treatment naïve. TE: Treatment experienced. III: Interferon ineligible or intolerant. N/A: Not applicable

Full results of corrections to manufacturer's model for F3 subpopulation				
ERG's corrections to manufacturer				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£31,003	10.41	Reference
	NT	£37,903	8.88	Dominated
	SMV+PR	£40,455	11.53	£8,428
	TVR+PR	£44,387	11.14	Dominated
	SOF+PR	£45,915	12.06	£10,330
	BOC+PR	£48,290	10.44	Dominated
	DCV+SOF	£63,178	12.64	£29,631
TE	NT	£37,903	8.88	Reference
	DCV+SOF	£61,339	12.84	£5,906
III	NT	£37,903	8.88	Reference
	DCV+SOF	£61,339	12.84	£5,906
	SMV+SOF	£61,794	12.56	Dominated
	SOF+RBV	£81,783	11.53	Dominated
Genotype 3				
TN	PR	£16,571	11.51	Reference
	NT	£38,598	8.38	Dominated
	DCV+SOF	£70,707	11.73	Extended dominance
	SOF+RBV	£75,237	12.53	£57,956
TE	PR	£28,682	10.66	Reference
	NT	£38,598	8.38	Dominated
	SOF+PR	£43,285	12.07	£10,349
	DCV+SOF	£72,056	11.57	Dominated
	SOF+RBV	£78,405	12.15	£470907
III	NT	£38,598	8.38	Reference
	DCV+SOF	£70,707	11.73	£9,607
	SOF+RBV	£84,788	11.39	Dominated
Genotype 4				
TN	PR	£31,104	10.29	Reference
	SMV+PR	£35,718	12.04	£2,639

	SOF+PR	£38,851	12.82	£4,010
	NT	£40,490	8.36	Dominated
	DCV+PR	£59,547	11.90	Dominated
	DCV+SOF	£61,339	12.84	£870,354
TE	NT	£40,490	8.36	Reference
	PR	£43,887	9.01	Extended dominance
	SMV+PR	£55,974	10.25	Extended dominance
	DCV+PR	£59,547	11.90	Extended dominance
	DCV+SOF	£61,339	12.84	£4,655
III	NT	£40,490	8.36	Reference
	DCV+SOF	£61,339	12.84	£4,655

Issue 1: Relevant comparators				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£31,003	10.41	Reference
	NT	£37,903	8.88	Dominated
	SMV+PR	£40,455	11.53	£8,428
	TVR+PR	£44,387	11.14	Dominated
	SOF+PR	£45,915	12.06	£10,330
	BOC+PR	£48,290	10.44	Dominated
	DCV+SOF	£63,178	12.64	£29,631
TE	NT	£37,903	8.88	Reference
	SOF+PR	£47,206.86	11.94	£3,033
	DCV+SOF	£61,339.14	12.84	£15,687
III	NT	£37,903	8.88	Reference
	DCV+SOF	£61,339	12.84	£5,906
	SMV+SOF	£61,793.53	12.56	Dominated
Genotype 3				
TN	PR	£16,571	11.51	Reference
	NT	£38,598	8.38	Dominated
	DCV+SOF	£70,706.76	11.73	£254,711
TE	PR	£28,682	10.66	Reference
	NT	£38,598	8.38	Dominated
	SOF+PR	£43,285	12.07	£10,349
	DCV+SOF	£72,056	11.57	Dominated
III	NT	£38,598	8.38	Reference
	DCV+SOF	£70,707	11.73	£9,607

Genotype 4				
TN	PR	£31,104	10.29	Reference
	SMV+PR	£35,718	12.04	£2,639
	NT	£40,490	8.36	Dominated
	DCV+PR	£59,547	11.90	Dominated
	DCV+SOF	£61,339	12.84	£31,740
TE	NT	£40,490	8.36	Reference
	PR	£43,887	9.01	Extended dominance
	SMV+PR	£55,974	10.25	Extended dominance
	DCV+PR	£59,547	11.90	Extended dominance
	DCV+SOF	£61,339	12.84	£4,655
III	NT	£40,490	8.36	Reference
	DCV+SOF	£61,339	12.84	£4,655
	SMV+SOF	£63,352	12.36	Dominated
Issue 2: Appropriate SVR estimates				
Genotype 1				
TN	PR	£31,003	10.41	Reference
	NT	£37,903	8.88	Dominated
	SMV+PR	£40,455	11.53	£8,428
	TVR+PR	£44,387	11.14	Dominated
	SOF+PR	£45,915	12.06	£10,330
	BOC+PR	£48,290	10.44	Dominated
	DCV+SOF	£61,339	12.84	£19,739
TE/III – N/A				
Genotype 3 and 4 – N/A				
Issue 3: Natural history genotype 4				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 4 – no impact in non-genotype 4 subpopulations				
TN	PR	£29,681	10.57	Reference
	SMV+PR	£35,276	12.12	£3,598
	NT	£37,903	8.88	Dominated
	DCV+PR	£59,055	12.00	Dominated
	DCV+SOF	£61,339	12.84	£36,203
TE	NT	£37,903	8.88	Reference
	PR	£41,739	9.43	Extended dominance
	SMV+PR	£54,525	10.53	Extended dominance
	DCV+PR	£59,055	12.00	Extended dominance

