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

Ombitasvir/paritaprevir/ritonavir with or without dasabuvir for treating chronic hepatitis C

Produced by Southampton Health Technology Assessments Centre

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Date completed

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 14/58/01.

Declared competing interests of the authors

None from the Authors. Dr Kathryn Nash has conducted clinical trials for Abbvie and has been a member of Abbvie's advisory board. Dr Stephen Ryder has attended paid advisory boards for Abbvie.

Acknowledgements

We are very grateful to the following experts who offered clinical advice and comments on the draft report: Dr Stephen Ryder, Consultant Physician in Hepatology and Gastroenterology, Nottingham University Hospitals NHS Trust; and Dr Kathryn Nash, Consultant Hepatologist, University Hospital Southampton NHS Foundation Trust.

We also thank: Karen Welch, Information Scientist, SHTAC, for commenting on the company's search strategy; and Geoff Frampton, Senior Research Fellow, SHTAC, for acting as internal editor for the ERG report.

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.

This report should be referenced as follows:

Jones J, Pickett K, Chorozogolou M, Colquitt JL, Picot J. Ombitasvir/paritaprevir/ritonavir with or without dasabuvir for treating chronic hepatitis C: A Single Technology Appraisal. Southampton Health Technology Assessments Centre, 2015.

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Word count:

Key to colour highlighting used in report

[redacted]

[redacted].

TABLE OF CONTENTS

1 Introduction to ERG Report 17
2 BACKGROUND 17
2.1 Critique of company's description of underlying health problem 17
2.2 Critique of company's overview of current service provision 17
2.3 Critique of company's definition of decision problem 18
3 CLINICAL EFFECTIVENESS 27
3.1 Critique of company's approach to systematic review 27
3.2 Summary statement of company's approach 48
3.3 Summary of submitted evidence 50
3.4 Summary 74
4 ECONOMIC EVALUATION 76
4.1 Overview of company's economic evaluation 76
4.2 Critical appraisal of the company's submitted economic evaluation 80
4.3 Additional work undertaken by the ERG 115
4.4 Summary of uncertainties and issues 131
5 End of life 132
6 Innovation 132
7 DISCUSSION 133
7.1 Summary of clinical effectiveness issues 133
7.2 Summary of cost effectiveness issues 134
8 REFERENCES 135
9 APPENDICES 140
9.1 Trial arms where treatment is outside the licensed indication for either some or all of the participants with HCV GT1 140
9.2 Trial arms where treatment is outside the licensed indication for either some or all of the participants with HCV GT4 144

LIST OF TABLES

Table 1: Treatment regimen and duration by patient population, as outlined in the SmPC 19
Table 2: List of comparators specified in the final scope and whether they have been included in the CS decision problem and economic model 21
Table 3: Comparators specified in the final scope which were excluded from the CS and economic model and reasons for exclusion 22
Table 4: Equality issues raised by the company 26
Table 5 Summary of key eligibility criteria in included studies 32
Table 6 Summary of licensed indications and corresponding trial arms or subgroups 33
Table 7 Company and ERG assessment of trial quality 38
Table 8 Summary of statistical analysis plan 44
Table 9 Quality assessment (CRD criteria) of CS review 49
Table 10: SVR12 outcome from trial arms or subgroups where treatment matches licensed indication 53
Table 11 Virologic relapse and failure results 55
Table 12 Normalisation of alanine aminotransferase levels 56

Table 13: SF36 physical component score results 57
Table 14: SF36 mental component score results 59
Table 15: EQ-5D-5L Health index score results 60
Table 16: HCV-PRO total score results 61
Table 17: Selected subgroup analyses from HCV GT1 trials 63
Table 18: SVR12 outcome from trial arms where treatment matches licensed indication 64
Table 19: SVR24 outcome in participants with HCV GT4 65
Table 20: Virologic relapse and failure in HCV GT4 patients 65
Table 21: EQ-5D-5L results in HCV GT4 trial participants 66
Table 22: HCV-PRO total score in HCV GT4 trial participants 66
Table 23: Summary adverse event results for HCV GT1 trials (except AVIATOR[26]) 68
Table 24: Summary adverse events reported in patients with HCV GT4 without cirrhosis 69
Table 25: SVR12 in HCV GT1/HIV-1 co-infected participants from the first phase of TURQUOISE-I 71
Table 26: SVR12 in adult liver transplant recipients with recurrent HCV GT1 infection from arm A of the CORAL-I study 72
Table 27: SVR12 in the MALACHITE I (treatment naïve, non-cirrhotic) 73
Table 28: SVR12 in MALACHITE II (treatment experienced, non-cirrhotic) 74
Table 29 Base case cost effectiveness results 79
Table 30 Critical appraisal checklist of economic evaluation 81
Table 31 NICE reference case requirements 82
Table 32 Dosing details and treatment duration for 3D ± RBV and 2D+RBV (by genotype and stage of fibrosis) 86
Table 33 Proportion of patients with SVR for 3D and comparators applied in the economic model: genotype 1, treatment-naïve, interferon-eligible population 89
Table 34 Proportion of patients with SVR for 3D and comparators applied in the economic model: genotype 1, treatment-experienced (all types), interferon-eligible population 90
Table 35 SVRs for comparator regimes applied in the economic model, in company submissions for comparator regimes and ERG estimate of SVR with simeprevir+PegIFN+RBV (using MTC output from simeprevir CS[28]): genotype 1, treatment-naive, interferon-eligible population 92
Table 36 Proportion of patients with SVR for 2D and comparators applied in the economic model: genotype 4, treatment-naïve, interferon-eligible population 93
Table 37 Natural history transition probabilities used in the economic model (extracted from Table 100 in CS) 95
Table 38 Summary of sources of adverse event data used in economic model by patient population and treatment regimen 97
Table 39 Baseline health state utilities and sources 99
Table 40 Dosage of comparator treatments included in the model 102
Table 41 Cost per week of component treatments of intervention and comparators 104
Table 42 Drug acquisition costs 105
Table 43 Key health state costs 106

Table 44 ERG replication of PSA reported in CS for GT1, treatment-naive, interferon-eligible. Mean total cost and QALY estimates by regimen 111
Table 45 ERG replication of PSA reported in CS for GT1, treatment-experienced, interferon-eligible. Mean total cost and QALY estimates by regimen 111
Table 46 ERG replication of PSA for GT1 interferon-eligible patients. ICERs calculated at mean cost and QALYs and mean ICERs compared with PegIFN+RBV 112
Table 47 ERG replication of PSA reported in CS for GT4, treatment-naive, interferon-eligible. Mean total cost and QALY estimates by regimen 112
Table 48 ERG replication of PSA reported in CS for GT4, treatment-experienced, interferon-eligible. Mean total cost and QALY estimates by regimen 113
Table 49 ERG replication of PSA for non-cirrhotic GT4 interferon-eligible patients. ICERs calculated at mean cost and QALYs and mean ICERs 113
Table 50 ERG analysis using SVRs from MALACHITE I trial: GT1 non-cirrhotic treatment-naive, interferon-eligible patients 116
Table 51 ERG analysis using SVRs from MALACHITE II trial: GT1 treatment-experienced, interferon-eligible patients 117
Table 52 ERG comparison of costs in base case and non-cirrhotic GT1 population... 118
Table 53 ERG replication of PSA reported in CS for GT1, treatment-naive, interferon-eligible. Mean total cost and QALY estimates by regimen 119
Table 54 ERG analysis c) adjustment of SVR for boceprevir+PegIFN+RBV compared with SVR for PegIFN+RBV in ADVANCE trial[28] 120
Table 55 ERG analysis c) Cost effectiveness results for GT1 treatment-naive patients after adjustment of SVR for boceprevir+PegIFN+RBV compared with SVR for PegIFN+RBV 121
Table 56 ERG analysis d) Cost effectiveness results for GT1 treatment-naive patients including simeprevir+PegIFN+RBV 123
Table 57 ERG analysis e) Odds ratios for SVR and estimated SVRs from ERG adjusted indirect comparison 124
Table 58 ERG analysis e) Cost effectiveness results for non-cirrhotic GT1 treatment-naive patients using SVRs from adjusted indirect comparison 124
Table 59 ERG analysis f) Threshold analysis on effectiveness (SVR) with 3D in GT1 treatment-naive patients 126
Table 60 ERG analysis g) cost effectiveness results using risk of HCC for patients who had cirrhosis prior to SVR from Bruno and colleagues 129
Table 61 ERG analysis h) cost effectiveness results using risk of HCC for patients with cirrhosis from Bruno and colleagues 130
Table 62 ERG analysis i) cost effectiveness results, combining ERG scenario g) and ERG scenario h) 131
Table 63: SVR12 outcome from trial arms or subgroups where treatment is outside the licensed indication for either some or all of the participants 140
Table 64: SVR24 outcome from trial arms of the AVIATOR study[26] 143
Table 65: SVR24 rates for arms E, G and L from AVIATOR stratified by sub-genotype 144
Table 66: SVR12 outcome from trial arm where treatment does not match licensed indication, GT4 144

LIST OF FIGURES

Figure 1 CS model schematic 83
Figure 2 ERG analysis c) Base case cost effectiveness and effect of adjustment of SVR for boceprevir+PegIFN+RBV compared with SVR for PegIFN+RBV 121
Figure 3 ERG analysis f) Threshold analysis on effectiveness (SVR) with 3D in GT1 treatment-naive patients on the cost-effectiveness plane..... 128

LIST OF ABBREVIATIONS

2D	Ombitasvir (25 mg daily) / paritaprevir (150 mg daily) / ritonavir (100 mg daily)
3D	Ombitasvir (25 mg daily) / paritaprevir (150 mg daily) / ritonavir (100 mg daily) plus dasabuvir (250 mg twice daily)
CHC	Chronic hepatitis C
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CS	Company's submission
CSR	Clinical study report
DC	Decompensated Cirrhosis
DSA	Deterministic sensitivity analysis
ERG	Evidence Review Group
EQ-5D-5L	EuroQol-5 Dimension 5-Level
FAD	Final appraisal determination
FDA	Food and Drug Administration
GT	Genotype
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCV-PRO	Hepatitis C Virus Patient Reported Outcomes Instrument
HIV	Human immunedeficiency virus
HRQoL	Health-related quality of life
HSUV	Health state utility values
IL28B	Interleukin 28B
ITT	Intention to treat
MTC	Mixed treatment comparison
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PegIFN	Pegylated interferon
PegIFN+RBV	Pegylated interferon and ribavirin
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
RCT	Randomised controlled trial
RBV	Ribavirin
SD	Standard deviation
SF-36	Short Form (36 item) health survey
SmPC	Summary of Product Characteristics
SVR12	Sustained virologic response 12 weeks after end of therapy
SVR24	Sustained virologic response 24 weeks after end of therapy

SUMMARY

Scope of the company submission

The company's submission (CS) generally reflects the scope of the appraisal issued by the National Institute for Health and Care Excellence (NICE). This was to appraise the clinical and cost effectiveness of ombitasvir / paritaprevir / ritonavir with dasabuvir ('3D') and ombitasvir / paritaprevir / ritonavir without dasabuvir ('2D') for the treatment of chronic hepatitis C (CHC). The scope stated that the population of interest in the appraisal was people with any of the hepatitis C virus (HCV) genotypes (GTs) (GTs 1 to 6), but the company restricted the population in their decision problem to people with HCV GTs 1 and 4, because the licence for 3D and 2D is for use in these populations, respectively. The ERG agrees that this was an appropriate approach.

Summary of submitted clinical effectiveness evidence

The company's systematic review of the clinical effectiveness of 2D and 3D identified the following trials:

HCV Genotype 1

- Six Phase 3 trials, two of which compared 3D + RBV (12 weeks of treatment) with placebo (SAPPHIRE I and SAPPHIRE II), and four of which compared different 3D treatment regimens with each other (TURQUOISE II compared 3D + RBV 12 weeks with 3D + RBV 24 weeks, and PEARL II, PEARL III and PEARL IV compared 3D + RBV 12 weeks with 3D 12 weeks). All of these trials included planned comparisons with a historical telaprevir comparator (i.e. with results from relevant previously conducted trials of telaprevir).
- Two Phase 2 trials, one was a dose finding study (AVIATOR) and which did not provide any data in line with the licensed indications (because a lower dose of dasabuvir was used than that specified in the licence). The other (M14-103) was a single arm study of 3D+RBV 12 weeks specifically in patients who were receiving opioid replacement therapy.
- Only one of the above GT1 trials included people with cirrhosis (TURQUOISE II) .
- Three of the trials included solely treatment naive patients (SAPPHIRE I, PEARL III and PEARL IV), two trials included solely treatment experienced patients (SAPPHIRE II and PEARL II) and three included both treatment naive and treatment experienced patients (TURQUOISE II, AVIATOR and M14-103).

- The ERG notes that in these trials only certain trial arms or subgroups provide data in line with the treatment regimens proposed for different HCV GT1 populations specified in the licence (i.e. the licence specified different regimens according to whether patients have genotype subgroup GT1a or GT1b and whether or not they have cirrhosis).

HCV Genotype 4

- One Phase 3 trial of treatment naive and treatment experienced patients without cirrhosis. This trial compared 2D + RBV 12 weeks with 2D 12 weeks in treatment naive patients and additionally examined 2D + RBV 12 weeks in treatment experienced patients.
- The ERG notes that the 2D + RBV 12 weeks arms are in line with the licensed indication for patients with HCV GT4 without cirrhosis. The 2D 12 weeks arm, however, is not relevant to the licence.

The company also presented interim results in the CS from two ongoing trials of people with HCV GT1:

- TURQUOISE I: a RCT evaluating 3D + RBV 12 weeks versus 24 weeks in HCV GT1 patients co-infected with HIV-1. The trial included both treatment naive and treatment experienced patients, and both cirrhotic and non-cirrhotic patients.
- CORAL I: a cohort study evaluating 3D with and without RBV in HCV GT1 patients after liver transplant.

In their response to NICE and the ERG's clarification letter, the company additionally provided NICE and the ERG with academic in confidence SVR12 (sustained virologic response 12 weeks after end of therapy) results from two ongoing studies that directly compared 3D with telaprevir regimens in HCV GT1 patients:

- MALACHITE I: RCT evaluating 3D + RBV versus telaprevir + PegIFN+RBV in treatment naive patients.
- MALACHITE II: RCT evaluating 3D + RBV versus telaprevir + PegIFN+RBV in treatment experienced patients.

The company presented three meta-analyses of the SVR12 findings from the completed studies of the 3D regimens, pooling results from single arms for different 3D regimens. One meta-analysis included only the trial arms or subgroups that provided data in line with the licence. The findings of the meta-analysis are not used in the economic model and the ERG considered them to be only illustrative of the average SVR12 rate from the 3D studies.

The company determined that it was not possible to conduct a robust NMA and the ERG agreed with this based on data available in the CS. The ERG notes, however, that with the data from the ongoing MALACHITE studies – which directly compare 3D with telaprevir regimens – it would be possible to conduct an NMA for the population included in these studies. The ERG considers that while it was not possible to conduct an NMA including the 3D and 2D regimes, the company could have conducted an NMA of the comparators to populate the economic model. The company carried out unadjusted indirect comparisons with SVR rates from published telaprevir studies. Data from these unadjusted indirect comparisons have been used in the economic model for 3D and telaprevir regimes ("unadjusted" essentially means that data from individual trial arms of studies for the relevant populations have been used).

The outcome measures included in the CS were SVR12, development of resistance to 3D or 2D therapy, mortality, adverse effects of treatment and health-related quality of life (HRQoL). These outcomes are all those that were specified to be of interest in NICE's scope.

We summarise here the results of individual trial arms or subgroups from the completed studies identified in the systematic review that were in line with the licensed indications. For GT1a patients, SVR12 rates ranged from 95.0% to 97% and for GT1b patients, ranged from 98.5% (patients with compensated cirrhosis) to 100%, with all GT1 studies demonstrating superiority of 3D to a historical telaprevir comparator on the SVR12 outcome. The meta-analysis of SVR12 from trial arms in line with the licensed indications for all participants for 3D in HCV GT1 showed an average SVR12 of 96.5% (95% CI 94.6 to 97.7). All GT4 patients in the one GT4 trial achieved SVR. On treatment relapse and failure rates were low for both GT1 and GT4 patients (0-1% and none, respectively). Treatment with 3D or 2D appeared to have a minimal impact on patients' HRQoL. Common AEs were fatigue, headache, nausea and insomnia. Up to 7.9% of patients with GT1 HCV experienced a serious AE, but few serious or severe AEs were observed in patients with GT4 HCV.

Summary of submitted cost effectiveness evidence

The MS includes:

- a review of published cost-effectiveness studies of pharmacological treatments for people with CHC (conducted as an update of the systematic review reported by Hartwell and colleagues[1] undertaken for a previous NICE appraisal [TA200[2]]);
- an economic evaluation estimating the cost-effectiveness of 3D (with or without RBV) and 2D (with RBV) compared with current standard care in patients infected with either GT1 or GT4 CHC, respectively.

An updated systematic review of the literature was undertaken by the company, identifying cost-effectiveness studies of pharmacological treatment for people with CHC. This was conducted for the period from 1st January 2009 to 2nd April 2014,as an update of a published systematic review up to 2009. Nine papers met the inclusion criteria; no economic evaluations including 3D and 2D (with or without ribavirin) were identified in the review. The ERG conducted an update, covering the period from April 2014 up to current date but no result additional relevant studies were identified.

A published Markov state-transition model was adapted for GT1 and GT4 HCV. Separate analyses are reported for stage of fibrosis (mild, moderate, and cirrhosis), treatment history (naïve or experienced), eligibility for treatment and duration. The patients in GT1 were further divided by genotypes sub-types (GT1a and GT1b). The model adopts a lifetime horizon, indicated as 70 years, with an annual cycle length. The model treats SVR as the primary treatment outcome, assessed at 12 weeks post-treatment, and assumes that SVR indicates lifelong cure of HCV. However the model includes a low probability of re-infection with HCV, and assumes that re-infected patients would re-enter the disease stage they had reached prior to experiencing SVR.

The modelling approach and structure adopted are based on previous models for HCV. The CS (7.2.1) states that characteristics of the patient groups follow the licensed indications for the 3D and 2D regimens and the patient populations studied in the clinical trials. However, baseline population characteristics in the model are primarily derived from previous assessments conducted for NICE (TA106[3] and TA200[2]) and there is no discussion of comparability against characteristics of patients identified in the clinical trials. Health related quality of life utility values in the model were taken from the UK Mild Chronic Hepatitis C Trial.[4] Disutilities associated with

treatment are based on regimen-specific estimates derived using the EQ-5D, comparing health state utility values for patients on- and off-treatment. Resource use and costs were based on two published studies and were uprated to 2012/13 prices.

Results are presented as incremental cost per quality adjusted life years (QALY) for 3D (with or without RBV) and for 2D+RBV for GT1 patients, and for 2D+RBV for GT4 patients. The MS reports an ICER of £10,258 for GT1 treatment-naïve, interferon eligible patients compared with PegIFN+RBV. For GT4 treatment-naïve, interferon eligible (non-cirrhotic) patients the base case incremental cost per QALY gain reported is £20,351 (compared with PegIFN+RBV) and £8,977 for GT4 treatment-experienced, interferon eligible patients (compared with BSC).

The company reports deterministic analyses, scenario analyses and probabilistic sensitivity analyses. Health state utilities appear to be the most influential on the cost effectiveness estimates across all DSAs, with only two exceptions where SVR seemed to be more influential. The CS presented a large number of scenario analyses, but did not provide a summary or conclusion, nor does it provide any indication of the priority or credibility of the scenarios being considered. Some scenario analyses were based on extreme values while others considered alternative data source. However there was no discussion of the selection of alternative sources or their validity or credibility. As a result the scenario analysis are difficult to interpret. The CS reports separate probabilistic sensitivity analyses for patient populations defined by genotype and prior treatment history.

In general the ERG considers that the modelling approach adopted in the submission is reasonable and is consistent with the sources of evidence used in its development. One major concern however, is that the company has not addressed the uncertainty introduced in the model by absence of evidence in the direct comparison of the clinical effectiveness. Additionally, the ERG suggests that, although the economic model captures most of the important aspects of the disease pathway, the number of assumptions and/or imputations required to populate the model might have introduced uncertainty within the results that is not properly addressed. The inclusion of comparators identified in the NICE scope is hampered by absence of evidence, a lack of specific information for particular patient subgroups (Q80K polymorphism in GT1a patients to be treated with simeprevir+PegIFN+RBV) or by trial results being reported for trial arms but not by fibrosis stage, genotype or treatment-experience.

Commentary on the robustness of submitted evidence

Strengths

- Although the ERG considered there to be some uncertainty about how systematic the company's searches for clinical effectiveness studies of 3D and 2D were, the company appears to have included all available relevant studies.
- The cost effectiveness analysis adopted a model that has been used in previous NICE appraisals[3 2 5] which has been updated in the CS with more recent evidence on costs and risk of HCC for cirrhotic patients

Weaknesses and Areas of uncertainty

- Of the clinical effectiveness studies identified in the clinical effectiveness systematic review, none directly compared 3D or 2D with the current standards of care for patients with HCV GT1 or GT4 (boceprevir + PegIFN+RBV and telaprevir + PegIFN+RBV for GT1, and PegIFN+RBV for GT4), other than by historical comparison to telaprevir studies. Instead the trials compared different 3D or 2D regimens to each other or placebo. (Although, as noted above, some academic in confidence data from two ongoing trials directly comparing 3D with telaprevir regimens was provided to the ERG during the appraisal.) Therefore, the clinical effectiveness evidence available does not directly meet the decision problem (due to the lack of comparison to relevant comparators) and the SVR12 estimates are mainly derived from what are essentially observational studies (i.e. individual trial arms, rather than randomised comparisons) and subgroup analyses within trials arms. This means that no data from robust, randomised comparisons of 3D or 2D regimens against comparators listed in the scope are available to inform the economic model.
- The company excluded potentially relevant simeprevir comparators from the decision problem (including the interferon-free regimen simeprevir + sofosbuvir), due to a lack of suitable data available to inform the economic model. The ERG agrees that the company's rationale for excluding these comparators is reasonable. However, this means that no estimates of clinical effectiveness or cost effectiveness in comparison to simeprevir or interferon-free regimens are available in the CS.

Superseded- see Erratum

- There were higher proportions of patients with mild fibrosis (e.g. fibrosis scores of F0 and F1) in the 3D studies than the historical comparator telaprevir studies, which may have biased the SVR estimates in favour of 3D.
- There were limited data available in the submission about SVR12 outcomes and other outcomes for the subgroups of patients specified to be of interest in the scope and decision problem: those with cirrhosis, HIV co-infection and patients who are post-liver transplant. In particular, no studies were identified that had been conducted in patients with HCV GT4 who had cirrhosis, who would be treated with 2D + RBV for 24 weeks, according to the licensed indication. Therefore, no data for this licensed indication are available. No efficacy data for people who are intolerant to or ineligible for interferon treatment were presented, which meant no efficacy data for this subgroup were available to inform the economic model. Instead, the company used the same efficacy data as for IFN-eligible patients for this subgroup in the model, but did not provide a justification for why this was considered appropriate.
- Overall the ERG considers that the SVR12 outcomes may be subject to bias due to the data essentially being observational data, and the 3D studies having a higher proportion of patients with mild fibrosis (e.g. fibrosis scores of F0 and F1) than the historical comparator telaprevir studies. However, the ERG acknowledges that the SVR12 rates associated with 3D and 2D are likely to be high.
- The ERG was unable to check all efficacy and transition probability data used in the CS. The layout of the electronic model did not assist critical assessment, quality assurance and error checking. The majority of referencing in the model uses cell addresses which have no logical meaning and a number of formulae in the model contain numerous nested statements and references to other worksheets.
- The model is not well validated against external data. This CS did not present any evidence of external validation of the model outputs against published evaluations of comparators (included in their systematic review of economic evidence) or against previous company submissions for NICE STAs of comparator technologies.[6 5 7]
- The economic model is dependent on the credibility of the unadjusted indirect comparisons. The ERG suggests that a more credible analysis could have been developed by ensuring consistency in the evidence base for comparators used to populate the model.

Superseded- see Erratum

Summary of additional work undertaken by the ERG

The ERG undertook additional work to:

a) include SVR data from head-to-head comparison of 3D and telaprevir+PegIFN+RBV

b) re-run the PSA using fibrosis stage-specific SVRs (mild and moderate fibrosis stages) from 3D trials rather values pooled across fibrosis stages

c) present an alternative base case analysis adjusting effectiveness of boceprevir+PegIFN+RBV

d) present an alternative base case analysis including simeprevir+PegIFN+RBV

e) present an alternative base case analysis (for non-cirrhotic patients, similar to additional analysis a) using an adjusted indirect comparison – to include PegIFN+RBV and boceprevir+PegIFN+RBV in addition to 3D and telaprevir+PegIFN+RBV

f) conduct a threshold analysis on relative effectiveness (SVR) for 3D and 2D

g) present a scenario using an alternative estimate of the risk of HCC for those patients who underwent SVR from the compensated cirrhosis health state

h) present a scenario using an alternative estimate for the risk of HCC for those in the compensated cirrhosis health state

i) present a scenario using an alternative estimate for the risk of HCC for those patients who underwent SVR from the compensated cirrhosis health state and for those remaining in the compensated cirrhosis health state

The additional analyses did not result in large changes in the cost effectiveness estimates for 3D and 2D. However the adjusted indirect comparisons reduced the number of comparators dominated by 3D and 2D. The threshold analysis indicated that a 5% reduction in the effectiveness (SVR) with 3D would reduce the number of dominated comparators and, where sofosbuvir+PegIFN+RBV is included as a comparator, further reduction in effectiveness may substantially affect the cost effectiveness of 3D.

1 Introduction to ERG Report

This report is a critique of the company's submission (CS) to NICE from AbbVie on the clinical effectiveness and cost effectiveness of ombitasvir / paritaprevir / ritonavir with or without dasabuvir for treating chronic hepatitis C (CHC). It identifies the strengths and weaknesses of the CS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the CS was requested from the company by NICE and the ERG on 19th January 2015. A response from the company via NICE was received by NICE and the ERG on 5th February 2015.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The CS provides a clear and accurate overview of CHC.

2.2 Critique of company's overview of current service provision

The CS generally provides a clear and accurate overview of how CHC is currently managed in clinical practice. An exception, however, is that the company states that PegIFN+RBV and boceprevir + PegIFN+RBV are not widely used for HCV genotype (GT) 1 in practice now (based on clinical expert advice and unreferenced pharmaceutical company and pharmacy data) (CS p. 45), which does not fully concur with clinical expert advice to the ERG. Our clinical experts have indicated that boceprevir is an appropriate comparator, with one expert suggesting that around half of patients with HCV GT1 are treated with boceprevir + PegIFN+RBV and around half are treated with telaprevir + PegIFN+RBV. Our clinical experts agreed with the company, though, that PegIFN+RBV is not the current standard of care for HCV GT1 patients and therefore not an appropriate comparator for this group. The CS correctly states that there is an unmet clinical need for interferon-free regimens for patients with HCV GT1 or GT4 who are intolerant to or ineligible for interferon treatment, as all the treatment regimens currently approved for use in the NHS for these patients involve co-administration of PegIFN and RBV.[2;3;8-10]

2.3 Critique of company's definition of decision problem

Population

The population defined in the decision problem is adults with GT1 and GT4 CHC, who are either treatment naïve or treatment experienced. The population is more specific than that described in the final scope issued by NICE (which did not specify HCV genotype), because the company notes that the licence for ombitasvir / paritaprevir / ritonavir with or without dasabuvir will be for use in GT1 and GT4 patients only. Therefore, this is appropriate for the potential use of ombitasvir / paritaprevir / ritonavir with or without dasabuvir in the NHS.

Intervention

In line with the final scope, the intervention described in the decision problem is co-formulated ombitasvir/paritaprevir/ritonavir (brand name: Viekirax) with or without dasabuvir (brand name: Exviera), co-administered with or without RBV. The marketing authorisation was granted in January 2015. The company provided the draft summaries of product characteristics (SmPCs) for Viekirax and Exviera in an appendix to the CS. The licences outline the following general regimens and doses of these drugs for patients with GT1 and GT4 CHC – the recommended specific regimens according to genotype, genotype subgroup and cirrhosis status are shown in Table 20 in the CS (CS p. 29), which is reproduced as Table 1 here:

- GT1: ombitasvir (25 mg daily) / paritaprevir (150 mg daily) / ritonavir (100 mg daily) plus dasabuvir (250 mg twice daily) (referred to in the CS and hereafter in this ERG report as '3D'), co-administered with or without RBV
- GT4: ombitasvir (25 mg daily) / paritaprevir (150 mg daily) / ritonavir (100 mg daily) (referred to in the CS and hereafter in this ERG report as '2D'), co-administered with RBV

The 3D and 2D treatment regimen doses and durations outlined in the CS match the licensed indications for Viekirax and Exviera. An exception to the latter is that there appears to be an error in CS Table 21 (CS p. 32) where it is stated that patients with GT4 HCV with compensated cirrhosis receive 24 weeks of 3D + RBV – this should be 24 weeks of 2D + RBV. This error also appears to have been replicated in the 'Average cost of a course of treatment' row of this table too, where two different average costs are presented for a 24 week course of treatment of 3D – the ERG believes that the last cost listed should be for a 24 week course of treatment with 2D rather than 3D as stated. The CS does not provide the dose of RBV. The ERG notes that the

draft SmPC for Viekirax states that this should be as per the RBV licence. Overall, the intervention described in the decision problem is appropriate for the NHS.

Table 1: Treatment regimen and duration by patient population, as outlined in the SmPC

Patient population	Treatment	Duration
Genotype 1b without cirrhosis	3D	12 weeks
Genotype 1b with cirrhosis	3D + RBV	
Genotype 1a without cirrhosis	3D + RBV[a]	
Genotype 1a with cirrhosis	3D + RBV[a]	24 weeks (see section 5.1 of SmPC)
Genotype 4, without cirrhosis	2D + RBV	12 weeks
Genotype 4, with cirrhosis	2D + RBV	24 weeks

This table is a direct reproduction of Table 20 in the CS (p. 29-30). [a]Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection. RBV, ribavirin; SmPC, Summary of Product Characteristics.

Comparators

The comparators which were listed in the final scope and which were included in the decision problem and economic model in the CS are shown in Table 2.

Table 3 gives further details about the comparators the company has excluded and the reasons given for exclusion. The ERG agrees that the company's rationales for excluding these comparators from the decision problem appear reasonable. The main reason for exclusion was a lack of suitable data for the economic model. The ERG has checked whether appropriate data are available and agrees with the company that no suitable data are publicly available and that it is therefore reasonable not to include these comparators in the decision problem. The company states that the only relevant comparator for patients with GT1 and GT4 who are intolerant to or ineligible for interferon treatment is best supportive care. In the CS best supportive care is specifically defined more narrowly than in the final scope, as care for patients with GT1 and GT4 who are interferon intolerant or ineligible. The ERG considers this is reasonable, but notes that in practice the patient group who may receive best supportive care is wider than just those who are interferon intolerant (e.g. some patients choose not to be treated).

Overall, the ERG considers the company has included all appropriate comparators from the scope in the decision problem. However, the lack of suitable data for the economic model means that no estimates of the clinical or cost effectiveness of 3D or 2D in comparison to simeprevir or interferon-free regimens are available in the CS.

Outcomes

In line with the final scope, the outcomes listed in the decision problem are:

- SVR12 (sustained virologic response 12 weeks after the end of therapy) (the scope more broadly specified 'SVR')
- development of resistance to 3D or 2D therapy
- mortality
- adverse effects of treatment
- health-related quality of life (HRQoL)

These outcomes are appropriate and clinically meaningful. Historically, SVR24 (sustained virologic response at 24 weeks post-treatment) has been used to measure response to treatment in CHC,[2] but SVR12 is now used for regulatory approval, is highly predictive of SVR24[11;12] and is a clinically suitable endpoint.

Economic analysis

The economic analysis proposed in the decision problem matches the final scope and is appropriate for the NHS. The company has used a lifetime time horizon, which is appropriate for capturing differences in outcomes and costs for interventions for CHC.

Table 2: List of comparators specified in the final scope and whether they have been included in the CS decision problem and economic model

Comparator specified in final scope (relevant population, in line with that specified in the CS decision problem)	**Included in the CS decision problem and economic model?**
PegIFN+RBV (GT1 and GT4)	Yes
Telaprevir + PegIFN+RBV (GT1)	Yes
Boceprevir + PegIFN+RBV (GT1)	Yes
Sofosbuvir + RBV, with or without PegIFN (GT1 and GT4) (subject to ongoing NICE appraisal ID654)	In part – sofosbuvir + PegIFN+RBV for GT1 and GT4 included. Sofosbuvir + RBV without PegIFN for GT1 and GT4 was excluded – see Table 3 below.
Simeprevir + PegIFN+RBV (GT1 and GT4) (subject to ongoing NICE appraisal ID668)	No – see Table 3
Simeprevir+sofosbuvir with or without RBV (for people who have GT1 or GT4 disease and are ineligible for or intolerant to interferon treatment) (subject to ongoing NICE appraisal ID668)	No – see Table 3 below.
Best supportive care (watchful waiting) (GT1 and GT4)	Yes, but the populations specified in the decision problem and economic model are more specifically patients with GT1 and GT4 who are interferon-intolerant.

GT, genotype; HCV, hepatitis C virus; NICE, National Institute for Health and Care Excellence; PegIFN+RBV, Pegylated interferon and ribavirin; RBV, ribavirin.

Table 3: Comparators specified in the final scope which were excluded from the CS and economic model and reasons for exclusion

Comparator (population)	Company's reason for exclusion	ERG's agreement or disagreement with exclusion
Simeprevir + PegIFN+RBV (GT1)	This regimen has received a preliminary recommendation from NICE,[13] but it is not licensed for patients with GT1a who have the Q80K positive polymorphism. The CS economic model requires data stratified by fibrosis status and the only data available by fibrosis status were for the ITT population and not patients who are Q80K negative.	Agree. The company's rationale appears reasonable – the ERG has checked available data and agrees that there is no publicly available suitable data broken down by stage of fibrosis to inform a model for patients who are Q80K negative. [The ERG notes that NICE has now issued final guidance on simeprevir (TA331)[14] and that this regimen has been approved for GT1 patients.]
Sofosbuvir + RBV [GT1, interferon intolerant or ineligible (12 week regimen) and GT4 interferon intolerant or ineligible (24 week regimen)]	NICE have preliminarily not recommended these regimens for these populations.	Agree. NICE has now published final guidance for sofosbuvir (TA330)[15] which does not recommend these regimens for these populations.
Simeprevir + sofosbuvir (GT1 and GT4, interferon intolerant or ineligible)	NICE have preliminarily not recommended these regimens for these populations. Additionally, the data available by disease severity (i.e. fibrosis and cirrhosis status) categorises this in a different way to the CS economic model and so is not appropriate to use.	Agree. The ERG considers the company's rationale for excluding this comparator on the basis of a lack of suitable data for the economic analysis appears reasonable. The ERG notes from the NICE FAD for simeprevir,[13] however, that a decision about this regimen has been postponed to allow for mature data on this combination for these patients to become available. The now published final guidance from NICE for simeprevir (TA331)[14] states that recommendations for this combination will be developed in separate guidance. It is therefore still

		possible that this regimen could be approved for use in the NHS in the future as an option for patients who are intolerant to or ineligible for interferon.
Simeprevir + PegIFN+RBV (GT4)	Data for the relevant simeprevir trial (RESTORE) were not presented by both fibrosis and cirrhosis status, as needed for the CS economic model structure. Additionally, the 2D trial (PEARL-I[16]) excluded cirrhotic patients, while the RESTORE trial population included cirrhotics (23% of the sample), meaning comparing data from the two trials would be unfair.	Agree. ERG notes that this regimen has now been approved by NICE for patients with HCV GT4 (TA331), but agrees with the company that it is appropriate to exclude it as a comparator from the decision problem due to a lack of suitable data for the economic model.

ERG, Evidence Review Group; FAD, final appraisal determination; GT, genotype; ITT, intention-to-treat; NICE, National Institute for Health and Care Excellence; PegIFN+RBV, Pegylated interferon and ribavirin; RBV, ribavirin

Other relevant factors

Relevant subgroups

In the decision problem, the company has specified the following subgroups for consideration, which are all those stated to be of interest in the final scope:

- Genotype (genotype subgroup was not specifically referred to in the NICE scope)
- Co-infection with human immunodeficiency virus (HIV)
- Patients with and without cirrhosis
- People who have received treatment post-liver transplant
- Response to previous treatment (non-response, partial response, relapsed)
- People who are intolerant to or ineligible for interferon treatment

The company notes in the decision problem, that while data for patients with HIV co-infection are presented, outcomes for these patients are not modelled separately in the economic model, as outcomes were similar to those of patients without HIV co-infection. The ERG agrees that SVR outcomes appear similar for patients with HIV co-infection and who do not have cirrhosis to patients without HIV co-infection and who do not have cirrhosis (only limited data are provided for HIV co-infected patients who have cirrhosis and as such are less conclusive) and it is

therefore reasonable not to model outcomes for these groups separately. The ERG considers one issue that may impact on the cost-effectiveness of 3D or 2D in this population is that they may require additional monitoring. Clinical expert advice to the ERG indicates that more supervision is needed of these patients, due to administration of ritonavir and the increased potential for drug interactions in these patients. However, the ERG and one of the clinical experts providing advice to the ERG consider that this is likely to have a minimal impact on the cost-effectiveness.

There are also limited data available on SVR rates for patients with cirrhosis, as the majority of the trials excluded patients with cirrhosis. Only one completed study (TURQUOISE II[17]) focussed solely on patients with cirrhosis, and one ongoing study (of patients co-infected with HIV; TURQUOISE I) included patients with (n = 6) and without cirrhosis (n = 25) and provided subgroup analyses of SVR by cirrhosis status (see Sections 3.1.3 and 3.3.4).