	DCV+SOF	£61,339	12.84	£5,906
III	NT	£37,903	8.88	Reference
	DCV+SOF	£61,339	12.84	£5,906
	SMV+SOF	£63,081	12.42	Dominated
ERG's base-case				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£31,003	10.41	Reference
	NT	£37,903	8.88	Dominated
	SMV+PR	£40,455	11.53	£8,428
	TVR+PR	£44,387	11.14	Dominated
	SOF+PR	£45,915	12.06	£10,330
	BOC+PR	£48,290	10.44	Dominated
	DCV+SOF	£61,339	12.84	£19,739
TE	NT	£37,903	8.88	Reference
	SOF+PR	£47,207	11.94	£3,033
	DCV+SOF	£61,339	12.84	£15,687
III	NT	£37,903	8.88	Reference
	DCV+SOF	£61,339	12.84	£5,906
	SMV+SOF	£61,794	12.56	Dominated
Genotype 3				
TN	PR	£16,571	11.51	Reference
	NT	£38,598	8.38	Dominated
	DCV+SOF	£70,707	11.73	£254,711
TE	PR	£28,682	10.66	Reference
	NT	£38,598	8.38	Dominated
	SOF+PR	£43,285	12.07	£10,349
	DCV+SOF	£72,056	11.57	Dominated
III	NT	£38,598	8.38	Reference
	DCV+SOF	£70,707	11.73	£9,607
Genotype 4				
TN	PR	£29,681	10.57	Reference
	SMV+PR	£35,276	12.12	£3,598
	NT	£37,903	8.88	Dominated
	DCV+PR	£59,055	12.00	Dominated
	DCV+SOF	£61,339	12.84	£36,203
TE	NT	£37,903	8.88	Reference

	PR	£41,739	9.43	Extended dominance
	SMV+PR	£54,525	10.53	Extended dominance
	DCV+PR	£59,055	12.00	Extended dominance
	DCV+SOF	£61,339	12.84	£5,906
III	NT	£37,903	8.88	Reference
	DCV+SOF	£61,339	12.84	£5,906
	SMV+SOF	£63,081	12.42	Dominated

Full results of corrections to manufacturer's model for F4 subpopulation				
ERG's corrections to manufacturer				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£36,558	9.17	Reference
	NT	£46,606	6.84	Dominated
	SMV+PR	£47,558	10.39	Extended dominance
	TVR+PR	£48,390	10.40	Extended dominance
	SOF+PR	£48,476	11.59	£4,912
	BOC+PR	£50,027	9.85	Dominated
	DCV+SOF	£121,989	12.77	£62,489
TE	NT	£46,606	6.84	Reference
	DCV+SOF	£121,989	12.77	£12,704
III	NT	£46,606	6.84	Reference
	SMV+SOF	£63,018	12.39	£2,956
	SOF+RBV	£99,013	8.98	Dominated
	DCV+SOF	£121,989	12.77	£154,258
Genotype 3				
TN	PR	£37,199	8.38	Reference
	NT	£45,208	6.56	Dominated
	SOF+RBV	£76,916	12.29	£10,177
	DCV+SOF+RBV	£119,882	12.76	£90,455
TE	PR	£32,275	9.77	Reference
	SOF+PR	£44,940	11.75	£6,398
	NT	£45,208	6.56	Dominated
	SOF+RBV	£90,835	10.28	Dominated
	DCV+SOF+RBV	£119,882	12.76	£73,964
III	NT	£45,208	6.56	Reference

	SOF+RBV	£107,516	7.87	Extended dominance
	DCV+SOF+RBV	£119,882	12.76	£12,042
Genotype 4				
TN	SMV+PR	£37,412	11.73	Reference
	PR	£43,696	8.23	Dominated
	NT	£46,606	6.84	Dominated
	SOF+PR	£61,921	9.80	Dominated
	DCV+PR	£62,853	11.35	Dominated
	DCV+SOF	£121,989	12.77	£81,490
TE	NT	£46,606	6.84	Reference
	PR	£49,137	7.72	£2,856
	SMV+PR	£59,850	9.35	Extended dominance
	DCV+PR	£62,853	11.35	£3,781
	DCV+SOF	£121,989	12.77	£41,630
III	NT	£46,606	6.84	Reference
	DCV+SOF	£121,989	12.77	£12,704
Issue 1: Relevant comparators				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£36,558	9.17	Reference
	NT	£46,606	6.84	Dominated
	SMV+PR	£47,558	10.39	Extended dominance
	TVR+PR	£48,390	10.40	Extended dominance
	SOF+PR	£48,476	11.59	£4,912
	BOC+PR	£50,027	9.85	Dominated
	DCV+SOF	£121,989	12.77	£62,489
TE	NT	£46,606	6.84	Reference
	SOF+PR	£49,638	11.47	£654
	DCV+SOF	£121,989	12.77	£55,808
III	NT	£46,606	6.84	Reference
	SMV+SOF	£63,018	12.39	£2,956
	DCV+SOF	£121,989	12.77	£154,258
Genotype 3				
TN	PR	£37,199	8.38	Reference
	NT	£45,208	6.56	Dominated
	SOF+PR	£47,030	11.75	£2,924
	DCV+SOF+RBV	£119,882	12.76	£71,768

TE	PR	£32,275	9.77	
	SOF+PR	£44,940	11.75	£6,398
	NT	£45,208	6.56	Dominated
	DCV+SOF+RBV	£119,882	12.76	£73,964
III	NT	£45,208	6.56	Reference
	SOF+RBV	£107,516	7.87	Extended dominance
	DCV+SOF+RBV	£119,882	12.76	£12,042
Genotype 4				
TN	SMV+PR	£37,412	11.73	Reference
	PR	£43,696	8.23	Dominated
	NT	£46,606	6.84	Dominated
	SOF+PR	£61,921	9.80	Dominated
	DCV+PR	£62,853	11.35	Dominated
	DCV+SOF	£121,989	12.77	£81,490
TE	NT	£46,606	6.84	Reference
	PR	£49,137	7.72	Extended dominance
	SOF+PR	£53,852	10.91	£1,778
	SMV+PR	£59,850	9.35	Dominated
	DCV+PR	£62,853	11.35	£20,508
	DCV+SOF	£121,989	12.77	£41,630
III	NT	£46,606	6.84	Reference
	SMV+SOF	£64,587	12.18	£3,366
	DCV+SOF	£121,989	12.77	£96,977
Issue 2: Appropriate SVR estimates				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1 – N/A				
Genotype 3				
TN/TE – N/A				
III	NT	£45,208	6.56	Reference
	SOF+RBV	£76,964	12.29	£5,546
	DCV+SOF+RBV	£119,882	12.76	£90,352
Genotype 4				
TN	SMV+PR	£37,412	11.73	Reference
	PR	£43,696	8.23	Dominated
	NT	£46,606	6.84	Dominated
	SOF+PR	£48,656	11.57	Dominated
	DCV+PR	£62,853	11.35	Dominated

	DCV+SOF	£121,989	12.77	£81,490
TE/III – N/A				
Issue 4: Progression of F4 SVR				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£38,050	8.89	Reference
	NT	£46,606	6.84	Dominated
	SMV+PR	£49,757	9.98	Extended dominance
	TVR+PR	£50,646	9.98	Dominated
	SOF+PR	£51,390	11.04	£6,180
	BOC+PR	£51,920	9.49	Dominated
	DCV+SOF	£125,630	12.08	£71,455
TE	NT	£46,606	6.84	Reference
	SOF+PR	£52,478	10.94	£1,432
	DCV+SOF	£125,630	12.08	£63,873
III	NT	£46,606	6.84	Reference
	SMV+SOF	£66,405	11.75	£4,030
	DCV+SOF	£125,630	12.08	£177,219
Genotype 3				
TN	PR	£38,465	8.12	Reference
	NT	£45,208	6.56	Dominated
	SOF+PR	£50,545	11.00	£4,184
	DCV+SOF+RBV	£124,100	11.87	£84,909
TE	PR	£34,552	9.29	Reference
	NT	£45,208	6.56	Dominated
	SOF+PR	£48,455	11.01	£8,091
	DCV+SOF+RBV	£124,100	11.87	£87,512
III	NT	£45,208	6.56	Reference
	SOF+RBV	£108,419	7.68	Extended dominance
	DCV+SOF+RBV	£124,100	11.87	£14,857
Genotype 4				
TN	SMV+PR	£40,431	11.16	Reference
	PR	£44,606	8.06	Dominated
	NT	£46,606	6.84	Dominated
	SOF+PR	£63,742	9.45	Dominated
	DCV+PR	£65,691	10.81	Dominated
	DCV+SOF	£125,630	12.08	£92,570