No subgroup analyses are presented for people who are intolerant to or ineligible for interferon treatment, so efficacy data for this subgroup is not available to inform the economic model. Instead, the economic model uses the same efficacy data as for IFN-eligible patients, but did not provide a justification for why this was considered appropriate. The ERG considers this to be a limitation of the available efficacy data and the economic analysis presented in the CS. Furthermore, the ERG notes that there is no information in the CS about the proportion of patients included in each trial who were IFN intolerant or ineligible, so it is unclear if the 3D and 2D trials included these patients and whether they are therefore represented in the efficacy data.

The company has also reported the results of a number of other subgroup analyses of SVR outcomes within trials, including by gender, race and ethnicity, age, body mass index, fibrosis score, interleukin 28B (IL28B) genotype, diabetes history, HCV RNA level, geographic region, IP-10, and for treatment history.

The patient subgroups represented in the economic model are those by HCV sub-genotype (GT1a and GT1b), stage of fibrosis (mild, moderate and cirrhosis), treatment history (naive or experienced) and eligibility for treatment with PegIFN (see Section 4.2.2 of this report).

Superseded- see Erratum

The results of subgroup analyses are presented for the GT1 trials only, as 100% of patients included in the one GT4 trial identified achieved SVR12.

The ERG considers that both the company's decision problem and the CS in general have included all important subgroups, but that the lack of efficacy data presented for people with cirrhosis or who are IFN intolerant or ineligible is a limitation of the trials and the CS.

Equality issues

The company has highlighted a number of equality issues in their decision problem, which the ERG has summarised in Table 4. The ERG and clinical experts consulted by the ERG consider the issues raised by the company to be appropriate and have not identified any additional equality issues. The ERG notes that potential equality issues relating to patients with HIV co-infection were raised in NICE's appraisals of sofosbuvir (TA330),[18] boceprevir (TA253)[19] and telaprevir (TA252).[20] The ERG also notes that the disproportionate representation of minority groups among patients with GT4 HCV was raised as an equality issue in the appraisals of sofosbuvir[18] and simeprevir.[13] Additionally, the ERG notes that differential recommendations for people with and without cirrhosis are made in NICE's guidance on the use of sofosbuvir for treating chronic hepatitis C.[15] Clinical expert advice to the ERG concurs with the company's assertion that the 3D and 2D regimens have the potential for reducing health inequalities in prison populations and among homeless people, as interferon-free regimes would likely be better tolerated in these populations. The clinical experts consulted by the ERG also agreed that the company's reason for suggesting that recommendations about the use of 3D and 2D should not differentiate between people with and without cirrhosis is reasonable. This is due to the potential for inaccurate classifications of the degree of fibrosis or cirrhosis from fibroscan assessments of liver fibrosis and sampling variations from liver biopsies (note, most assessments of fibrosis are performed by fibroscan rather than liver biopsy in clinical practice now). Clinical expert advice to the ERG is that patients with F3 or F4 would both be considered to have advanced fibrosis and would be treated the same.

Table 4: Equality issues raised by the company

Patient group (type of equality issue)	Equality issue raised[a]
Ethnic groups disproportionately affected by GT4 (equality legislation)	HCV GT4 infection predominantly affects people from North Africa, the Middle East, Central Africa and Egypt. Therefore, differential recommendations on the use of 3D or 2D for patients with HCV GTs 1 and 4 could potentially disadvantage and discriminate against migrants from these countries.
People with HIV co-infection (equality legislation)	People with HIV co-infection may be classified as disabled under disability discrimination legislation. Therefore, as evidence is presented to show the efficacy of 3D does not differ in patients with HIV co-infection, recommendations on the use of 3D or 2D should not differ for patients with or without HIV co-infection.
Prison populations and homeless people (health inequalities)	Effective HCV treatments for these patients have potential for reducing health inequalities given that these groups have a higher prevalence of HCV infection.
Patients with cirrhosis (type of equality issue not specified)	Differential recommendations on the use of 3D or 2D should not be made for patients with and without cirrhosis, as some patients may be misclassified as having a metavir score of F3 when they have a score of F4.

[a] Equality issues are raised in CS section 3 p. 49-50

Impact of treatment on onward HCV transmission

The final scope specified that, if evidence allowed, the impact of treatment on reduced onward HCV transmission could be considered in the CS. The company has not presented data about the impact of treatment on preventing onward transmission in the CS.

3 CLINICAL EFFECTIVENESS

3.1 Critique of company's approach to systematic review

3.1.1 Description of company's search strategy

Despite some minor errors, the searches are overall sound and considered unlikely to have missed anything of significance that was not identified in the submission reference list. In the Clinical Evidence search section, Cochrane was not listed, however additional alternative databases have been included such as 'Citeline Trialtrove' (which claims to gather its clinical trial intelligence from over 20,000 sources, so was deemed a suitable alternative). The hosts of the databases have not been listed and all sources have been simultaneously cross-searched and de-duplicated, rather than recording numbers from individual separate searches. The outcome term (SVR) is included in the search strategy, rendering it highly specific; a broader approach in a systematic review would have been preferable. No additional adverse event searching was undertaken, with data taken from the trials that met the inclusion criteria. The clinical searches were three months out of date (conducted September 2014). The ERG ran checks on Medline, Embase, Cochrane Central and NICE Evidence, replicating searches and adding some terms such as product trade names, 3-DAA and 3D, and omitting the SVR terms. No extra relevant results were identified from modification of the search.

A flow diagram was provided by the company on request from NICE and the ERG (clarification points A5 and A8). Although a summary of reasons for exclusion was provided in the flow chart, a list of excluded studies with reasons for exclusion was not provided. Full citations and abstracts, where available, for the 30 studies identified on searching were presented in CS Appendix 2. However, only two [PEARL II (Andreone et al. 2014[21]) and PEARL I (Hezode et al. 2014[22])] of the eight published primary study references given in CS Table 24 p. 61 were among the 30 studies identified on searching. As the searches were conducted in September 2014 and the other six primary study references were published prior to this, it is not clear why these were not identified by the company's searches.

The cost effectiveness and quality of life searches used appropriate databases, subject terms and filters, named the host and searched and recorded results for each database separately.

Typographical errors occur in Section 10.12.4 in the reporting of the quality of life/ health state utility values (HSUV) searches (lines: 45 of Medline, 39 of Embase and 39 of Econlit, relating to English language restriction). PRISMA flow diagrams of results are given. The ERG updated the cost and quality of life searches as the company's searches were conducted 8 months before submission. The results were checked by two reviewers. No cost effectiveness studies including 3D or 2D were identified by these searches. Additional cost effectiveness studies including comparator regimens identified by these searches were non-UK studies, applying efficacy estimates from the comparator registration trials. No additional primary sources for quality of data to populate the economic model were identified in these searches.

Additional searching was also undertaken by the ERG on UKCRN, UKCTG, clinicaltrials.gov ISRCTN and WHO ICTRP to check for any extra ongoing trials not mentioned in the CS. The results were checked by two reviewers (see section 3.1.3).

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

There are some differences between the eligibility criteria for the CS systematic review and the NICE decision problem. The NICE scope refers to adults with CHC and does not limit by genotype. However, the trial evidence and the licensed indications of the interventions are limited to people with HCV genotypes 1a, 1b or 4.

The inclusion and exclusion criteria for selection of trials of the intervention (3D or 2D) are clearly stated (CS Table 23 p. 57). Inclusion is limited to patients with HCV genotype 1 or 4. Eligible comparators are 'Any', rather than those listed in the NICE scope. As a result, several of the included RCTs do not have an appropriate randomised comparison. Instead, the CS provides what it refers to as planned 'historical comparisons' with data from previous trials of telaprevir. Phase II or III clinical trials were eligible for inclusion in the systematic review. RCT quality and study setting were not specified as inclusion or exclusion criteria. The CS does not explicitly consider bias in study selection.

On request from NICE and the ERG, the company clarified that a systematic review was not undertaken to identify the studies used to estimate the telaprevir SVR rates used as the historical controls (clarification point A1), and inclusion and exclusion criteria for trials of the historical controls were not reported in the CS. The company also clarified that a systematic

review was not undertaken to identify studies to derive the SVRs for certain disease characteristics for different HCV GT1 regimens (PegIFN+RBV, telaprevir + PegIFN+RBV, boceprevir + PegIFN+RBV, sofosbuvir + PegIFN+RBV, simeprevir + PegIFN+RBV) presented in CS Table 58, p. 199. The company stated that, with the exception of PegIFN+RBV all the regimens in the table had been assessed by the STA process and therefore company submissions to NICE and ERG reports for these previous STAs were used to identify the data (clarification point A2).

3.1.3 Identified studies

Study designs

The CS identified nine studies: eight of 3D and one of 2D (Table 5). Of these nine studies, seven were phase 3 trials, and two were phase 2 studies (one RCT and one single arm study, both of 3D) that were reported in less detail. Although the trials were described in the CS as RCTs, only the two placebo controlled trials (SAPPHIRE I[23] and II[24]) have a comparator relevant to the decision problem. However, only data on HRQoL and adverse events were collected from the placebo arm in these two trials. The comparators in the remaining six RCTs were not relevant to the decision problem. Therefore there is no direct randomised comparison against any of the comparators listed in the scope for SVR in any of the trials. SVR data are essentially observational data.

Details of the nine 3D and 2D studies[16;17;21;23-27] are reported as methodology (Tables 26-31, p. 68-93), eligibility criteria (CS Tables 32, p. 95), baseline participant characteristics (CS Table 33-34, p. 119-123), trial outcomes (CS Table 35, p, 126-132), statistical analyses (CS Table 36, p, 134-141) and participant flow charts [CS Figures 5-11, p. 143-149 (note: not provided for the two phase 2 studies: AVIATOR[26] or M14-103[27])]. The CS states on p. 142 that pre-planned subgroup analyses were undertaken in all studies to assess any differences in the percentage of people with SVR12 according to various pre-specified demographic and baseline clinical characteristics.

In addition, limited SVR data from the telaprevir (ADVANCE, ILLUMINATE and REALIZE) boceprevir (SPRINT-2), sofosbuvir (NEUTRINO) and simeprevir (QUEST 1, QUEST 2, ATTAIN) trials are reported in the CS (CS Table 58, p. 199).

Electronic copies of the 2D and 3D trial publications were provided with the CS. Copies of the CSRs were requested by the ERG. Some comparator trial references were provided (telaprevir ADVANCE and REALIZE trials; boceprevir RESPOND-2 and SPRINT trials; sofosbuvir NEUTRINO, POSITRON and FUSION trials) but others (e.g. simeprevir trial references) were not provided and were requested by the ERG.

All included 3D and 2D studies were sponsored by the company.

Non-randomised studies

As noted above, the CS reports one non-randomised phase 2 single arm study (M14-103[27]), which is relevant to the decision problem as it assessed efficacy of 3D in treatment naive and PegIFN+RBV treatment experienced HCV GT1 patients on stable opioid therapy without cirrhosis. However, as noted, all included 2D and 3D trials provide essentially non-randomised observational data for the primary outcome of SVR12.

Characteristics of the studies

The eligibility criteria differ between the included trials with respect to genotype and genotype subgroup, treatment history, and cirrhosis status. A summary of the key criteria and treatment regimens studied or compared is presented in Table 5. Only certain arms or subgroups from the included studies are in line with the licensed indications for 3D and 2D; these are summarised in Table 6. In the ERG summary of results (section 3.3), data are presented in line with the licensed indications.

Among the GT1 phase 3 trials, the proportion of men varied from about 45% in PEARL III[25] to about 70% in TURQUOISE II.[17] Other characteristics were as follows: proportion of white people 83.4% (PEARL IV[25] 3D+placebo arm) to 95.7% (TURQUOISE II[17] 3D 12 week arm), mean age 48.4yrs (PEARL III[25] 3D+RBV arm) to 57.1yrs (TURQUOISE II[17] 3D 12 week arm), fibrosis score F2 or F3 23.3% (SAPPHIRE I[23] 3D+RBV arm) to 37% (PEARL IV[25] 3D+RBV arm), IL28B CC genotype subgroup 7.2% (SAPPHIRE II[24] placebo arm) to 31.6% (SAPPHIRE I[23] placebo arm), HCV RNA 6.29 (PEARL III[25] 3D+RBV arm) to 6.64 log10IU/ml (PEARL IV[25]).

The corresponding characteristics across the three groups from the PEARL I trial[21] in GT4 patients were 54.5% to 73.5% men, age 44.2 to 50.9 years, fibrosis score F2 or F3 13.6% to

32.6%, IL28B CC genotype subgroup 12.2% to 27.3%, HCV RNA 6.10 to 6.27 log10IU/ml, genotype subgroup 4a/c/d 47.7% to 65.3%.

One of the phase 2 RCTs (the AVIATOR study[26]) does not meet the inclusion criteria because dasabuvir (brand name Exviera), which is a component of the 3D regimen, is provided at a dose of 400mg twice daily whereas the licensed dose is 250mg twice daily. The CS did not provide the doses of each drug used in the 3D + RBV treatment regimen for the other Phase 2 trial – the M14-103 trial, and NICE and the ERG requested clarification about this. The company responded (clarifications point A16) that the licenced regimen was used. As noted above, all of the other RCTs meet the inclusion criteria of the CS systematic review, however they do not fully meet the decision problem.

Table 5 Summary of key eligibility criteria in included studies

Trial	Treatment history			Genotype / subgroup				Cirrhosis status		ORT	Comparison in trial[a]
	Tx Naive	**Tx Exp**	**Tx Exp & Naive**	**GT1**	**GT1a only**	**GT1b only**	**GT4**	**Non-cirrhotic**	**Cirrhotic**		
SAPPHIRE I[23]	✓			✓				✓			3D+RBV vs placebo
SAPPHIRE II[24]		✓		✓				✓			3D+RBV vs placebo
TURQUOISE II[17]			✓	✓					✓		3D+RBV 12 wks vs 24 wks
PEARL II[21]		✓				✓		✓			3D+RBV vs 3D
PEARL III[25]	✓					✓		✓			3D+RBV vs 3D
PEARL IV[25]	✓				✓			✓			3D+RBV vs 3D
AVIATOR[26]			✓	✓				✓			*phase 2 dose finding, 14 arms*
M14-103[27]			✓	✓				✓		✓	*phase 2 single arm 3D+RBV*
PEARL I[16]			✓				✓	✓			2D+RBV vs 2D (Tx Naive) 2D+RBV (Tx Exp)

[a] Treatment duration was 12 weeks unless stated otherwise.
GT, genotype; ORT, opioid replacement therapy; RBV, ribavirin; Tx, treatment; Tx Exp, treatment experienced.
Table data drawn from information presented in CS Tables 26-32 p.68-118

Table 6 Summary of licensed indications and corresponding trial arms or subgroups

SmPC recommendation			Trial evidence			
Patient population	**Treatment**	**Duration, wks**	**Trial**	**Genotype enrolled in trial**	**Comparison in trial[a]**	**Trial arm or subgroup meeting licence**
Genotype 1b without cirrhosis	3D	12	PEARL II[21]	1b	3D+RBV vs 3D	Arm with 3D, n=91
			PEARL III[25]	1b	3D+RBV vs 3D	Arm with 3D, n = 209
Genotype 1b with cirrhosis	3D + RBV	12	TURQUOISE II[17]	1a and 1b	3D+RBV 12 wks vs 24 wks	Subgroup with GT1b AND 12 wks duration, n=68/208
Genotype 1a without cirrhosis	3D + RBV	12	SAPPHIRE I[23]	1a and 1b	3D+RBV vs placebo	Subgroup with GT1a, n=322/473
			SAPPHIRE II[24]	1a and 1b	3D+RBV vs placebo	Subgroup with GT1a, n=173/297
			PEARL IV[25]	1a	3D+RBV vs 3D	Arm with 3D+RBV, n=100
			M14-103	1a and 1b	3D + RBV (single arm trial)	Subgroup with GT1a, n=[redacted][b]
Genotype 1a with cirrhosis	3D + RBV	24	TURQUOISE II[17]	1a and 1b	3D+RBV 12 wks vs 24 wks	Subgroup with GT1a AND 24 wks duration, n=121/172
Genotype 4 without cirrhosis	2D + RBV	12	PEARL I[16]	4	2D+RBV vs 2D (TxN) 2D+RBV (TxExp)	Arms with 2D+RBV, TxN n=42, TxEx, n=49
Genotype 4 with cirrhosis	2D + RBV	24	No data			

[a] Treatment duration in trials was 12 weeks unless stated otherwise.
[b] The company provided the ERG with the results of a subgroup analysis of SVR12 by HCV sub-genotype, in response to NICE and the ERG's request for this (clarification point A15).
Tx, treatment; Tx Exp, treatment experienced.

Baseline characteristics of the seven phase 3 and two phase 2 trials are provided in CS Tables 33-34 (p. 119-123). The ERG has examined differences in baseline characteristics of patients and controls in the two placebo controlled trials (SAPPHIRE I[23] and II[24]) as these comparisons are relevant to the decision problem. Randomised groups were generally similar, although there was a greater proportion of men in the 3D+RBV group compared with the placebo group in SAPPHIRE I[23] (57.3% vs 46.2%, p=0.02 and the 3D+RBV group were younger on average than the placebo group in SAPPHIRE II[24] (51.7 yrs vs 54.9 yrs, p=0.005).

The CS does not comment on the similarity of patients in the 3D studies to those in the studies of telaprevir used for the historical comparison (ADVANCE, ILLUMINATE and REALIZE) or the other comparators (boceprevir, simeprevir, sofosbuvir) relevant to the decision problem. In response to a request from NICE and the ERG, the company provided baseline characteristics for the telaprevir studies ADVANCE and REALIZE, but not ILLUMINATE (clarification point A9). In addition, the company provided baseline characteristics for two ongoing head-to-head RCTs of 3D+/-RBV versus telaprevir+PegIFN+RBV, MALACHITE I and MALACHITE II (for details of these and other ongoing studies, please see below).

The company stated that it was not possible to examine the baseline characteristics for the specific matched historical control rates, as the baseline data for telaprevir are not available at the disaggregated level (clarification point A9). See section 3.1.6 for details on the selection of data for the historical telaprevir controls.

For studies of treatment naive patients (SAPPHIRE I:[23] GT1, PEARL III:[25] GT1b, and PEARL IV:[25] GT1a), the telaprevir trials used for the historical comparison were ADVANCE and ILLUMINATE (both include GT1). The company commented on the similarity of SAPPHIRE I[23] and ADVANCE, and stated that other than the inclusion of cirrhotic patients in ADVANCE (6%), the key baseline characteristics are broadly similar. The ERG notes that the proportion of patients with fibrosis score F0 or F1 is higher in SAPPHIRE I[23] (76%), PEARL III[25] (70%) and PEARL IV[25] (64%) than in ADVANCE (37%) and ILLUMINATE (27%). The company did not comment on the similarity of ADVANCE with PEARL III[25] and PEARL IV,[25] or of ILLUMINATE with the three 3D studies. Other differences noted by the ERG include the lower proportion of Hispanic patients in PEARL III[25] (2% compared with approximately 10% in ADVANCE).

For treatment experienced patients (SAPPHIRE II:[24] GT1, and PEARL II:[21] GT1b), the telaprevir trial used for the historical comparison is REALIZE (GT1). The company comments on the similarity of SAPPHIRE II[24] and REALIZE, and notes that SAPPHIRE II[24] excluded cirrhotic patients and purposefully included a much higher proportion of null responders. The company did not comment on the similarity of REALIZE with PEARL II.[21] The ERG notes that the proportion of patients with fibrosis score F0 or F1 is higher in SAPPHIRE II[24] (68%) and PEARL II[21] (67%) than in REALIZE (23%).

For cirrhotic patients (TURQUOISE II,[17] both treatment naive and treatment experienced patients), the data used for the historical comparisons are from the subgroups of patients with cirrhosis from ADVANCE and ILLUMINATE (for treatment naive patients) and REALIZE (for treatment experienced patients). Baseline data for these subgroups are not available.

The baseline characteristics of the randomised groups in MALACHITE I and MALACHITE II were generally similar, although there were differences between trial arms in the proportion of men and proportion from different geographic regions in MALACHITE I.

Ongoing trials

The CS lists the following ongoing trials (CS Section 1.6 p. 30):

- MALACHITE-I (M13-774) and MALACHITE-II (M13-862): RCTs evaluating 3D + RBV versus telaprevir + PegIFN+RBV in treatment naive (MALACHITE I) and treatment experienced (MALACHITE II) HCV GT1 patients. Final data collection for the SVR12 primary outcome measure was expected December 2014.
- TURQUOISE I (M14-004): RCT evaluating 3D + RBV 12 weeks versus 24 weeks in HCV GT1 patients co-infected with HIV-1. Treatment naive and treatment experienced patients, and both cirrhotic and non-cirrhotic patients are eligible. Due to complete May 2016. The randomised comparison is not relevant to the decision problem.
- CORAL I (M12-999): cohort study evaluating 3D with and without RBV in HCV GT1 patients -after liver transplant. Due to complete February 2016.
- TURQUOISE-CPB (M14-277): RCT evaluating 3D + RBV in HCV GT1 patients with decompensated cirrhosis. Final data collection for primary outcome measure (not specified) expected July 2015.
- TURQUOISE-III (M14-490): single arm study of 3D in HCV GT1b patients with cirrhosis. Final data collection for primary outcome measure (not specified) expected May 2015.

The CS states that 17 studies are currently ongoing but as not all were expected to complete within 12 months of the STA only the five trials listed above were summarised in the CS.

Additional searching undertaken by the ERG identified two ongoing relevant studies of 3D and 2D that are due to complete within the next 12 months which were not mentioned in the CS [RUBY-I, (NCT02207088) and NCT02194998]. However, neither of these studies compared 3D or 2D against the comparators listed in the decision problem and scope, and as such are not directly relevant to the appraisal. One was a single arm trial of 3D in people with renal impairment (RUBY-I), and the other compared different 3D regimes in people with HIV/HCV co-infection who are taking antiretroviral therapy (NCT02194998).

Interim results were presented for TURQUOISE I and CORAL I in CS sections 6.5.1.9 and 6.5.1.10 (CS p. 179-182). References were not provided by the company and only limited details of the methodology were provided. In addition, in their response to the clarification letter from NICE and the ERG, the company provided baseline characteristics and interim data from the two ongoing MALACHITE studies (clarification point A9).

TURQOISE I: Estimated enrolment for the study is 300. Interim analysis is presented for 63 patients. Overall patients had a median age of 51 years; 24% were Black; 81% had IL28B non-CC genotype; 19% had compensated cirrhosis; 67% were treatment-naïve; and 89% had GT1a infection.

CORAL I: Estimated enrolment for the study is 70. Interim analysis is available for Cohort 1, comprising of 34 patients from the US and Spain. Cohort 1 patients had fibrosis score ≤ F2 (Metavir), and were treatment-naïve after transplantation but may have received previous HCV treatment (PegIFN or IFN with or without RBV) prior to liver transplantation. Patients received 24 weeks of 3D+RBV. Dose of RBV was at the discretion of the investigator, mostly ranging 600-800 mg/day. 79.4% were men, 85.3% were white, 85.3% had HCV GT 1a infection, and 76.5% had IL28B non-CC genotype. The mean time since liver transplantation was approximately 4 years. The CS does not report average age. Immunosuppression medication at baseline is reported.

3.1.4 Description and critique of the approach to validity assessment

Critical appraisal is provided for all the included phase 3 RCTs and one phase 2 RCT (PEARL I[16]) (CS Table 37 p. 151 and CS Appendix 10.3). The detailed quality assessment for PEARL I[16] was missing from Appendix 10.3 and was supplied by the company on request by NICE and the ERG (clarification point A7). Quality assessment is not provided for the two phase 2 trials that do not contribute data to the economic model (AVIATOR[26] and M14-103[27]). The quality assessment is presented in tabular format without comment or discussion by the company.

The company used the quality assessment criteria suggested in the NICE STA company's submission template, however it is not appropriate to apply these criteria where no randomised comparison with placebo or an appropriate comparator treatment is available for the outcome(s) of interest. Of the seven RCTs that the company quality assessed, randomised comparisons of intervention versus placebo were only available from the SAPPHIRE I[23] and SAPPHIRE II[24] trials for the outcomes of adverse events and HRQoL. The ERG has checked the company's assessment of quality for these two trials (Table 7).

It was not appropriate to quality assess the SVR12 outcomes from SAPPHIRE I[23] and SAPPHIRE II[24] using the NICE quality assessment criteria because the validity of the of the trial SVR12 results needs to be judged in relation to how they are used subsequently in the economic model. For example, the company's response to the question "Were the groups similar at the outset of the study in terms of prognostic factors" the assessment of within trial treatment and placebo groups is not relevant, because for the SVR12 outcome it is the validity of the comparison between the SVR12 trial outcome and the historical SVR12 data from the telaprevir trials contributing to the economic model that is important.

For the remaining five RCTs that the company quality assessed, the use of the NICE criteria for quality assessment of RCTs was not appropriate because the randomised comparison groups addressed different treatment lengths (TURQUOISE II[17]) or presence or absence of RBV in the treatment regimen (PEARL I,[16] PEARL II,[21] PEARL III[25] and PEARL IV[25]). Therefore for the outcome data from these studies that is of particular interest (SVR12, adverse events, HRQoL), there is no randomised comparison with placebo or an appropriate comparator treatment. The presented data come from a single trial arm.

No quality assessment is presented in the CS for the telaprevir trials (ADVANCE,[28] ILLUMINATE[29] and REALIZE[30]) that provide the data for historical SVR rates or for trials of other comparators used in the economic model (boceprevir, sofosbuvir, simeprevir).

Table 7 Company and ERG assessment of trial quality

		SAPPHIRE I[23]	SAPPHIRE II[24]
1. Was randomisation carried out appropriately?	CS:	Yes	Yes
	ERG:	Yes	Yes
Comment: SAPPHIRE I - Randomisation was stratified according to HCV genotype (1a vs. non-1a) and IL28B (CC vs non-CC). SAPPHIRE II - Randomisation was stratified according to HCV genotype (1a vs non-1a) and previous treatment response to pegIFN+RBV (null responder, partial responder, or relapser).			
2. Was concealment of treatment allocation adequate?	CS:	Yes	Yes
	ERG:	Yes	Yes
Comment: SAPPHIRE I and SAPPHIRE II- The company's comment for this question refers to blinding rather than concealment of allocation, however the ERG judges the latter to be adequate.			
3. Were groups similar at outset in terms of prognostic factors?	CS:	Yes	Yes
	ERG:	Yes, for AE and HRQoL outcomes Unclear for SVR12 (no randomised comparison)	Yes, for AE and HRQoL outcomes [except for mean age which was lower in the intervention group (51.7 years vs 54.9 years) but the impact of the age difference on prognosis is not discussed]. Unclear for SVR12 (no randomised comparison)
Comment: SAPPHIRE I had a higher proportion of men in the 3D+RBV group, but groups were similar for key prognostic factors. For both SAPPHIRE I and SAPPHIRE II only patients with GT1a genotype have been treated in line with the draft SmPC treatment recommendations. Although baseline characteristics are not presented for GT1a participants in each group it is likely that that the groups would have been similar because, as noted above, randomisation was stratified according to HCV genotype in both trials. For the SVR12 outcome data the appropriate comparison for SAPPHIRE I is with the baseline characteristics of the populations included in the telaprevir trials ADVANCE and ILLUMINATE from which the historical SVR12 rates were obtained. For SAPPHIRE II the appropriate comparison is the telaprevir trial REALIZE from which the historical SVR12 rates for comparison were obtained. Baseline characteristics for the participants from these three telaprevir trials were not provided in the study publications or the CS. However, in response to a request from NICE and the ERG, the company provided baseline characteristics for the telaprevir studies ADVANCE and REALIZE, but not ILLUMINATE (clarification point A9).			
4. Were care providers, participants and outcome assessors blind to treatment allocation?	CS:	Yes	Yes
	ERG:	Yes	Yes
Comment:			
5. Were there any unexpected imbalances in drop-outs between groups?	CS:	No	No
	ERG:	No	No
Comment: Although in both trials there were more discontinuations in the intervention groups than the placebo groups (SAPPHIRE I 1.9% vs 0.6%; SAPPHIRE II 1.7% vs 1.0%) these were low and appear unlikely to have been due to treatment assignment. Discontinuations due to adverse events between groups in SAPPHIRE I were the same (0.6% both arms) and low in SAPPHIRE II (1% intervention vs 0%			

		SAPPHIRE I[23]	SAPPHIRE II[24]
placebo).			
6. Is there any evidence that authors measured more outcomes than reported?	CS:	No	No
	ERG:	No	No
Comment:			
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	CS:	Yes	Yes
	ERG:	Yes, although modified ITT (all patients who underwent randomisation and received at least one dose of the study drug during the double-blind period)	Yes, modified ITT (all patients who underwent randomisation and received at least one dose of the study drug during the double-blind period).
Comment: In SAPPHIRE I only four participants (0.8%) in the intervention arm and one participant (0.6%) in the placebo arm did not receive study drug. In SAPPHIRE II zero participants in the intervention arm and one participant (1%) in the placebo arm did not receive study drug.			

The company assessment of trial quality is presented in CS Table 37 p. 151 and CS Appendix 10.3

3.1.5 Description and critique of company's outcome selection

The outcomes selected by the company in their decision problem (CS p. 54), (SVR12, development of resistance to 3D or 2D therapy, mortality, adverse effects, HRQoL) are appropriate and match the NICE scope/decision problem. However, whilst amino acid variants that are known to confer resistance to one of the three direct-acting antiviral agents were reported for patients who experienced post-treatment relapse, the CS does not state whether all participants were tested for these at baseline. Furthermore the CS does not state how any new resistance conferring mutations emerging during therapy would be identified.

The primary outcome in each of the seven phase 3 trials was SVR12. Secondary outcome measures of the seven phase III trials included:

- normalisation of the alanine aminotransferase level (SAPPHIRE I,[23] II[24]);
- proportion with haemoglobin below the lower limit of normal (PEARL II,[21] III[25] IV[25]);
- virologic failure during treatment (SAPPHIRE I,[23] II,[24] TURQUOISE II,[17] PEARL II,[21] III,[25] IV,[25] PEARL I[16]);
- post-treatment relapse (SAPPHIRE I,[23] II,[24] TURQUOISE II,[17] PEARL II,[21] III,[25] IV,[25] PEARL I[16]);
- SRV24 (PEARL I[16]).

Virologic failure was defined as two consecutive HCV RNA measurements of more than 1 log10 IU per millilitre above the nadir at any time during treatment, an HCV RNA level of 25 IU per millilitre or more at all assessments during treatment among patients who received at least 6 weeks of treatment, or a confirmed HCV RNA level of 25 IU per millilitre or more after a level of less than 25 IU per millilitre during treatment. Virologic relapse was defined as a confirmed HCV RNA level of 25 IU per millilitre or more between the end of treatment and 12 weeks after the last dose of study drug among patients who completed treatment and had an HCV RNA level of less than 25 IU per millilitre at the final visit during the treatment period. No definition of virologic failure or relapse is provided for the PEARL I study.[16]

The following 'exploratory' outcome measures were also reported:

- HRQoL: EQ-5D-5L, SF-36 (SAPPHIRE I,[23] II,[24] TURQUOISE II,[17] PEARL II,[21] III,[25] IV[25]). EQ-5D-5L, HCV-PRO (PEARL I[16]);
- Treatment compliance (SAPPHIRE I,[23] II,[24] TURQUOISE II,[17] PEARL I,[16] II,[21] III,[25] IV[25]).

The primary outcomes of the two phase 2 studies (AVIATOR[26] and M14-103[27]) were SVR24 and SVR12, respectively. Note, however, that the ERG considers the AVIATOR study[26] not to meet the NICE scope. Secondary outcomes of M14-103[27] were virologic failure and relapse.

Adverse events were reported for all nine trials. Mortality occurring during the trials was reported in the adverse event section.

HRQoL was assessed using the generic EQ-5D (visual analogue scale and health index score) and the SF-36 mental component score and physical component score.

The CS states that EQ-5D-5L health index scores were derived using where possible country specific algorithms to cross-walk the 5L values to the 3L tariff scores, as country specific tariffs for the EQ-5D-5L are currently in development. Where an individual country does not have a crosswalk, the US crosswalk to convert the 5L values to 3L was used. Therefore, the mean health index values for the EQ-5D-5L presented in CS Table 39, Table 41, Table 44, Table 46, Table 48, Table 50, and Table 57 were calculated using a number of different countries algorithms, which make the data difficult to interpret. For the economic modelling, the UK cross-walk was applied to the entire data set to ensure consistency in the methodology of obtaining utility values, and thus any differences can be attributed to an actual change in HRQoL rather than sampling of country-specific tariff differences. The ERG considers this approach to be appropriate.

The studies also collected data from a newly developed patient reported outcome tool specifically for HCV, the Hepatitis C Virus Patient Reported Outcomes Instrument (HCV-PRO).[31] The 16 item questionnaire focuses on aspects of physical health, emotional health, productivity, social interactions, intimacy and perception. The CS reports that the validity, responsiveness and identification of the minimally important difference in score have been tested in trials.

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

The CS reports the proportion of patients with SVR12 and 95% CIs. All phase 3 trials except PEARL I[16] (GT4) planned a historical comparison with telaprevir. The CS states that sample sizes were calculated to demonstrate noninferiority and superiority using specified margins, however details of the power calculations were not provided. Note that in some trials the power

calculations are based on the overall number in the active arm (for example 450 in SAPPHIRE I,[23] 300 in SAPPHIRE II[24]), however the licensed indication is for a subgroup. The subgroups are therefore unlikely to be powered for inferiority/superiority. See Table 8 below for summary of assumptions used in power calculations and data for historical comparisons.

Non-inferiority: the studies (apart from PEARL III[25] and PEARL IV,[25] see below) have greater than 90% power to demonstrate non-inferiority with a (2-sided) 95% CI lower limit for 3D or 2D greater than the 95% CI upper limit of telaprevir minus 10.5 percentage points. The non-inferiority margin of 10.5% is based on the ILLUMINATE telaprevir study, which used the same non-inferiority margin.[24] The clinical experts consulted by the ERG agreed that this margin is appropriate.

Superiority: the studies have a greater than 90% power to demonstrate superiority with a 95% CI lower limit for 3D or 2D greater than the 95% CI upper limit of telaprevir. Power to demonstrate superiority was not reported for PEARL II.[21]

For PEARL III,[25] the CS states that the sample has 95% power for non-inferiority to historical telaprevir for each regimen (CS Table 36, p. 138), but gives the upper 95% CI limit value of 84% instead of 73% (based on 10.5% non-inferiority margin as stated in CS Table 28). For PEARL IV,[25] the CS also states that the sample has 95% power for non-inferiority to historical telaprevir, but gives the upper 95% CI limit value of 75% instead of 65% (based on 10.5% non-inferiority margin as stated in CS Table 26).

NICE and the ERG asked the company to provide details about the dosing regimens used in the historical comparison telaprevir studies (clarification point A10). The company stated that the dosing was that used in the phase 3 telaprevir trials. The ERG agrees that the trials arms that provided data for the historical comparisons in the CS from the ADVANCE[28] and ILLUMINATE[29] trials used the licensed telaprevir treatment regimen.[32] However, it is unclear from the CS and the company's response to NICE and the ERG's clarification questions whether the estimated historical comparison SVR rates for treatment experienced participants with cirrhosis from the REALIZE trial[30] were based solely on the licensed telaprevir treatment regimen or whether they included data from the unlicensed 'lead-in T12PR48' regimen (i.e. four weeks of PegIFN + RBV followed by telaprevir for 12 weeks and PegIFN + RBV for 48 weeks in total). Therefore, it is unclear whether the estimated historical comparison SVR rates for treatment experienced

participants with cirrhosis in the TURQUOISE II study were based on the licensed telaprevir treatment regimen.

The CS states no adjustment for dropout was applicable because patients without data at post treatment week 12 (after imputing) were counted as failures for SVR.

Analyses were performed on the ITT (TURQUOISE II[17]) or modified ITT (SAPPHIRE I,[23] II,[24] PEARL II,[21] III,[25] IV[25]) population. The ERG notes that ITT analysis does not have a conservative effect in non-inferiority trials, and that ideally both ITT and per-protocol analysis should be reported to see if these confirm one another. Details of analysis in the telaprevir trials were not reported.

There was no historical comparison reported for the phase 2 AVIATOR[26] and M14-103[27] trials.

Interim results from TURQUOISE 1 (GT 1/HIV co-infected patients), CORAL I (GT1 post-transplant patients) are reported and clearly labelled as such.