TE	NT	£46,606	6.84	Reference
	PR	£49,756	7.61	Extended dominance
	SOF+PR	£56,350	10.44	£2,704
	SMV+PR	£61,451	9.05	Dominated
	DCV+PR	£65,691	10.81	£24,955
	DCV+SOF	£125,630	12.08	£47,220
III	NT	£46,606	6.84	Reference
	SMV+SOF	£67,846	11.56	£4,493
	DCV+SOF	£125,630	12.08	£111,172
Issue 5: HRQoL of F4 SVR for the F4 sub-population				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£36,558	8.26	Reference
	NT	£46,606	6.84	Dominated
	SMV+PR	£47,558	9.06	Extended dominance
	TVR+PR	£48,390	9.04	Dominated
	SOF+PR	£48,476	9.83	£7,612
	BOC+PR	£50,027	8.70	Dominated
	DCV+SOF	£121,989	10.56	£100,016
TE	NT	£46,606	6.84	Reference
	SOF+PR	£49,638	9.75	£1,040
	DCV+SOF	£121,989	10.56	£89,224
III	NT	£46,606	6.84	Reference
	SMV+SOF	£63,018	10.34	£4,690
	DCV+SOF	£121,989	10.56	£258,872
Genotype 3				
TN	PR	£37,199	7.72	Reference
	NT	£45,208	6.56	Dominated
	SOF+PR	£47,030	9.91	£4,497
	DCV+SOF+RBV	£119,882	10.55	£112,679
TE	PR	£32,275	8.58	Reference
	SOF+PR	£44,940	9.91	£9,502
	NT	£45,208	6.56	Dominated
	DCV+SOF+RBV	£119,882	10.55	£116,252
III	NT	£45,208	6.56	Reference
	SOF+RBV	£107,516	7.40	Extended dominance
	DCV+SOF+RBV	£119,882	10.55	£18,695

Genotype 4				
TN	SMV+PR	£37,412	9.90	Reference
	PR	£43,696	7.68	Dominated
	NT	£46,606	6.84	Dominated
	SOF+PR	£61,921	8.69	Dominated
	DCV+PR	£62,853	9.63	Dominated
	DCV+SOF	£121,989	10.56	£128,053
TE	NT	£46,606	6.84	Reference
	PR	£49,137	7.35	Extended dominance
	SOF+PR	£53,852	9.40	£2,830
	SMV+PR	£59,850	8.38	Dominated
	DCV+PR	£62,853	9.63	£38,889
	DCV+SOF	£121,989	10.56	£63,248
III	NT	£46,606	6.84	Reference
	SMV+SOF	£64,587	10.20	£5,341
	DCV+SOF	£121,989	10.56	£159,370
Issue 6: Lifetime costs of F4 SVR				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£37,465	9.17	Reference
	NT	£46,606	6.84	Dominated
	SMV+PR	£48,894	10.39	Extended dominance
	TVR+PR	£49,762	10.40	Extended dominance
	SOF+PR	£50,247	11.59	£5,268
	BOC+PR	£51,178	9.85	Dominated
	DCV+SOF	£124,202	12.77	£62,866
TE	NT	£46,606	6.84	Reference
	SOF+PR	£51,364	11.47	£1,026
	DCV+SOF	£124,202	12.77	£56,184
III	NT	£46,606	6.84	Reference
	SMV+SOF	£65,077	12.39	£3,327
	DCV+SOF	£124,202	12.77	£154,663
Genotype 3				
TN	PR	£37,863	8.38	Reference
	NT	£45,208	6.56	Dominated
	SOF+PR	£48,874	11.75	£3,274
	DCV+SOF+RBV	£122,095	12.76	£72,132

TE	PR	£33,470	9.77	Reference
	NT	£45,208	6.56	Dominated
	SOF+PR	£46,784	11.75	£6,726
	DCV+SOF+RBV	£122,095	12.76	£74,329
III	NT	£45,208	6.56	Reference
	SOF+RBV	£107,990	7.87	Extended dominance
	DCV+SOF+RBV	£122,095	12.76	£12,399
Genotype 4				
TN	SMV+PR	£39,247	11.73	Reference
	PR	£44,249	8.23	Dominated
	NT	£46,606	6.84	Dominated
	SOF+PR	£63,028	9.80	Dominated
	DCV+PR	£64,579	11.35	Dominated
	DCV+SOF	£124,202	12.77	£81,855
TE	NT	£46,606	6.84	Reference
	PR	£49,513	7.72	Extended dominance
	SOF+PR	£55,370	10.91	£2,151
	SMV+PR	£60,823	9.35	Dominated
	DCV+PR	£64,579	11.35	£20,982
	DCV+SOF	£124,202	12.77	£41,973
III	NT	£46,606	6.83706821	Reference
	SMV+SOF	£66,568	12.17912394	£3,737
	DCV+SOF	£124,202	12.77103679	£97,369
ERG's base-case				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£38,889	8.05	Reference
	NT	£46,606	6.84	Dominated
	SMV+PR	£50,993	8.74	Extended dominance
	TVR+PR	£51,915	8.71	Dominated
	BOC+PR	£52,984	8.43	Dominated
	SOF+PR	£53,027	9.41	£10,399
	DCV+SOF	£127,676	10.04	£118,636
TE	NT	£46,606	6.84	Reference
	SOF+PR	£54,074	9.34	£2,983
	DCV+SOF	£127,676	10.04	£105,972
III	NT	£46,606	6.84	Reference