Table 8 Summary of statistical analysis plan

Trial	GT	Tx	Planned sample size	% assumed to achieve SVR12 in power calculation	TPV 95%[a] CI upper limit minus 10.5 (noninferiority)	TPV 95%[a] CI upper limit (superiority)	Source of telaprevir data, SVR (95% CI)
SAPPHIRE I[23]	1	N	450 in active arm	92	70 for GT1	80 for GT1 75 for GT1a 84 for GT1b	MA of ILLUMINATE & ADVANCE non-cirrhotic patients G1: 78 (75,80) G1a: 72 (68,75) G1b: 80 (75,84)
SAPPHIRE II[24]	1	Ex	300 in active arm	85	60 for GT1	70 for GT1 65 for GT1a 77 for GT1b	REALIZE[b] G1: 65 (60, 70) G1a: 59 (53,65) G1b: 71 (64,77)
TURQUOISE II[17] (*cirrhotic*)	1	B	380 overall randomised in 1:1 ratio i.e. 190 each group (12 or 24 wk)	68	43	54	MA of cirrhotic patients ILLUMINATE & ADVANCE for TxN, REALIZE for TxEx, and a weighted average of corresponding SVR rates for TxN and TxEx.[c] Population based weighted average: 47 (41, 54)
PEARL II[21]	1b	Ex	210 overall randomised in 1:1 ratio i.e. 105 each group (+ or - RBV)	82	64	75	REALIZE[d] 69 (62,75)
PEARL III[25]	1b	N	+RBV = 200 -RBV = 200	92	73	84	MA of ILLUMINATE & ADVANCE non-cirrhotic patients 80 (75, 84)
PEARL IV[25]	1a	N	+RBV = 100 -RBV = 200	90 85	65	75	MA of ILLUMINATE & ADVANCE 72 (68, 75)

Information drawn from CS Tables 26-32 p. 68-118 and CS Table 36 p. 134-141
Tx = Treatment, N = naive, Ex = experienced, B = Both, MA = meta-analysis, TPV = telepravir
[a]For TURQUISE II, 97.5 CIs were used (based on the normal approximation of a single binomial proportion in a one-sample test for superiority using EAST 5.4).
[b] The rates were based on a weighted average of relapsers, partial responders, and null-responders, with the weighting reflecting the distribution of patients expected to enroll in SAPPHIRE II (30:35:35) but the actual distribution of patients differed in the trial (approximately 29:22:49). Also with adjustment factors to account for the exclusion of patients with cirrhosis from SAPPHIRE II.
[c] calculated to reflect the population expected to enrol (expected 53% TxN, 12% relapsers,12% partial responders, 23% null responders; actual enrolment 42%, 14%, 8%, 36%)
[d] with an adjustment factor to account for exclusion of non-cirrhotic patients from PEARL II. Projected enrolment in PEARL II was 30% for each of relapsers/partial responders/null responders; actual enrolment was 37%, 28%, 35%, respectively)

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

A narrative review of the evidence is presented in the CS. Where possible, the ERG has checked key data presented in the CS against those in the publications and CSRs provided by the company. HRQoL data and most treatment compliance data are not reported in the published papers. There is no published paper yet for study M14-103 and so data for this study is drawn from the CSR.[27]

The CS notes that the tabulated data presented in CS Table 38 (SAPPHIRE I[23]), Table 42 (TURQUOISE II[17]) , Table 45 (PEARL II[21]), Table 47 (PEARL III[25]) differ slightly from the SVR rates reported in the primary publication and the CSR. This was due to SVR status not being recorded for one patient in each study (2 patients in PEARL III[25]) prior to data lockdown; these data were subsequently collected and contribute to the CS tables listed above (but are not included in all results).

As there is only one trial of the 2D regimen in patients with HCV GT4 no meta-analysis was required for this intervention.

There is more than one trial evaluating the 3D regimen in HCV GT1 and three meta-analyses with different groupings of trials were conducted. As already noted none of the included trials had an appropriate comparator arm, therefore standard meta-analysis to calculate relative or absolute risk reduction was not possible. Instead a software package was used that allows a pooled estimate of efficacy to be generated from single arm studies. The SVR12 rate is the only outcome meta-analysed. The three meta-analyses presented in the CS are as follows:

1) CS Figure 17, p. 189 included single trial arms from all the completed phase III trials of 3D in participants with HCV GT1 and one phase II study (with another phase II dose finding study (AVIATOR[26]) excluded).
2) CS Figure 18, p. 190 restricted the included data to those study arms that were in line with the licence of 3D in HCV GT1.
3) CS Figure 19, p. 192 included single arms from all the completed trials (including the dose finding study) and interim data from two ongoing trials.

As noted above three meta-analyses were conducted with different groupings of trials. For this appraisal, the most appropriate meta-analysis combines the data from study arms that are in line with the licence for 3D in HCV GT1 (CS Figure 18). Although clinical

heterogeneity between the populations enrolled in the trials is noted (e.g. treatment naive, treatment experienced, GT1a, GT1b, cirrhosis status) statistical measures of heterogeneity are not commented on. The I^2 statistic, which is a measure of the degree of inconsistency in the studies' results, is reported in the tables under each of the meta-analysis forest plots (in the column headed I^2, CS Figure 17, Figure 18 and Figure 19). The I^2 value is lowest for the meta-analysis of study arms that are in line with the licence of 3D in HCV GT1 (I^2 = 0.182) and is higher for the other two meta-analyses suggesting that there is more inconsistency between these trial groupings [single trial arms from all the completed phase III trials of 3D in participants with HCV GT1 and one phase II study (with another phase II dose finding study excluded) I^2 = 0.411; single arms from all the completed trials (including the dose finding study) and interim data from two ongoing trials I^2 = 0.362].

Results from a random effects model are presented for the meta-analysis of single trial arms from all the completed phase III trials of 3D in participants with HCV GT1 and one phase II study (with another phase II dose finding study excluded) (CS Figure 17). The random effects model was considered to be a better fit given the heterogeneity in the included trials. The results from a fixed effect model were stated as producing a similar estimate but with tighter confidence intervals but data were not presented. NICE and the ERG requested the results from the fixed effects model, however the company indicated that problems with software used for the meta-analysis meant they had been unable to rerun the fixed effects analysis (clarification point A13). For the other two meta-analyses the CS does not state whether a fixed or random effects model was used but the ERG assumes that the results presented in CS Figure 18 and CS Figure 19 are from random effects models. There are some minor differences in 95% CIs for the SVR12 rates for each study presented in CS Section 6.5.1 (CS Tables 38, 40, 42, 45, 47, 49) and those presented from the meta-analysis (CS figures 17, 18 and 19) which are may be a consequence of the different software packages used to generate these sets of data.

No relative or absolute differences between intervention and comparator treatment can be reported because, as noted above the trials did not have appropriate comparator arms to enable this. Instead the single arm meta-analysis presented a pooled efficacy estimate with 95% confidence intervals. The impact of excluding the dose finding study (AVIATOR[26]) and the two ongoing studies [TURQUOISE I and CORAL I (no references provided in CS)] was investigated by the third meta-analysis listed above which included these studies in the overall pooled efficacy estimate.

As described in section 3.1.6, the company also conducted unadjusted indirect comparisons with historical SVR rates from published telaprevir studies. Data from these unadjusted indirect comparisons have been used in the economic model for the 3D and telaprevir regimes ("unadjusted" essentially means that data from individual trial arms of studies for the relevant populations have been used).

The company investigated the feasibility of conducting a network meta-analysis (NMA) to generate efficacy estimates for the 3D and 2D treatment regimens in comparison to "the comparators outlined in the decision problem" (CS p. 193). Two mixed treatment comparison (MTC) methodologies were considered but neither could be used. The preferred NICE approach,[33] which is the treatment-effect model, requires the included studies to have a comparator arm, but none of the company's trials have an appropriate comparator arm. The treatment response model which offers an alternative approach was also not a possible solution because it was not possible to perform a covariate adjustment to account for the uneven distribution of factors across the network that influence the outcome of interest. The company concluded it was not possible to conduct a robust NMA.

The company did not present any potential network diagrams and did not provide any details of the specific sources of evidence that were considered for inclusion in an NMA. Nevertheless the ERG agrees that limitations in the available data, particularly the absence of a suitable comparator arm from the company's trials, means that a robust NMA of 3D and 2D regimes for all the relevant patient populations would not have been possible. However, the ERG notes that the company has since made available to NICE and the ERG the results from the MALACHITE studies (which directly compare 3D with telaprevir regimens) (clarification point A9.2), and it would be possible to conduct an NMA for the population included in these studies. In terms of populating the economic model, the ERG considers that the company could have done an NMA for the comparators, even if an NMA for the 3D and 2D regimes was not possible (this is discussed further in Section 4.2.4 of this report). In the response to clarification questions (A12) the company indicated that conducting an NMA for comparators where complete networks existed was considered. The company point out that had they done this they would not have been able to connect the 2D or 3D treatment regimens to this and therefore would not have been able to obtain estimates of the relative treatment effectiveness of 2D or 3D in comparison to the comparator treatment regimens.

3.2 Summary statement of company's approach

The ERG's quality assessment of the CS is summarised in Table 9. The processes for inclusion/exclusion screening, data extraction and quality assessment were not described. NICE and the ERG requested clarification on the processes, however the description provided in the company's clarification (A8) was not transparent and did not appear to follow standard accepted systematic review methodology.

The submitted evidence generally reflects the decision problem. However, in the absence of any head-to-head trials with any of the comparators listed in the scope, the trials were designed and powered to detect efficacy non-inferiority and superiority in comparison to historical telaprevir SVR rates in similar populations. No comparisons with other relevant comparators (e.g. boceprevir) are presented.

The chance of systematic error in the systematic review is uncertain due to the lack of transparency in the processes undertaken.

Table 9 Quality assessment (CRD criteria) of CS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes - eligibility criteria are reported (CS Table 23 p. 57). However a list of studies with reason for exclusion was not provided.
2. Is there evidence of a substantial effort to search for all relevant research? Ie all studies identified	Uncertain - although two search strategies for clinical effectiveness evidence are documented in CS Appendix 10.2, no search to identify evidence for relevant comparators is reported although one should have been undertaken to inform the NMA (CS section 6.7 on p. 193 suggests an NMA was undertaken but the results were not considered robust and were therefore not reported). The method that was used to identify the telaprevir trials which provide the historical SVR rates is not reported in the CS. In their response to clarification question A1 the company stated that no systematic review was undertaken; the telaprevir SVR rates were those agreed with the US Food and Drug Administration (FDA) and CHMP for use in showing non-inferiority and superiority. The company also had access to CSRs.
3. Is the validity of included studies adequately assessed?	No - the assessment of the validity of the included studies did not take into account that for SVR outcomes from the SAPPHIRE I[23] and II[24] trials, and for all the outcomes from the TURQUOISE II[17] and four separate PEARL studies,[16;21;25] there was no comparison with placebo or an appropriate comparator. In effect these outcomes come from single trial arms. No assessment of the validity of the telaprevir trials (ADVANCE,[28] ILLUMINATE[29] and REALIZE[30]) that provided the data for historical SVR rates is presented.
4. Is sufficient detail of the individual studies presented?	4. Yes - individual study information for RCT summary characteristics (CS Tables 24-25, p. 61-63; CS Table 25 p. 63) with further detail on trial methodology (CS Tables 26-31, p. 69-93), eligibility criteria (CS Table 32, p. 95-118), participant characteristics (CS Tables 33 & 34, p. 119-123), trial outcome measures & statistical analyses (CS Tables 35 & 36, p. 126-132, p. 134-141), trial flow diagrams (CS Figures 5-11, p. 143-149). However, details of the telaprevir studies used for the historical comparison were not reported in the CS. Following a request by NICE and the ERG baseline characteristics for participants included in these studies were provided (clarification point A9).
5. Are the primary studies summarised appropriately?	Results are summarised and presented in narrative form with accompanying charts and tables. Where detail is lacking in the CS (e.g. CS Figure 12 p. 154 where 95% CIs for the historical telaprevir control SVR rates are only presented graphically) detail is available within published papers (including supplementary material). Conventional meta-analysis of the HCV GT1 studies to calculate relative or absolute risk reduction was not possible because none of the included trials had an appropriate comparator arm. Instead pooled efficacy estimates (with

	95% confidence intervals) using a random effects model were generated for SVR12 from single trial arms for 3 groups of trials. The grouping of study arms in line with the licence for 3D in HCV GT1 was the most appropriate for the STA assessment. The company also conducted an unadjusted indirect comparison with SVR rates from published telaprevir studies but concluded it was not possible to conduct a robust NMA.

3.3 Summary of submitted evidence

Results are presented for four groups of patients with HCV genotype-1:

- treatment naive, non-cirrhotic (SAPPHIRE I,[23] PEARL IV,[25] PEARL III[25])
- treatment experienced, non-cirrhotic (SAPPHIRE II,[24] PEARL II[21])
- treatment naive & treatment experienced, compensated cirrhosis (TURQUOISE II[17])
- treatment naive & treatment experienced, non-cirrhotic on stable opioid replacement therapy (M14-103 single arm study[27])

Results are then presented from the single study in patients with HCV genotype-4 (PEARL I[16]).

For SVR12 the results are presented for the trials arms or subgroups where treatment meets the licensed indication (as summarised in Table 6), with outcomes from trial arms outside the licensed indication presented in the Appendices. For other outcomes, data from the trial arms (or subgroup of participants in the trial arm) that meet the licensed indication are clearly indicated in bold font. The results from the trial arms or subgroups where the treatment meets the licensed indication are the most relevant to this appraisal, as NICE's scope states that guidance can only be issued in line with the marketing authorisation. We have presented the data from trial arms outside of the licence because results in the CS are not always presented by the relevant licensed subgroup (e.g. in some cases data for patients with HCV GT1a or GT1b are not separated out in studies including both GT1 subgroups). The ERG considers the data from the trial arms outside of the licence to be supporting data. Not all outcomes are reported by each trial.

Data have been reproduced from the CS, supplemented with data from trial journal publications where necessary.

3.3.1 Patients with HCV genotype 1

Summary of SVR12 results

Trial arms or subgroups where treatment is within the licensed indication

Treatment naive, non-cirrhotic patients (SAPPHIRE I,[23] PEARL IV,[25] PEARL III[25])
Evidence is available from two trials for HCV GT1a (SAPPHIRE I[23] subgroup and PEARL IV[25]) and for one trial for HCV GT1b (PEARL III[25]). Participants from the SAPPHIRE I[23] and PEARL IV[25] trials with HCV GT1a treated with 3D + RBV for 12 weeks had SVR12 rates that were similar and high (95.7% and 97% respectively) (Table 10). The lower 95% CIs for the SVR12 rates from these trials (93.4% and 93.7% respectively) exceed the upper 95% CI for the historical telaprevir comparator (75%) and hence the 3D+RBV 12 week regimen is considered superior to telaprevir for treatment of naive non-cirrhotic patients with HCV GT1a.

All participants with HCV GT1b treated with 3D for 12 weeks in the PEARL III trial[25] achieved SVR12. The 3D 12 week regimen is considered superior to telaprevir for the treatment of naive non-cirrhotic patients with HCV GT1b because the lower 95% CI for SVR12 from the PEARL III[25] (98.2%) exceeds the upper 95% CI for the historical telaprevir comparator (84%).

Treatment experienced, non-cirrhotic patients (SAPPHIRE II,[24] PEARL II[21])
Evidence is available from one trial for HCV GT1a (SAPPHIRE II[24] subgroup) and one for HCV GT1b (PEARL II[21]). Of the participants from the SAPPHIRE II[24] trial with HCV GT1a treated with 3D + RBV for 12 weeks 96% achieved SVR12 (Table 10). The lower 95% CI for SVR12 of 93.0% exceeds the upper 95% CI for the historical telaprevir comparator (65%) and hence the 3D+RBV 12 week regimen is considered superior to telaprevir for treatment of treatment experienced, non-cirrhotic patients with HCV GT1a. SVR12 rates are also broken down by the type of prior response to previous treatment with PEGIFN+RBV: prior null responder (95.4%), prior partial responder (100%) or prior relapser (94.0%).

All participants with HCV GT1b treated with 3D for 12 weeks in the PEARL II trial[21] achieved SVR12, regardless of their type of response to previous therapy. The 3D 12 week regimen is considered superior to telaprevir for the treatment of naive non-cirrhotic patients with HCV GT1b because the lower 95% CI for SVR12 from the PEARL II[21] (95.9%) exceeds the upper 95% CI for the historical telaprevir comparator (75%).

Treatment naive & treatment experienced, non-cirrhotic patients (M14-103 single arm study[27])

Evidence for the treatment within the licenced indication is available from a subgroup of patients with HCV GT1a from the single arm, Phase 2 study (M14-103[27]), provided in clarification point A15. The SVR12 rate for HCV GT1a participants treated with 3D + RBV for 12 weeks was [redacted]. The company did not use any data from this study in the economic model.

Treatment naive & treatment experienced, compensated cirrhosis patients (TURQUOISE II[17])

Evidence for treatment within the licensed indication is available from subgroups of one trial (TURQUOISE II[17]) with results broken down by genotype subgroup and prior treatment history (Table 10). The SVR12 rate for HCV GT1a participants treated with 3D + RBV for 24 weeks was 95.0% and for HCV GT1b participants treated with 3D+RBV for 12 weeks 98.5%. A historical comparator was not provided separately for HCV GT1a and GT1b however superiority to telaprevir is indicated in comparison to the historical telaprevir comparator for HCV GT1 overall which was 47%, with an upper CI of 54% that was exceeded by the lower 95% CIs for GT1a and GT1b groups from TURQUOISE II[17] (91.2% and 95.7% respectively). SVR12 rates are also broken down into treatment naive, and by the type prior response to previous treatment with PEGIFN+RBV (HCV GT1a: treatment naive 94.6%; prior null responder 92.9%; prior partial responder 100% or prior relapser 100%. HCV GT1b: treatment naive 100%; prior null responder 100%; prior partial responder 85.7% or prior relapser 100%).

Table 10: SVR12 outcome from trial arms or subgroups where treatment matches licensed indication

Trial & Details	Group or subgroup	n/N SVR12	% SVR12	95% CI	Telaprevir comparator % SVR12 (95% CI)
Genotype 1, treatment naive, non-cirrhotic (CS Table 38 p. 153, Table 49 p. 173, Table 47 p. 170)					
SAPPHIRE I[23] GT1 3D+RBV vs placebo 12wk	GT1a 3D+RBV 12wk	308/322	95.7	93.4 to 97.9	72 (68 to 75)
PEARL IV[25] GT1a 3D+RBV vs 3D 12wk	GT1a 3D+RBV 12wk	97/100	97.0	93.7 to 100.0	72 (68 to 75)
PEARL III[25] GT1b 3D+RBV vs 3D	GT1b 3D 12w	209/209	100.0	98.2 to 100.0	80 (75 to 84)
Genotype 1, treatment experienced, non-cirrhotic (CS Table 40 p. 158, Table 45 p. 168)					
SAPPHIRE II[24] GT1 3D+RBV vs placebo 12wk	GT1a 3D+RBV 12wk	166/173	96.0	93.0 to 98.9	59 (53 to 65)
	Prior null responder	83/87	95.4	91.0 to 99.8	
	Prior partial responder	36/36	100	100.0 to 100.0	
	Prior relapser	47/50	94.0	87.4 to 100.0	
PEARL II[21] GT1b 3D+RBV vs 3D	Overall (GT1b) 3D 12wk	91/91	100	95.9 to 100.0	69 (62 to 75)
	Prior null responder	32/32	100	89.3 to 100.0	
	Prior partial responder	26/26	100	87.1 to 100.0	
	Prior relapser	33/33	100	89.6 to 100.0	
Genotype 1, treatment naive & treatment experienced, non-cirrhotic					
M14-103 GT1 3D+RBV 12 wks	GT1a 3D+RBV 12wk	[redacted]	[redacted][b]	not reported	
Genotype 1, treatment naive & treatment experienced, compensated cirrhosis (CS Table 42 p. 163)					
TURQUOISE II[17] GT1 3D+RBV 12 wks vs 24 wks	GT1a 3D+RBV 24wk	115/121	95.0	91.2 to 98.9	
	Tx Naive	53/56	94.6		
	Prior null responder	39/42	92.9		
	Prior partial responder	10/10	100		
	Prior relapser	13/13	100		
	GT1b 3D+RBV 12wk	67/68	98.5	95.7 to 100.0	not reported[a]
	Tx Naive	22/22	100		
	Prior null responder	25/25	100		
	Prior partial responder	6/7	85.7		
	Prior relapser	14/14	100		

[a] SVR12 for the telaprevir comparator was calculated as a population based weighted average for the whole TURQUOISE II study (Telaprevir SVR12 47%, 95% CI 41 to 54). A historical comparator value was not available for HCV GT1a and HCV GT1b separately.

[b] The company provided the ERG with the results of this subgroup analysis of SVR12 for participants with HCV GT1a in response to NICE and the ERG's request for this (clarification point A15).

Meta-analysis of SVR12 from trial arms in line with the licensed indication for all participants for 3D in HCV GT1

The 1084 participants represented by the trial arms presented in Table 10 were included in a single arm meta-analysis. This yielded an overall pooled estimate for SVR12 from a random effects model of 96.5% (95% CI 94.6 to 97.7). The ERG obtained similar results using an alternative software package (random effects model 96.5% 95% CI 94.6 to 97.7, fixed effect model 96.2% 95% CI 94.7 to 97.3). The company did not use the meta-analysis findings in the economic model and the ERG considers the meta-analysis only provides illustrative information about the average efficacy of 3D across a range of the licensed treatment regimens in patients with HCV GT1.

Trial arms where treatment is outside the licensed indication for either some or all of the participants with HCV GT1

A summary of SVR data from trial arms or subgroups where treatment does not meet the licensed indication is presented in Appendix 9.1

Summary of virologic relapse and failure results

Virologic relapse and failure results are presented in Table 11, with data from trial arms or subgroups meeting the licensed indication in bold font. Where the treatment received was within the licensed indication (3 trial arms), on-treatment failure was absent or low (ranging from 0 to 1%) and relapse following treatment was also absent or low (ranging from 0 to 1%). Other reasons for failure included participants who did not achieve SVR12 (e.g. due to missing HCV RNA values during the SVR12 window) but who did not meet the criteria for on-treatment failure or relapse after treatment. Rates for 'other' reasons were similarly absent or low (0% to 1%) where the treatment received was within the licensed indication.

Table 11 Virologic relapse and failure results

Study details	Trial arms	On-treatment virological failure n/N (%)	Relapse n/N (%)	Other n/N (%)
Genotype 1, treatment naive, non-cirrhotic (CS Table 38 p. 153, Table 49 p. 173, Table 47 p. 170)				
SAPPHIRE I[23] (GT1a and b)	3D+RBV 12 wks (licensed Tx for n=322 GT1a only	1/473 (0.2)	7/463 (1.5)	9/473 (1.9)
PEARL IV[25] GT1a	**3D+RBV 12 wks (licensed Tx)**	**1/100 (1.0)**	**1/98 (1.0)**	**1/100 (1.0)**
	3D 12 wks (unlicensed Tx)	6/205 (2.9)	10/194 (5.2)	4/205 (2.0)
PEARL III[25] GT1b	3D+RBV 12 wks (unlicensed Tx)	1/210 (0.5)	0/210 (0)	0/210 (0)
	3D 12 wks (licensed Tx)	**0/209 (0)**	**0/209 (0)**	**0/209 (0)**
Genotype 1, treatment experienced, non-cirrhotic (CS Table 40 p. 158, Table 45 p. 168)				
SAPPHIRE II[24] (GT1a and b)	3D+RBV 12 wks (licensed Tx for n=173 GT1a only)	0/297 (0)	7/293 (2.4)	4/297 (1.3)
PEARL II[21] GT1b	3D+RBV 12 wks (unlicensed Tx)	0/88 (0)	0/88 (0)	2/88 (2.3)
	3D 12 wks (licensed Tx)	**0/91 (0)**	**0/91 (0)**	**0/91 (0)**
Genotype 1, treatment naive & treatment experienced, non-cirrhotic on stable opioid replacement therapy (Single arm study) (CS Table 53 p. 178)				
M14-103[27]	3D+RBV 12 wks	0/38 (0)	0/38 (0)	1/38 (2.6)
Genotype 1, treatment naive & treatment experienced, compensated cirrhosis (CS Table 42 p. 163)				
TURQUOISE II[17] (GT1a and b)	3D+RBV 12 wks (licensed Tx for n=68 GT1b only)	1/208 (0.5) [95% CI 0 to 1.4]	12/203 (5.9)	4/208 (1.9)
	3D+RBV 24 wks (licensed Tx for n=121 GT1a only)	3/172 (1.7) [95% CI 0 to 3.7]	1/164 (0.6)	2/172 (1.21)

Summary of normalisation of the alanine aminotransferase level results

Two trials SAPPHIRE I[23] and SAPPHIRE II[24] reported on the normalisation of alanine aminotransferase levels (Table 12). Results are only available for the whole trial population but the treatment received was the licensed treatment only for those with HCV GT1a (68% of SAPPHIRE I[23] and 58% of SAPPHIRE II[24]). In both trials the proportion of participants whose alanine aminotransferase level normalised was statistically significantly higher ($p<0.001$) in the 3D + RBV group than in the placebo group (SAPPHIRE I[23] 97.0% vs 14.9 %; SAPPHIRE II[24] 96.9% versus 12.8%).

Table 12 Normalisation of alanine aminotransferase levels

Genotype 1, treatment naive, non-cirrhotic (CS p. 155)			
SAPPHIRE I[23] (GT1a and b)	**3D + RBV 12 wks, n=473** (licensed Tx for n=322 GT1a only)	Placebo, n=158	p-value
Normalisation of alanine aminotransferase level, % (n/N)	97.0% (352/363)	14.9% (17/114)	<0.001
Genotype 1, treatment experienced, non-cirrhotic (CS p. 159)			
SAPPHIRE II[24] (GT1a and b)	**3D + RBV 12 wks, n=297** (licensed Tx for n=173 GT1a only)	Placebo, n=97	p-value
Normalisation of alanine aminotransferase level, % (n/N)	96.9% (217/224)	12.8% (10/78)	<0.001

Summary of health-related quality of life

HRQoL was an exploratory outcome measure in those trials that reported HRQoL outcomes. Results are presented here for the SF36 physical component score (PCS) and mental component score (MCS), the EQ-5D-5L health index score (which were the only HRQoL data from the trials used in the economic model, as the basis of the on-treatment utilities; see Section 4.2.4 of this report for more details), and the HCV-PRO score. Results are also available in the CS for the EQ-5D-5L visual analogue score but this outcome has not been included here as it does not contribute to the economic model and the EQ-5D-5L health index score is available which is the preferred measure. In the CS, the company narratively reports where there are statistically significant differences in mean changes from baseline between groups on the HRQoL measures, and only provides p-values for some findings and not others (95% CIs are not reported). However, with the exception of the SAPPHIRE I[23] and II[24] trials where the comparison is against placebo the statistical comparisons in the other trials are not relevant to the scope or decision problem and these are not presented here.

SF36 physical component score

[redacted]Table 13[redacted]

Table 13: SF36 physical component score results

	N	Baseline mean	Mean change (SD)	N	Baseline mean	Mean change (SD)
Genotype 1, treatment naive, non-cirrhotic (CS Table 39 p. 157, Table 50 p. 174, Table 48 p. 172)						
SAPPHIRE I[23] (GT1a and b)	**3D + RBV for 12 weeks** (licensed Tx for n=322 GT1a only)			Placebo		
Final double-blind treatment period visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final post-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]		
PEARL IV[25] (GT1a)	**3D + RBV for 12 weeks** (licensed Tx)			3D for 12 weeks (unlicensed Tx)		
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEARL III[25] (GT1b)	3D + RBV for 12 weeks (unlicensed Tx)			**3D for 12 weeks** (licensed Tx)		
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genotype 1, treatment experienced, non-cirrhotic (CS Table 41 p. 161, Table 46 p. 169)						
SAPPHIRE II[24] (GT1a and b)	**3D + RBV for 12 weeks** (licensed Tx for n=173 GT1a only)			Placebo		
Final double-blind treatment period visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final post-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]		
PEARL II[21] (GT1b)	3D + RBV for 12 weeks (unlicensed Tx)			**3D for 12 weeks (licensed Tx)**		
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genotype 1, treatment naive & treatment experienced, compensated cirrhosis (CS Table 44 p. 167)						
TURQUOISE II[17] (GT1a and b)	**3D + RBV for 12 weeks** (licensed Tx for n=68 GT1b only)			**3D + RBV for 24 weeks** (licensed Tx for n=121 GT1a only)		
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data from trial arms or subgroups meeting the licensed indication in bold font.

SF36 mental component score

[redacted]Table 14[redacted]

EQ5D-5L health index score

Table 15

HCV-PRO total score

Table 16

Table 14: SF36 mental component score results

	N	Baseline mean	Mean change (SD)	N	Baseline mean	Mean change (SD)
Genotype 1, treatment naive, non-cirrhotic (CS Table 39 p. 157, Table 50 p. 174, Table 48 p. 172)						
SAPPHIRE I[23] (GT1a and b)	**3D + RBV 12 weeks** (licensed Tx for n=322 GT1a only)			Placebo		
Final double-blind treatment period visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final post-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]		
PEARL IV[25] (GT1a)	**3D + RBV for 12 weeks** (licensed Tx)			3D for 12 weeks (unlicensed Tx)		
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEARL III[25] (GT1b)	3D + RBV for 12 weeks (unlicensed Tx)			**3D for 12 weeks** (licensed Tx)		
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genotype 1, treatment experienced, non-cirrhotic (CS Table 41 p. 161, Table 46 p. 169)						
SAPPHIRE II[24] (GT1a and b)	**3D + RBV 12 weeks** (licensed Tx for n=173 GT1a only)			Placebo		
Final double-blind treatment period visit[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final post-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]		
PEARL II[21] (GT1b)	3D + RBV for 12 weeks (unlicensed Tx)			**3D for 12 weeks** (licensed Tx)		
Final treatment visit [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genotype 1, treatment naive & treatment experienced, compensated cirrhosis (CS Table 44 p. 167)						
TURQUOISE II[17] (GT1a and b)	**3D + RBV for 12 weeks** (licensed Tx for n=68 GT1b only)			**3D + RBV for 24 weeks** (licensed Tx for n=121 GT1a only)		
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Statistically significant difference between treatment groups at *P* = 0.05 level. Data from trial arms or subgroups meeting the licensed indication in bold font.

Table 15: EQ-5D-5L Health index score results

	N	Baseline mean	Mean change (SD)	N	Baseline mean	Mean change (SD)
Genotype 1, treatment naive, non-cirrhotic (CS Table 39 p. 157, Table 50 p. 174, Table 48 p. 172)						
SAPPHIRE I[23] (GT1a and b)	**3D + RBV 12 weeks** (licensed Tx for n=322 GT1a only)			Placebo		
Final double-blind treatment period visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final post-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]		
PEARL IV[25] (GT1a)	**3D + RBV for 12 weeks** (licensed Tx)			3D for 12 weeks (unlicensed Tx)		
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEARL III[25] (GT1b)	3D + RBV for 12 weeks (unlicensed Tx)			**3D for 12 weeks** (licensed Tx)		
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genotype 1, treatment experienced, non-cirrhotic (CS Table 41 p. 161, Table 46 p. 169)						
SAPPHIRE II[24] (GT1a and b)	**3D + RBV 12 weeks** (licensed Tx for n=173 GT1a only)			Placebo		
Final double-blind treatment period visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final post-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]		
PEARL II[21] (GT1b)	3D + RBV for 12 weeks (unlicensed Tx)			**3D for 12 weeks** (licensed Tx)		
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genotype 1, treatment naive & treatment experienced, compensated cirrhosis (CS Table 44 p. 167)						
TURQUOISE II[17] (GT1a and b)	**3D + RBV for 12 weeks** (licensed Tx for n=68 GT1b only)			**3D + RBV for 24 weeks** (licensed Tx for n=121 GT1a only)		
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data from trial arms or subgroups meeting the licensed indication in bold font.

Table 16: HCV-PRO total score results

	N	Baseline mean	Mean change (SD)	N	Baseline mean	Mean change (SD)
Genotype 1, treatment naive, non-cirrhotic (CS Table 39 p. 157, Table 50 p. 174, Table 48 p. 172)						
SAPPHIRE I[23] (GT1a and b)	**3D + RBV 12 weeks** (licensed Tx for n=322 GT1a only)			Placebo		
Final double-blind treatment period visit[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final post-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]		
PEARL IV[25] (GT1a)	**3D + RBV for 12 weeks** (licensed Tx)			3D for 12 weeks (unlicensed Tx)		
Final treatment visit [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEARL III[25] (GT1b)	3D + RBV for 12 weeks (unlicensed Tx)			**3D for 12 weeks** (licensed Tx)		
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genotype 1, treatment experienced, non-cirrhotic (CS Table 41 p. 161, Table 46 p. 169)						
SAPPHIRE II[24] (GT1a and b)	**3D + RBV for 12 weeks** (licensed Tx for n=173 GT1a only)			Placebo		
Final double-blind treatment period visit[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final post-treatment visit	[redacted]	[redacted]	[redacted]	[redacted]		
PEARL II[21] (GT1b)	3D + RBV for 12 weeks (unlicensed Tx)			**3D for 12 weeks** (licensed Tx)		
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genotype 1, treatment naive & treatment experienced, compensated cirrhosis (CS Table 44 p. 167)						
TURQUOISE II[17] (GT1a and b)	**3D + RBV for 12 weeks** (licensed Tx for n=68 GT1b only)			**3D + RBV for 24 weeks** (licensed Tx for n=121 GT1a only)		
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Statistically significant difference between treatment groups at $P = 0.05$ level.
[b] Statistically significant difference between treatment groups at $P \leq 0.05$ level.
Data from trial arms or subgroups meeting the licensed indication in bold font.

Sub-group analyses results

The 6 key trials of 3D treatment regimens in HCV GT1 patients (SAPPHIRE I,[23] SAPPHIRE II,[24] TURQUOISE II,[17] PEARL II,[21] III,[25] and IV[25]) all undertook subgroup analyses. However the amount of detailed reporting of these varies in the CS. For SAPPHIRE I,[23] and II,[24] figures showing SVR rates by patient characteristics are supplied with accompanying text (CS Figures 13, 14), for TURQUOISE II[17] the results are tabulated with accompanying text (CS Table 43) whereas for the PEARL studies (II,[21] III,[25] IV[25]) brief text describes the results of sub-group analyses and the full list of analyses undertaken for these studies is not presented in the CS however a full list of the predictors of SVR response is available in the supplementary appendix accompanying the published paper for the PEARL III and IV studies.[25]

Rates of SVR were reported as high across all subgroups.

Table 17 below shows a selection of subgroup outcomes for those characteristics which most closely align with the subgroups of interest listed in the NICE scope, excluding those already reported elsewhere (genotype, co-infection with HIV, patients with and without cirrhosis, people who have received treatment pre- and post-liver transplant, response to previous treatment, people who are intolerant to or ineligible for interferon treatment). The subgroup of people who are intolerant to or ineligible for interferon treatment has not been considered by the CS.

Table 17: Selected subgroup analyses from HCV GT1 trials

Genotype 1, treatment naive, non-cirrhotic (CS Figure 13 p. 156, CS p. 175, p. 171)		
SAPPHIRE I[23]	**n=473**	**3D+RBV for 12 weeks % with SVR12 (95% CI)**
Fibrosis score		
F0 or F1	363	97.0 (95.2 to 98.7)
F2	70	94.3 (88.9 to 99.7)
F3	40	92.5 (84.3 to 100)
IL28B genotype		
CC	144	96.5 (93.5 to 99.5)
non-CC	329	96.0 (93.9 to 98.2)
PEARL IV[25]		
CS states (p175) that only IL28B CC genotype was associated with an increased rate of SVR among patients with HCV GT1a infection (p=0.03).		
PEARL III[25]		
CS states (p. 171) that there were no significant predictors or response as SVR rates were high across all the different characteristics.		
Genotype 1, treatment experienced, non-cirrhotic (CS Figure 14 p. 160, CS p. 169)		
SAPPHIRE II[24]	**n=297**	**3D+RBV for 12 weeks % with SVR12 (95% CI)**
Fibrosis score		
F0 or F1	202	97.5 (95.4 to 99.7)
F2	53	94.3 (88.1 to 100)
F3	42	92.9 (85.1 to 100)
IL28B genotype		
CC	34	91.2 (81.6 to 100)
non-CC	263	97.0 (94.9 to 99.0)
PEARL II[21a]		**3D+RBV for 12 weeks % with SVR12 (95% CI)**
IL28B genotype	**n=88**	
CC	Not reported	100%
CT	Not reported	96.4%
TT	Not reported	95.5%
CS states (p. 169) that SVR12 rates were 100% in all subgroups of group 2 (licensed dose 3D for 12 weeks)		
Genotype 1, treatment naive & treatment experienced, compensated cirrhosis (CS Table 43 p. 165)		
TURQUOISE II[17] (GT1a and b)[a]	**n=208**	**3D+RBV for 12 weeks % with SVR12 (95% CI)**
Baseline Child-Pugh score		
5	158/170	92.9 (89.1 to 96.8)
6	33/38	86.8 (76.1 to 97.6)
>6	0	0
IL28 genotype		
CC	33/35	94.3 (86.6 to 100)
non-CC	158/173	91.3 (87.1 to 95.5)
TURQUOISE II[17] (GT1a and b)[a]	**n=172**	**3D+RBV for 24 weeks % with SVR12 (95% CI)**
Baseline Child-Pugh score	136/140	97.1 (94.4 to 99.9)
5	24/27	88.9 (77.0 to 100.0)
6	5/5	100 (n/a)
>6		
IL28 genotype		
CC	33/34	97.1 (91.4 to 100.0)
non-CC	132/138	95.7 (92.2 to 99.1)

[a] For HCV GT1b the licensed treatment is 12 weeks. For HCV GT1a the licensed treatment is 24 weeks.

3.3.2 Patients with HCV genotype 4

Summary of SVR12 results

Trial arms where treatment is within the licensed indication

Evidence is available from two trial arms of the PEARL I study[16] on patients with HCV GT4 that meet the licensed indication for 2D + RBV therapy. Treatment naive participants without cirrhosis treated with 2D + RBV for 12 weeks all achieved SVR12 and a 100% SVR12 rate was also achieved by treatment experienced participants (Table 18). In contrast to the phase III trials in HCV GT1 participants there was no planned historical comparison with telaprevir in the PEARL I study.[16]

Table 18: SVR12 outcome from trial arms where treatment matches licensed indication

Trial & Details	Group or subgroup	n/N SVR12	% SVR12	95% CI	Telaprevir comparator % SVR12 (95% CI)
Genotype 4, treatment naive & treatment experienced, non-cirrhotic (CS Table 56 p. 184)					
PEARL I[16] 2D+RBV vs 2D (TxN) 2D+RBV (TxExp)	Tx Naive 2D + RBV 12wks	42/42	100%	91.6 to 100	not reported
	Tx Experienced 2D + RBV 12wks	49/49	100%	92.7 to 100	not reported

TxExp = treatment experienced; TxN = treatment naive.