	SMV+SOF	£68,308	9.84	£7,216
	DCV+SOF	£127,676	10.04	£311,193
Genotype 3				
TN	PR	£39,065	7.51	Reference
	NT	£45,208	6.56	Dominated
	SOF+PR	£52,211	9.33	£7,228
	DCV+SOF+RBV	£126,100	9.86	£139,045
TE	PR	£35,632	8.20	Reference
	NT	£45,208	6.56	Dominated
	SOF+PR	£50,121	9.33	£12,813
	DCV+SOF+RBV	£126,100	9.86	£143,489
III	NT	£45,208	6.56	Reference
	SOF+RBV	£82,703	9.61	£12,282
	DCV+SOF+RBV	£126,100	9.86	£172,219
Genotype 4				
TN	SMV+PR	£42,127	9.47	Reference
	PR	£45,117	7.54	Dominated
	NT	£46,606	6.84	Dominated
	SOF+PR	£53,183	9.39	Dominated
	DCV+PR	£67,287	9.22	Dominated
	DCV+SOF	£127,676	10.04	£150,076
TE	NT	£46,606	6.84	Reference
	PR	£50,103	7.26	Extended dominance
	SOF+PR	£57,754	9.03	£5,072
	SMV+PR	£62,351	8.14	Dominated
	DCV+PR	£67,287	9.22	£52,459
	DCV+SOF	£127,676	10.04	£73,768
III	NT	£46,606	6.84	Reference
	SMV+SOF	£69,678	9.73	£7,974
	DCV+SOF	£127,676	10.04	£190,379

Full results of sensitivity analysis for F3 sub-population				
1.1 Exclusion of SMV + PR				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£31,003	10.41	Reference

	NT	£37,903	8.88	Dominated
	TVR+PR	£44,387	11.14	Extended dominance
	SOF+PR	£45,915	12.06	£9,037
	BOC+PR	£48,290	10.44	Dominated
	DCV+SOF	£61,339	12.84	£19,739
TE/III – N/A				
N/A for genotypes 3 and 4				
1.2 Exclusion of SMV + SOF				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN/TE – N/A				
III	NT	£37,903	8.88	Reference
	DCV+SOF	£61,339	12.84	£5,906
Genotype 3 – N/A				
Genotype 4				
TN/TE – N/A				
III	NT	£37,903	8.88	Reference
	DCV+SOF	£61,339	12.84	£5,906
2.1 Treatment duration of DCV + SOF				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN – N/A				
TE	NT	£37,903	8.875340497	Reference
	SOF+PR	£47,207	11.94282976	£3,033
	DCV+SOF	£120,840	12.8437291	£81,733
III – N/A				
Genotype 3 – N/A				
Genotype 4				
TN – N/A				
TE – N/A				
III – N/A				
2.2 Treatment duration of SMV + PR				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotypes 1 and 3 – N/A				
Genotype 4				
TN – N/A				

TE	NT	£37,903	8.88	Reference
	PR	£41,739	9.43	Extended dominance
	SMV+PR	£53,343	10.53	Extended dominance
	DCV+PR	£59,055	12.00	Extended dominance
	DCV+SOF	£61,339	12.84	£5,906
III – N/A				
2.3 Treatment duration of SOF + PR				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£31,003	10.41	Reference
	NT	£37,903	8.88	Dominated
	SMV+PR	£40,455	11.53	£8,428
	TVR+PR	£44,387	11.14	Dominated
	SOF+PR	£83,194	12.06	Dominated
	BOC+PR	£48,290	10.44	Dominated
	DCV+SOF	£61,339	12.84	£15,943
TE	NT	£37,903	8.88	Reference
	SOF+PR	£84,486	11.94	Dominated
	DCV+SOF	£61,339	12.84	£5,906
III – N/A				
Genotype 3				
TN – N/A				
TE	PR	£28,682	10.66	Reference
	NT	£38,598	8.38	Dominated
	SOF+PR	£80,564	12.07	£36,768
	DCV+SOF	£72,056	11.57	Extended dominance
III – N/A				
Genotype 4 – N/A				
3. Discontinuation rates (F3)				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£31,003	10.41	Reference
	NT	£37,903	8.88	Dominated
	BOC+PR	£40,099	10.46	Extended dominance
	SMV+PR	£40,859	11.53	£8,794
	TVR+PR	£42,698	11.15	Dominated
	SOF+PR	£45,838	12.06	£9,409