Trial arms where treatment is outside the licensed indication for participants with HCV GT4

See Appendix 9.2 for summary.

Summary of SVR24 results

Licenced treatment with 2D + RBV for treatment naive patients without cirrhosis resulted in 97.6% of participants achieving an SVR24 (Table 19).

Table 19: SVR24 outcome in participants with HCV GT4

Genotype 4, treatment naive, non-cirrhotic (CS p. 185)		
	2D for 12 weeks, n=44 (Group 1, unlicensed Tx)	**2D + RBV for 12 weeks, n=42 (Group 4, licensed Tx)**
Participants with SVR24, % (n/N; 95% CI)	86.4% (38/44; 72.6 to 94.8)	**97.6% (41/42; 87.4 to 99.9)**

Note - not reported for treatment experienced patients. Data from trial arms or subgroups meeting the licensed indication in bold font.

Summary of virologic relapse and failure results

Where the treatment received was within the licensed indication (two of the three trial arms of PEARL I[16] reported in the CS), on-treatment virological failure and relapse following treatment did not occur (Table 20). There were also no other reasons for failure.

Table 20: Virologic relapse and failure in HCV GT4 patients

Genotype 4, treatment naive & treatment experienced, non-cirrhotic (CS Table 56 p. 184)				
Study	**Trial arms**	**On-treatment virological failure n/N (%)**	**Relapse n/N (%)**	**Other n/N (%)**
PEARL I[16]	Tx Naive (Group 1) 2D 12 wks (unlicensed Tx)	1/44 (2.3)	2/44 (4.5)	1/44 (2.3)
	Tx Naive (Group 4) 2D + RBV 12 wk (licensed Tx)	**0/42 (0)**	**0/42 (0)**	**0/42 (0)**
	Tx Experienced (Group 6) 2D + RBV 12 wks (licensed Tx)	**0/49 (0)**	**0/49 (0)**	**0/49 (0)**

TxExp = treatment experienced; TxN = treatment naive. Data from trial arms or subgroups meeting the licensed indication in bold font.

Summary of health-related quality of life

HRQoL was an exploratory outcome measure in the PEARL I trial.[16] Results were presented in the CS for the EQ-5D-5L health index score, the EQ-5D-5L visual analogue score and the HCV-PRO score. Results for the EQ-5D-5L visual analogue score have not been included here as it does not contribute to the economic model and the EQ-5D-5L health index score is available which is the preferred measure. In the CS, the company narratively reports where there are statistically significant differences in mean changes from baseline between groups 1 and 4 on the HRQoL measures (no p-values or 95% CIs are provided). However, this is not relevant to the scope or decision problem and thus is not presented here.

EQ-5D-5L health index score

Data are presented in Table 21.

Table 21: EQ-5D-5L results in HCV GT4 trial participants

EQ-5D-5L Health Index score						
	N	**Baseline mean**	**Mean change from baseline(SD)**	**N**	**Baseline mean**	**Mean change from baseline (SD)**
Genotype 4, treatment naive, non-cirrhotic (CS Table 57 p. 186)						
	2D for 12 weeks (Group 1)			**2D + RBV for 12 weeks (Group 4, licensed Tx)**		
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genotype 4, treatment experienced, non-cirrhotic (CS Table 57 p. 186)						
				2D + RBV for 12 weeks (Group 6, licensed Tx)		
Final treatment visit				[redacted]	[redacted]	[redacted]

Data from trial arms or subgroups meeting the licensed indication in bold font.

HCV-PRO total score

HCV-PRO total score data are summarised in Table 22.

Table 22: HCV-PRO total score in HCV GT4 trial participants

HCV-PRO total score						
	N	**Baseline mean**	**Mean change from baseline(SD)**	**N**	**Baseline mean**	**Mean change from baseline (SD)**
Genotype 4, treatment naive, non-cirrhotic (CS Table 57 p. 186)						
	2D for 12 weeks (Group 1, unlicensed Tx)			**2D + RBV for 12 weeks (Group 4, licensed Tx)**		
Final treatment visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genotype 4, treatment experienced, non-cirrhotic (CS Table 57 p. 186)						
				2D + RBV for 12 weeks (Group 6, licensed Tx)		
Final treatment visit				[redacted]	[redacted]	[redacted]

Data from trial arms or subgroups meeting the licensed indication in bold font.

Sub-group analyses results

The CS states (CS p. 186) that as all HCV GT4-infected participants treated with 2D + RBV achieved SVR12 (100%) this did not differ across subgroups.

3.3.3 Summary of adverse events

Adverse events were tabulated in the CS for all trials, including the single arm study M14-103[27] and the dose finding study AVIATOR[26] (CS p. 201 – 215). Adverse event data from the trials, with the exception of M14-103,[27] were used in the economic model. A brief summary is provided here, excluding AVIATOR[26] (not used in the economic model and dasabuvir dose different to licence in all arms).

Patients with HCV genotype 1

Participants in treatment arms that included ribavirin typically experienced statistically significantly more adverse events than participants in treatment arms lacking ribavirin when a statistical comparison was reported (SAPPHIRE I[23] 3D+RBV 87.5% vs placebo 73.4%, p>0.001; PEARL IV[25] 3D+RBV 92% vs 3D 82.4%, p=0.03; PEARL III[25] 3D+RBV 80% vs 3D 67%, p=0.003; SAPPHIRE II[24] 3D+RBV 91.2% vs placebo 82.5%, p=0.02) (Table 23). Fatigue, headache, nausea and insomnia were common adverse events (typically defined as occurring in more than 10% in any group) reported by all the studies. Other common adverse events were diarrhoea (6 studies), pruritus (6 studies), asthenia (4 studies), rash (4 studies), anaemia (3 studies), dyspnoea and irritability (each by 2 studies), and myalgia and cough (1 study). Anxiety, arthralgia and vomiting were only reported by the M14-103[27] study of patients on stable opioid replacement therapy. The proportion of adverse events leading to discontinuation, where this was reported, was low (range 0.6% - 2.6%, Table 23). Similarly the proportions of serious or severe adverse events, where reported, were typically 3% or less, apart from serious adverse events occurring in TURQUOISE II[17] (6.2% in 3D+RBV 12 weeks group and 4.7% in 3D+RBV for 24 weeks group), and severe adverse events in occurring in M14-103[27] (7.9%, participants on stable opioid replacement therapy during treatment with 3D+RBV).

Elevated total bilirubin levels and low haemoglobin levels were the most common grade 3 or 4 chemical or haematological abnormalities reported (CS p. 202-214, Tables 59, 60, 61, 62, 63, 64 and 65).

Table 23: Summary adverse event results for HCV GT1 trials (except AVIATOR[26])

Genotype 1, treatment naive, non-cirrhotic (CS Table 59 p. 202, Table 63 p. 210)			
SAPPHIRE I[23] (GT1a and b)	**3D + RBV 12 wks, n=473** (licensed Tx for n=322 GT1a only)	Placebo, n=158	p-value
Any AE, n (%)	414 (87.5)	116 (73.4)	<0.001
Any AE leading to discontinuation of study drug, n (%)[a]	3 (0.6)	1 (0.6)	nr
Any serious AE, n (%)[a]	10 (2.1)	0	nr
PEARL IV[25] (GT1a)	**3D + RBV for 12 wks, n=100 (licensed Tx)**	3D for 12 wks, n=205 (unlicensed Tx)	p-value
Any AE, n (%)	**92 (92.0)**	169 (82.4)	0.03
Any severe AE, n (%)[b]	**2 (2.0)**	4 (2.0)	
Any serious AE, n (%)[c]	**3 (3.0)**	1 (0.5)	
PEARL III[25] (GT1b)	3D + RBV for 12 wks, n=210 (unlicensed Tx)	**3D for 12 wks, n=209 (licensed Tx)**	p-value
Any AE, n (%)	168 (80.0)	**140 (67.0)**	0.003
Any severe AE, n (%)[b]	2 (1.0)	**1 (0.5)**	
Any serious AE, n (%)[c]	4 (1.9)	**4 (1.9)**	
Genotype 1, treatment experienced, non-cirrhotic (CS Table 60 p. 204, Table 62 p. 207)			
SAPPHIRE II[24] (GT1a and b)	**3D + RBV 12 wks, n=297** (licensed Tx for n=173 GT1a only)	Placebo, n=97	p-value
Any AE, n (%)	271 (91.2)	80 (82.5)	0.02
Any AE leading to discontinuation of study drug, n (%)[a]	3 (1.0)	0	>0.10
Any serious AE, n (%)[a]	6 (2.0)	1 (1.0)	>0.10
PEARL II[21] (GT1b)	3D + RBV for 12 wks, n=91 (unlicensed Tx)	**3D for 12 wks, n=95 (licensed Tx)**	
TEAE, n (%)	72 (79.1)	**74 (77.9)**	nr
TEAE leading to discontinuation of study drug, n (%)	2 (2.2)	**0**	nr
Any serious TEAE, n (%)	2 (2.2)	**2 (2.1)**	nr
Genotype 1, treatment naive & treatment experienced, non-cirrhotic on stable opioid replacement therapy (CS Table 65 p. 214)			
M14-103 single arm study[27] (GT1)	**3D + RBV, n=38** (licensed treatment for n=32 GT1a only)		
Any AE, n (%)	35 (92.1)		n/a
TEAE leading to discontinuation of study drug, n (%)	1 (2.6)		n/a
Any severe AE, n (%)	3 (7.9)		n/a
Genotype 1, treatment naive & treatment experienced, compensated cirrhosis (CS Table 61 p. 205)			
TURQUOISE II[17] (GT1a and b)	**3D + RBV for 12 wks, n=208**	**3D + RBV for 24 wks, n=172**	

	(licensed Tx for n=46 GT1b only)	(licensed Tx for n=65 GT1a only)	
Any AE, n (%)	191 (91.8)	156 (90.7)	
Any AE leading to discontinuation of study drug, n (%)[d]	4 (1.9)	4 (2.3)	
Any serious AE, n (%)[d]	13 (6.2)	8 (4.7)	

Data from trial arms or subgroups meeting the licensed indication in bold font. AE = adverse event; nr = not reported; n/a = not applicable; TEAE = treatment-emergent adverse event.
[a] Details of the events that occurred can be found in the CS below the tables reporting adverse events (CS Table 59 for SAPPHIRE I, CS Table 60 for SAPPHIRE II, CS Table 61 for TURQUOISE II, CS Table 62 for PEARL II, CS Table 663 for PEARL III and PEARL IV)
[b] A severe AE was defined as one that caused considerable interference with the usual activities of the patient and that may have been incapacitating or life-threatening.
[c] A serious AE was defined as one that resulted in hospitalisation, persistent or clinically significant disability or death or that was life-threatening or required medical intervention or hospitalisation to prevent a serious outcome.
[d] Details of the events that occurred can be found in the supplementary appendix to the published paper for this study but are not presented in the CS.

Patients with HCV genotype 4

Adverse events were experienced by a large proportion of each trial arm (range 88.1% to 87.8% within licensed indication), but no adverse events led to discontinuation of study drug and there were few serious or severe adverse events (Table 24). The reported common adverse events (fatigue, headache, nausea, pruritus, insomnia, diarrhoea, asthenia) were similar to those observed in the trials of HCV GT1 patients.

Elevated total bilirubin level was the most common grade 3 or 4 chemical or haematological abnormality reported (CS p. 215, Table 66).

Table 24: Summary adverse events reported in patients with HCV GT4 without cirrhosis

PEARL I[16] (CS Table 66 p. 215)	**Treatment naive**		**Treatment experienced**
	2D n=44 (Group 1)	**2D+RBV n=42 (Group 4, licensed Tx)**	**2D+RBV n=49 (Group 6, licensed Tx)**
Any adverse event, n (%)	34 (77.3)	**37 (88.1)**	**43 (87.8)**
Any adverse event leading to discontinuation of study drug, n (%)	0	**0**	**0**
Any serious adverse event, n (%)	1 (2.3)	**0**	**0**
Any severe adverse event, n (%)	1 (2.3)	**1 (2.4)**	**1 (2.0)**

Treatment duration is 12 weeks. Tx = treatment.

3.3.4 Summary of available results from ongoing trials

Interim results are provided in the CS for the TURQUOISE I and CORAL I trials (CS sections 6.5.1.9 and 6.5.1.10 p. 179-182). Additional information was provided to NICE and the ERG in the company's response to the clarification questions for the ongoing MALACHITE I and II studies including data for the primary end point (clarification response A9.2).

TURQUOISE I

TURQUOISE I is a randomised phase II/III trial enrolling HCV GT1 and HIV-1 coinfected patients. Treatment naive and PegIFN+RBV treatment-experienced patients are eligible, as are those with compensated cirrhosis. The estimated enrolment for the study is 300 and an interim analysis for 63 patients from the first phase of the study is presented in the CS (CS p. 179-181).

From the information provided on patient demographics these seem broadly similar to the other included trials in the CS although the proportion of black people is likely to be higher (24%). The majority of the participants in this interim analysis were HCV treatment naive (67%) and had HCV GT1a infection (89%). A minority had compensated cirrhosis (19%).

Randomisation was stratified by prior HCV treatment history and presence of cirrhosis. Treatment naive participants were also stratified by interleukin 28B genotype. Treatment experienced participants were stratified by type of previous response to PegIFN+RBV therapy. Participants were randomised to receive 3D+RBV for 12 weeks (n=31) or 3D+RBV for 24 weeks (n=32).

Summary of SVR12 results in the first phase of the TURQUOISE-I RCT

The SVR12 rates were over 90% in both study arms (Table 25) which is consistent with SVR12 results from the other phase III studies which ranged from 87.5-100% across different study arms (Table 10). SVR12 results are presented according to by HCV GT1 subgroup (GT1a or GT1b) and by cirrhosis status (cirrhotic or non-cirrhotic).

Table 25: SVR12 in HCV GT1/HIV-1 co-infected participants from the first phase of TURQUOISE-I

SVR12	3D + RBV for 12 weeks			3D+ RBV for 24 weeks		
	n/N	**%**	**95% CI**	**n/N**	**%**	**95% CI**
Overall	29/31	93.5	79.3,98.2	29/32	90.6	75.8, 96.8
Subgroups						
GT1a	25/27	93		26/29	90	
GT1b	4/4	100		3/3	100	
Cirrhotic	5/6	83		5/6	83	
Non-cirrhotic	24/25	96		24/26	92	

Data from CS Table 54 p. 181

Summary of virologic relapse and failure results in the first phase of TURQUOISE I RCT

Of the two participants who did not achieve SVR12 in the 3D+RBV 12 weeks arm, one experienced an HCV virologic relapse and the was due to 'other' reasons (e.g. missing data). In the 3D+RBV 24 weeks arm three patients did not achieve SVR12, in one case due to on-treatment virological failure and in two cases, recorded as relapse, it was believed that the participants had been re-infected with HCV.

Summary of adverse events in the first phase of TURQUOISE I RCT

The safety profile is described in the CS as similar to that of the HCV mono-infected participants in the other phase III RCTs. However it should be noted that the interim analysis includes data through to post-treatment week 12 but participants will be followed up for 48 weeks after the end of treatment.

CORAL I

CORAL I is a non-randomised open-label phase II study enrolling adult liver transplant recipients with recurrent HCV GT1 infection. The participants are treatment naive after transplantation but may have received previous HCV treatment prior to transplant. The clinicaltrials.gov record[34] indicates that overall this study will have nine study arms A-I (seven for liver transplant recipients, two for renal transplant recipients) however the CS describes two cohorts, cohort 1 (arm A) and cohort 2 (arms B & C) with an estimated enrolment of 70.

Enrolment in Arm A is complete (n=34) and interim data for this arm are presented in the CS (CS p. 181-182).

From the information provided on patient demographics these seem broadly similar to the other included trials in the CS although the proportion of men is likely to be higher (79.4%). The majority of the participants in arm A had HCV GT1a infection (85.3%). The mean time since liver transplantation was approximately 4 years. Participants were taking immunosuppressive medication (at baseline tacrolimus 85.3%, ciclosporin 14.7%).

Summary of SVR12 results in Cohort 1 (arm A) of the CORAL-I study

The SVR12 rate was 97.1% (33/34 participants). The one participant who did not achieve SVR12 had a virological relapse. SVR12 results are also broken down by HCV GT1 subtype (GT1a or GT1b) (Table 26).

Table 26: SVR12 in adult liver transplant recipients with recurrent HCV GT1 infection from arm A of the CORAL-I study

SVR12	**3D+/- RBV for 24 weeks**	
	n/N	**%**
Overall	33/34	97.1
Subgroup		
GT1a	28/29	96.6
GT1b	5/5	100

Data from CS Table 55 p. 182

MALACHITE I and II studies

The MALACHITE I and II studies are randomised open label trials enrolling HCV GT1 patients without cirrhosis. MALACHITE I participants are treatment naive whereas MALACHITE II participants are PegIFN+RBV treatment-experienced. The MALACHITE trials are testing head-to-head comparisons of 3D +/- RBV (for 12 weeks) vs. telaprevir + PegIFN+RBV (12 or 36 weeks according to response guided therapy rules).[35;36] Enrolment into these studies is complete [redacted]. Data for the primary endpoint (SVR12) were released at the end of December 2014 and will be presented at the EASL conference in April 2015. Data were provided in the company response to the clarification questions (clarification response A9.2)

From the information provided on patient demographics these seem broadly similar to the other included trials in the CS

[redacted]

No details are provided regarding the stratification of randomisation by participant characteristics. Participants in MALACHITE I were randomised in to one of five treatment groups:

1. Arm A: GT1a, 3D+RBV, [redacted] (treatment in line with 3D license)
2. Arm B: GT1a, TPV+PR, [redacted]
3. Arm C: GT1b, 3D+RBV, [redacted] (treatment not in line with 3D licence)
4. Arm D: GT1b, 3D, n=83 (treatment in line with 3D licence)
5. Arm E: GT1b, TPV+PR, [redacted]

Participants in MALACHITE II were randomised to 3D+RBV (n=101) or TPV+PR (n=47).

[redacted]

Summary of SVR12 results in the MALACHITE I and II RCTs

[redacted] Table 27 and Table 28[redacted].

Virologic relapse, virologic failure and adverse event data are not presented.