	DCV+SOF	£61,339	12.84	£19,838
TE/III – N/A				
Genotypes 3 and 4 – N/A				
4. SVR estimates				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£31,003	10.41	Reference
	NT	£37,903	8.88	Dominated
	SMV+PR	£40,455	11.53	Extended dominance
	SOF+PR	£43,892	12.28	£6,897
	TVR+PR	£44,387	11.14	Dominated
	BOC+PR	£48,290	10.44	Dominated
	DCV+SOF	£61,339	12.84	£31,005
TE/III – N/A				
Genotypes 3 and 4 – N/A				
5.1 Progression F3 to F4 (UK non-tertiary)				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£27,246	11.03	Reference
	NT	£31,535	9.92	Dominated
	SMV+PR	£38,417	11.87	£13,312
	TVR+PR	£41,776	11.57	Dominated
	BOC+PR	£44,533	11.06	Dominated
	SOF+PR	£44,705	12.26	£16,015
	DCV+SOF	£61,339	12.84	£28,542
TE	NT	£31,535	9.92	Reference
	SOF+PR	£45,806	12.17	£6,337
	DCV+SOF	£61,339	12.84	£23,152
III	NT	£31,535	9.92	Reference
	DCV+SOF	£61,339	12.84	£10,196
	SMV+SOF	£61,348	12.63	Dominated
Genotype 3				
TN	PR	£14,978	11.83	Reference
	NT	£33,067	9.47	Dominated
	DCV+SOF	£69,324	12.00	£317,490
TE	PR	£26,138	11.16	Reference
	NT	£33,067	9.47	Dominated

	SOF+PR	£42,361	12.26	£14,855
	DCV+SOF	£70,474	11.88	Dominated
III	NT	£33,067	9.47	Reference
	DCV+SOF	£69,324	12.00	£14,354
Genotype 4				
TN	PR	£26,178	11.14	Reference
	NT	£31,535	9.92	Dominated
	SMV+PR	£34,187	12.30	£6,912
	DCV+PR	£57,845	12.19	Dominated
	DCV+SOF	£61,339	12.84	£50,174
TE	NT	£31,535	9.92	Reference
	PR	£36,454	10.30	Extended dominance
	SMV+PR	£50,959	11.12	Extended dominance
	DCV+PR	£57,845	12.19	Extended dominance
	DCV+SOF	£61,339	12.84	£10,196
III	NT	£31,535	9.92	Reference
	DCV+SOF	£61,339	12.84	£10,196
	SMV+SOF	£62,412	12.53	Dominated
5.2 Progression F3 to F4 (UK tertiary)				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£28,770	10.79	
	NT	£34,117	9.52	Dominated
	SMV+PR	£39,244	11.74	£11,067
	TVR+PR	£42,835	11.41	Dominated
	SOF+PR	£45,195	12.19	£13,398
	BOC+PR	£46,057	10.83	Dominated
	DCV+SOF	£61,339	12.84	£24,525
TE	NT	£34,117	9.52	
	SOF+PR	£46,374	12.09	£4,784
	DCV+SOF	£61,339	12.84	£19,736
III	NT	£34,117	9.52	
	DCV+SOF	£61,339	12.84	£8,199
	SMV+SOF	£61,529	12.60	Dominated
Genotype 3				
TN	PR	£15,658	11.70	
	NT	£35,428	9.04	Dominated

	DCV+SOF	£69,914	11.89	£289,250
TE	PR	£27,224	10.96	
	NT	£35,428	9.04	Dominated
	SOF+PR	£42,755	12.18	£12,746
	DCV+SOF	£71,149	11.75	Dominated
III	NT	£35,428	9.04	
	DCV+SOF	£69,914	11.89	£12,102
Genotype 4				
TN	PR	£27,599	10.93	
	NT	£34,117	9.52	Dominated
	SMV+PR	£34,628	12.23	£5,370
	DCV+PR	£58,336	12.12	Dominated
	DCV+SOF	£61,339	12.84	£43,855
TE	NT	£34,117	9.52	
	PR	£38,597	9.97	Extended dominance
	SMV+PR	£52,405	10.90	Extended dominance
	DCV+PR	£58,336	12.12	Extended dominance
	DCV+SOF	£61,339	12.84	£8,199
III	NT	£34,117	9.52	
	DCV+SOF	£61,339	12.84	£8,199
	SMV+SOF	£62,683	12.48	Dominated
5.3 Transition following cirrhosis				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£30,097	10.26	
	NT	£36,367	8.61	Dominated
	SMV+PR	£39,963	11.45	£8,273
	TVR+PR	£43,757	11.03	Dominated
	SOF+PR	£45,623	12.01	£10,056
	BOC+PR	£47,384	10.29	Dominated
	DCV+SOF	£61,339	12.84	£18,901
TE	NT	£36,367	8.61	
	SOF+PR	£46,869	11.88	£3,209
	DCV+SOF	£61,339	12.84	£15,091
III	NT	£36,367	8.61	
	DCV+SOF	£61,339	12.84	£5,901
	SMV+SOF	£61,686	12.54	Dominated

Genotype 3				
TN	PR	£16,010	11.40	
	NT	£36,650	8.00	Dominated
	DCV+SOF	£70,220	11.63	£238,497
TE	PR	£27,786	10.48	
	NT	£36,650	8.00	Dominated
	SOF+PR	£42,959	12.01	£9,951
	DCV+SOF	£71,499	11.45	Dominated
III	NT	£36,650	8.00	
	DCV+SOF	£70,220	11.63	£9,238
Genotype 4				
TN	PR	£28,836	10.42	
	SMV+PR	£35,013	12.08	£3,733
	NT	£36,367	8.61	Dominated
	DCV+PR	£58,763	11.95	Dominated
	DCV+SOF	£61,339	12.84	£34,413
TE	NT	£36,367	8.61	
	PR	£40,464	9.21	Extended dominance
	SMV+PR	£53,665	10.39	Extended dominance
	DCV+PR	£58,763	11.95	Extended dominance
	DCV+SOF	£61,339	12.84	£5,901
III	NT	£36,367	8.61	
	DCV+SOF	£61,339	12.84	£5,901
	SMV+SOF	£62,919	12.39	Dominated

Full results of sensitivity analysis for F4 sub-population				
1.1 Exclusion of SMV + PR				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£38,889	8.05	Reference
	NT	£46,606	6.84	Dominated
	TVR+PR	£51,915	8.71	Extended dominance
	BOC+PR	£52,984	8.43	Dominated
	SOF+PR	£53,027	9.41	£10,399
	DCV+SOF	£127,676	10.04	£118,636
TE/III – N/A				

N/A for genotypes 3 and 4				
1.2 Exclusion of SMV + SOF				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN/TE – N/A				
III	NT	£46,606	6.84	Reference
	DCV+SOF	£127,676	10.04	£25,349
Genotype 3 – N/A				
Genotype 4				
TN/TE – N/A				
III	NT	£46,606	6.84	Reference
	DCV+SOF	£127,676	10.04	£25,349
2.1 Treatment duration of DCV + SOF				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£38,889	8.046	Reference
	NT	£46,606	6.837	Dominated
	SMV+PR	£50,993	8.742	Extended dominance
	TVR+PR	£51,915	8.707	Dominated
	BOC+PR	£52,984	8.427	Dominated
	SOF+PR	£53,027	9.406	£10,399
	DCV+SOF	£68,175	10.035	£24,074
TE/III – N/A				
Genotype 3 – N/A				
Genotype 4				
TN	SMV+PR	£42,127	9.465	Reference
	PR	£45,117	7.544	Dominated
	NT	£46,606	6.837	Dominated
	SOF+PR	£53,183	9.393	Dominated
	DCV+PR	£67,287	9.217	Dominated
	DCV+SOF	£68,175	10.035	£45,695
TE/III – N/A				
2.2 Treatment duration of SMV + PR				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotypes 1 and 3 – N/A				
Genotype 4				

TN – N/A				
TE	NT	£46,606	6.84	Reference
	PR	£50,103	7.26	Extended dominance
	SOF+PR	£57,754	9.03	£5,072
	SMV+PR	£61,169	8.14	Dominated
	DCV+PR	£67,287	9.22	£52,459
	DCV+SOF	£127,676	10.04	£73,768
III – N/A				
2.3 Treatment duration of SOF + PR				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£38,889	8.05	Reference
	NT	£46,606	6.84	Dominated
	SMV+PR	£50,993	8.74	£17,409
	TVR+PR	£51,915	8.71	Dominated
	BOC+PR	£52,984	8.43	Dominated
	SOF+PR	£90,306	9.41	£59,186
	DCV+SOF	£127,676	10.04	£59,390
TE	NT	£46,606	6.84	
	SOF+PR	£91,353	9.34	£17,873
	DCV+SOF	£127,676	10.04	£52,297
III – N/A				
Genotype 3				
TN	PR	£39,065	7.51	Reference
	NT	£45,208	6.56	Dominated
	SOF+PR	£89,490	9.33	£27,724
	DCV+SOF+RBV	£126,100	9.86	£68,893
TE	PR	£35,632	8.20	
	NT	£45,208	6.56	Dominated
	SOF+PR	£87,400	9.33	£45,780
	DCV+SOF+RBV	£126,100	9.86	£73,086
III – N/A				
Genotype 4				
TN	SMV+PR	£42,127	9.47	Reference
	PR	£45,117	7.54	Dominated
	NT	£46,606	6.84	Dominated
	SOF+PR	£90,462	9.39	Dominated

	DCV+PR	£67,287	9.22	Dominated
	DCV+SOF	£127,676	10.04	£150,076
TE	NT	£46,606	6.84	Reference
	PR	£50,103	7.26	£8,304
	SOF+PR	£95,033	9.03	Dominated
	SMV+PR	£62,351	8.14	Extended dominance
	DCV+PR	£67,287	9.22	£8,775
	DCV+SOF	£127,676	10.04	£73,768
III – N/A				
4. SVR estimates				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1 – N/A				
Genotype 3				
TN	PR	£39,065	7.51	Reference
	NT	£45,208	6.56	Dominated
	SOF+PR	£52,211	9.33	£7,228
	DCV+SOF+RBV	£141,624	8.46	Dominated
TE	PR	£35,632	8.20	Reference
	NT	£45,208	6.56	Dominated
	SOF+PR	£50,121	9.33	£12,813
	DCV+SOF+RBV	£137,457	8.84	Dominated
III	NT	£45,208	6.56	Reference
	SOF+RBV	£108,847	7.25	Extended dominance
	DCV+SOF+RBV	£126,100	9.86	£24,477
Genotype 4				
TN	SMV+PR	£42,127	9.47	Reference
	PR	£45,117	7.54	Dominated
	NT	£46,606	6.84	Dominated
	SOF+PR	£64,765	8.43	Dominated
	DCV+PR	£67,287	9.22	Dominated
	DCV+SOF	£127,676	10.04	£150,076
TE/III – N/A				
5.3 Transition following cirrhosis				
Population	**Treatment regimen**	**Total cost**	**Total QALYs**	**ICER**
Genotype 1				
TN	PR	£37,782	7.66	Reference
	NT	£44,044	6.40	Dominated

	SMV+PR	£50,575	8.38	Extended dominance
	TVR+PR	£51,553	8.35	Dominated
	BOC+PR	£52,267	8.06	Dominated
	SOF+PR	£53,305	9.07	£11,004
	DCV+SOF	£128,664	9.73	£114,967
TE	NT	£44,044	6.40	Reference
	SOF+PR	£54,282	9.00	£3,929
	DCV+SOF	£128,664	9.73	£102,821
III	NT	£44,044	6.40	Reference
	SMV+SOF	£69,048	9.53	£7,990
	DCV+SOF	£128,664	9.73	£298,134
Genotype 3				
TN	PR	£37,409	6.98	Reference
	NT	£42,250	5.98	Dominated
	SOF+PR	£52,869	8.88	£8,127
	DCV+SOF+RBV	£127,481	9.44	£133,822
TE	PR	£35,016.52	7.71	Reference
	NT	£42,250.27	5.98	Dominated
	SOF+PR	£50,778.32	8.88	£13,395
	DCV+SOF+RBV	£127,481.35	9.44	£138,039
III	NT	£42,250	5.98	Reference
	SOF+RBV	£83,750	9.18	£12,979
	DCV+SOF+RBV	£127,481	9.44	£165,620
Genotype 4				
TN	SMV+PR	£42,508	9.13	Reference
	PR	£43,442	7.14	Dominated
	NT	£44,044	6.40	Dominated
	SOF+PR	£53,448	9.06	Dominated
	DCV+PR	£67,494	8.88	Dominated
	DCV+SOF	£128,664	9.73	£145,415
TE	NT	£44,044	6.40	Reference
	PR	£48,144	6.84	Extended dominance
	SOF+PR	£57,628	8.69	£5,938
	SMV+PR	£61,351	7.76	Dominated
	DCV+PR	£67,494	8.88	£50,837
	DCV+SOF	£128,664	9.73	£72,177
III	NT	£44,044	6.40	Reference
	SMV+SOF	£70,294	9.41	£8,718

	DCV+SOF	£128,664	9.73	£183,308