Table 27: SVR12 in the MALACHITE I (treatment naïve, non-cirrhotic)

Group	3D+RBV	3D	TPV+PR	p-value
GT1a	[redacted]		[redacted]	[redacted]
GT1b	[redacted]	[redacted]	[redacted]	3D +RBV vs TPV+PR, [redacted] 3D vs TPV+PR, [redacted]

Data from the Company clarification response A9.2

Superseded- see Erratum

Table 28: SVR12 in MALACHITE II (treatment experienced, non-cirrhotic)

3D+RBV	TPV+PR	p-value
[redacted]	[redacted]	[redacted]

Data from the Company clarification response A9.2

[redacted]

3.4 Summary

In their systematic review, the company identified seven Phase III RCTs (six in HCV GT1 patients and one in HCV GT4 patients) that provided outcome data from individual study arms that were relevant to the licensed indications for 3D and 2D. Additionally, the company identified two Phase II trials in HCV GT1 patients, one of which provided information relevant to the licensed indications (M14-103[27]), while the other (AVIATOR[26]) – a dose finding study – did not. Interim results for ongoing trials were additionally presented. All GT1 trials compared different 3D regimens to either each other (four trials) or to placebo (two trials), and to a historical telaprevir comparator. The GT4 trial compared different 2D regimens in different GT4 patient populations.

In the licence for 3D and 2D, the recommended treatment duration and co-administration of ribavirin depends on cirrhosis status and, for GT1 patients, on HCV genotype subgroup (i.e. GT1a or GT1b). We summarise here the results for the trial arms or subgroups within trial arms where the treatment regimens were in line with the licensed indications, as not all data presented by the company were relevant to the licence. For GT1a patients, SVR12 rates ranged from 95.0% to 97% and for GT1b patients, ranged from 98.5% (patients with compensated cirrhosis) to 100%, with all the GT1 studies demonstrating superiority of 3D to a historical telaprevir comparator on the SVR12 outcome. A meta-analysis of SVR12 from trial arms in line with the licensed indications for all participants for 3D in HCV GT1 showed an average SVR12 of 96.5% (95% CI 94.6 to 97.7). All GT4 patients (n = 91) in the one GT4 trial achieved SVR. On treatment relapse and failure rates were low for both GT1 and GT4 patients (0-1% and none, respectively). Treatment with 3D or 2D appeared to have a minimal impact on patients' HRQoL. Common adverse events were fatigue, headache, nausea and insomnia. Up to 7.9% of patients with GT1 HCV experienced a serious adverse event, but few serious or severe adverse events were observed in patients with GT4 HCV.

Superseded - see Erratum

The company's interpretation of the evidence in the CS is generally justified, although the estimates of the treatment effect may be subject to bias. The ERG has identified the following uncertainties and concerns:

- The chance of systematic error in the company's systematic review of clinical effectiveness is uncertain due to the lack of transparency in the processes undertaken, but the company appears to have included all available 3D and 2D studies.
- Of the completed studies identified and presented in the CS, none directly compared 3D or 2D with the current standards of care for GT1 and GT4 HCV (boceprevir + PegIFN+RBV and telaprevir + PegIFN+RBV for GT1, and PegIFN+RBV for GT4), other than by historical comparison to telaprevir studies. The company did, however, provide NICE and the ERG with results for two ongoing trials of randomised head-to-head comparisons of 3D +/- RBV versus telaprevir + PegIFN+RBV in patients with GT1 HCV (MALACHITE I and II) in their clarification letter. The SVR12 data from these two trials showed that [redacted], [redacted]. The company did not identify data of historical comparison with other relevant comparators (e.g. boceprevir). Given the lack of head-to-head trial data available, the data presented in the CS do not fully meet the decision problem and the SVR estimates included in the CS are essentially observational data (which are less robust than RCT data). The company acknowledges this is a limitation.
- The company excluded potentially relevant simeprevir comparators from the decision problem (including the interferon-free regimen simeprevir + sofosbuvir), due to a lack of suitable data available to inform the economic model. The ERG agrees that the company's rationale for excluding these comparators is reasonable. However, this means that no estimates of clinical effectiveness or cost effectiveness in comparison to simeprevir or interferon-free regimens are available in the CS.
- There were higher proportions of patients with mild fibrosis in the 3D studies than the historical comparator telaprevir studies, which may have biased the SVR estimates in favour of 3D.
- The company states that the evidence shows high SVR rates were "across a broad population of patients including … those with cirrhosis" (CS p. 216). However, only one completed study provided data on patients with HCV GT1 with cirrhosis, and no studies provided data for patients with HCV GT4 with cirrhosis. Efficacy data available for cirrhotic patients are therefore limited. Additionally, only interim data are available for

patients with HIV co-infection (TURQUOISE-I) or who were post liver transplant (CORAL-I) and no data were presented for patients who are IFN intolerant or ineligible.

4 ECONOMIC EVALUATION

4.1 Overview of company's economic evaluation

The company's submission to NICE includes:

i) a review of published cost-effectiveness studies of pharmacological treatments for people with CHC (conducted as an update of the systematic review reported by Hartwell and colleagues[1] undertaken for a previous NICE appraisal [TA200]);

ii) a report of an economic evaluation undertaken for the NICE STA process. The objective was to estimate the impact of achieving SVR (virologic cure) on final outcomes for patients infected with either GT1 or GT4 CHC, the former receiving 3D (with or without RBV) and the latter receiving 2D (with RBV) compared with current standard care (comparator pharmacological treatments identified in the NICE scope, where evidence allows, or best supportive care) .

Company's review of published economic evaluations

The company updated the systematic literature review undertaken by Hartwell and colleagues[1] identifying cost-effectiveness studies of pharmacological treatment for people with CHC, conducting for the period from 1st January 2009 to 2nd April 2014. See section 3.1.1 of this report for the ERG critique of the search strategy.

The ERG has conducted an update of the searches reported in the CS, covering the period 2nd April 2014 to date, but found no published economic evaluations of 3D or 2D or any additional relevant cost or quality of life studies.

CEA Methods

The cost effectiveness analysis (CEA) uses a Markov state-transition model to estimate the cost-effectiveness of 3D or 2D (with or without ribavirin) for GT1 and GT4 patients separately. Separate analyses are presented for GT1 interferon-eligible treatment-naive and treatment-experienced patients, for GT4 interferon-eligible treatment-experienced patients,

for GT1 interferon-ineligible and for GT4 interferon-ineligible patients. The model was adapted from the model used in previous technology appraisals ([TA106 and TA200] sourced to Hartwell and colleagues[1] and Shepherd and colleagues[37]). The model adopts a lifetime horizon with an annual cycle. Patients enter the model with chronic HCV infection and are distributed across three fibrosis progression states (mild, moderate or compensated cirrhosis). Patients may achieve one of three SVR (cure) states (the SVR state depends on the patient's state of fibrosis prior to treatment response) if they respond to treatment. Alternatively, patients in the chronic HCV states may progress through these states (from mild to moderate to compensated cirrhosis, depending on their initial state and rates of fibrosis progression included in the model) and those with compensated cirrhosis may progress to one of three more advanced liver disease states (decompensated cirrhosis [DC], liver transplant and hepatocellular carcinoma [HCC]). Patients in all states face a risk of death – higher state-specific death probabilities are applied for the DC and HCC states. Treatment effect data were based on the SVRs taken from clinical trials of 3D and 2D and included comparators. Since the 3D and 2D clinical trials were not designed with comparator arms relevant to current standards of care the SVRs (and AEs) are included in the model on the basis of an unadjusted indirect comparison – i.e. the model uses efficacy data from single arms of separate clinical trials, without any adjustment based on a common comparator or other network of evidence. The CS argues that the validity of this method has been maximised by including fibrosis stage-specific SVRs (given that stage of fibrosis is considered to be the major determinant of variation in SVR, other than efficacy of treatment agent, when comparing treatment). The main determinants of HRQoL in the model were taken from utilities from the UK Mild Chronic Hepatitis C Trial.[4]

NHS reference costs were used, consistent with previous NICE assessments(TA106 and TA200). Costs reflect the NHS and Personal Social Services (PSS) perspective and have four components: treatment costs; on-treatment monitoring costs; adverse event costs; and health state costs .

The results from the economic evaluation are presented in Tables 137 to 141 of the CS for the base case assumptions (base case assumptions are listed in Tables 100 and 101, pages 282 to 286 of the CS). The CS presents base case results by genotype, prior treatment experience and IFN-treatment-eligibility. The CS presents results for subgroup analysis by GT1 sub-type (GT1a and GT1b).

CEA Results

Results from the economic model are presented (section 7.7.6 pages 409 to 412 of the CS, in Tables 137 to 141) as incremental cost per QALY gained for 3D (with or without RBV) compared with sofosbuvir+PegIFN+RBV, telaprevir+PegIFN+RBV, boceprevir+PegIFN+RBV and PegIFN+RBV for GT1 patients and for 2D+RBV compared with PegIFN+RBV or best supportive care for GT4 patients

For the base case an incremental cost per QALY gained of £13,864 for GT1 treatment-naïve, interferon eligible patients (compared with PegIFN+RBV) is reported (see Table 29). For GT1 treatment-experienced, interferon eligible patients the equivalent ICER is £10,258.

For GT4 treatment-naïve, interferon eligible (non-cirrhotic) patients the base case incremental cost per QALY gained is £20,351 (compared with PegIFN+RBV) (see Table 29). For GT4 treatment-experienced, interferon eligible patients the ICER is £8,977 (compared with BSC).

The CS concluded in Section 7.7.10 that the incremental cost per QALY results [are] most sensitive to utility values for progressive disease states and their associated recovered states, based on the results of their deterministic sensitivity analysis.

Table 29 Base case cost effectiveness results

Base-case results for GT1, treatment-naïve, interferon eligible patients

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER incremental
PegIFN+RBV	£22,872	13.72	NA	NA	NA
Boceprevir + PegIFN+RBV	£32,147	14.22	£9,275	0.50	Extended dominance
Telaprevir + PegIFN+RBV	£35,887	14.55	£13,014	0.83	Extended dominance
3D	£43,624	15.21	£20,752	1.50	£13,864
Sofosbuvir + PegIFN+RBV	£44,337	15.01	£21,465	1.29	Dominated

Base-case results for GT1, treatment-experienced (overall) interferon eligible patients

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER incremental
PegIFN+RBV	£30,128	11.07	NA	NA	NA
Telaprevir + PegIFN+RBV	£42,646	12.10	£12,518	1.04	Extended dominance
3D	£51,882	13.19	£21,754	2.12	£10,258

GT4, treatment-naïve, interferon-eligible patients (non-cirrhotic only)

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER incremental
PegIFN+RBV	£19,286	15.00	NA	NA	NA
2D	£36,490	15.84	£17,204	0.85	£20,351
Sofosbuvir + PegIFN+RBV	£41,237	15.81	£21,951	0.81	Dominated

GT4, treatment-experienced (overall) interferon eligible patients (non-cirrhotic only)

Regimen	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER incremental
No treatment	£16,186	12.58	NA	NA	NA
2D	£36,536	14.84	£20,350	2.27	£8,977

Source: CS Tables 137, 138, 139, 140

4.2 Critical appraisal of the company's submitted economic evaluation

Company's review of published economic evaluations

The CS presents a systematic review of published economic evaluations including ombitasvir/paritaprevir/ritonavir and dasabuvir (with or without ribavirin) and selected comparators listed in the NICE scope (full details of search strategies are presented in Appendix 10 of the CS). The objectives for the review (Table 67 on pages 224 to 225 of the CS) list the included comparators as telaprevir+PegIFN+RBV and boceprevir+PegIFN+RBV and make no reference to sofosbuvir, simeprevir or PegIFN+RBV dual therapy. The review was carried out as an update to the review report by Hartwell and colleagues[1] with a start date of 1st January 2009 and end date of 2nd April 2014. This was approximately eight months prior to the submission of the CS and the ERG feels that update searches should have been conducted prior to submission (see discussion in section 3.1.1 of this report). The company presented a PRISMA flow diagram (Figure 22, page 227 of CS). The searches identified 1,386 references (1,108 after de-duplication) of which 1,094 were excluded on the basis of title and abstract and 5 were excluded on the basis of full-text assessment. The 9 included studies are summarised in Table 68 (pages 228 to 238) of the CS.

No economic evaluations including 3D or 2D (with or without ribavirin) were identified in the review. The majority of the included studies reported comparisons of either telaprevir+PegIFN+RBV or boceprevir+PegIFN+RBV (or both) against PegIFN+RBV dual therapy, although two reported evaluations of shortened duration of therapy with PegIFN+RBV. Quality assessment of included studies is reported in Table 69 (pages 239 to 242) of the CS. However, no interpretation or conclusions of this quality assessment were provided in the CS, nor is there any narrative review of the results of included studies

Critical appraisal of company's submitted economic evaluation

The ERG has considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in Table 30 below, drawn from common checklists for economic evaluation methods (e.g. Drummond and colleagues[38]).

Superseded - see Erratum

Table 30 Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment (if applicable)
Is there a well defined question?	Yes	
Is there a clear description of alternatives?	Yes	
Has the correct patient group / population of interest been clearly stated?	Yes	
Is the correct comparator used?	Yes	**NOTE** that the economic model does not include simeprevir (for any genotype) – argued due to lack of suitable publicly available data Limited comparisons are available for some genotype subgroups due to limited available data
Is the study type reasonable?	Yes	
Is the perspective of the analysis clearly stated?	Yes	
Is the perspective employed appropriate?	Yes	
Is effectiveness of the intervention established?	No	The economic model is based on an adjusted indirect comparison (due to nature of evidence base). The CS argues that using fibrosis stage-specific outcomes removes the major source of variation in response to treatment. Additional uncertainty arises from the fact that data needed to be imputed for many subgroup.
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	Yes	
Are the costs and consequences consistent with the perspective employed?	Yes	
Is differential timing considered?	Yes	
Is incremental analysis performed?	Yes	
Is sensitivity analysis undertaken and presented clearly?	Yes	

NICE reference case

The NICE reference case requirements have also been considered for critical appraisal of the submitted economic evaluation in Table 31.

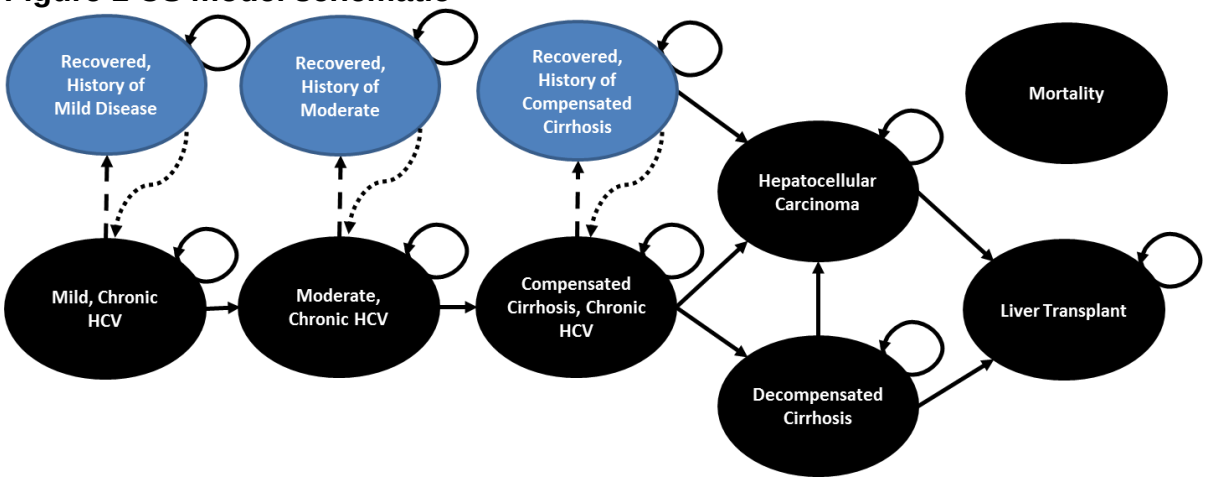
Table 31 NICE reference case requirements

NICE reference case requirements:	Included in submission	Reviewer Comment
Decision problem: As per the scope developed by NICE	Yes	The economic model does not include simeprevir (for any genotype) – argued due to lack of suitable publicly available data Limited comparisons are available for some genotype subgroups due to limited available data
Comparator: Alternative therapies routinely used in the UK NHS	Yes	
Perspective on costs: NHS and PSS	Yes	
Perspective on outcomes: All health effects on individuals	Yes	
Type of economic evaluation: Cost effectiveness analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	?	Evidence searched for systematically but method of synthesis (unadjusted indirect comparison) does not reflect current methodological standards
Measure of health benefits: QALYs	Yes	
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	Yes	
Method of preference elicitation for health state values: Choice based method (e.g. TTO, SG, not rating scale)	Yes	
Source of preference data: Representative sample of the public	Yes	
Discount rate: 3.5% pa for costs and health effects	Yes	
Notes: ? = uncertain		

4.2.1 Modelling approach / Model Structure

A Markov state-transition model was adapted from the model used in previous technology appraisals ([TA106 and TA200] sourced to Hartwell and colleagues[1] and Shepherd and colleagues[37]). A schematic of the model is given in Figure 1.

Figure 1 CS model schematic



Note: Health states are depicted by ellipses, while arrows represent permissible transitions between health states. Hashed arrows depict the possibility of an SVR. Dotted arrows depict a potential reinfection. Death is possible from any health state. Liver death is possible from decompensated cirrhosis, hepatocellular carcinoma, and/or liver transplant.

Source: CS Figure 23

Patients enter model with chronic HCV infection and are distributed across three fibrosis progression states (mild, moderate or compensated cirrhosis). Those with mild fibrosis, moderate fibrosis or compensated cirrhosis move to “Recovered with history of mild fibrosis”, “Recovered with history of moderate fibrosis” or “Recovered with history of compensated cirrhosis”, respectively, if they have undetectable HCV RNA twelve weeks after completing treatment (SVR12). Patients with an SVR are assumed to no longer face a probability of progressing through the disease. However re-infection with CHC is included in the model, as a constant risk.

Patients without an SVR may progress from no cirrhosis to compensated cirrhosis, and from compensated cirrhosis to either HCC or DC. Patients in the DC state may move to the HCC state, die from liver disease or undergo a liver transplant. Patients in the HCC state may also undergo liver transplant or die from liver disease. Following liver transplant, patients face a probability of dying or moving to the post-transplantation phase. Patients in the HCC and DC health states patients face higher risk of death than the general population (which are applied to all other health states in the model). Age-specific general population mortality rates are applied to each health state in the model.

The CS states that the model structure and inputs were subjected to clinical validation, through presentation at an expert advisory board meeting (section 7.3.5, page 282 of CS). The advisory board included an epidemiologist, health economist and specialist viral-

hepatitis pharmacist who also commented on the model and considered assumptions regarding monitoring of patients while on-treatment with IFN-containing and IFN-free regimens. The model was also subjected to an independent technical validation by an independent modelling team at an academic institution. The company provided additional information on the organisations conducting the external validation process in response to a request for clarification (Priority Question 18), but did not provide much additional information on the validation process or on the outcomes of this process.

The model has a lifetime horizon indicated as 70 years (Table 100, page 282 of CS). SVR status at 12 weeks post-treatment is extrapolated using probabilities obtained from the literature and previous Health Technology Assessments of pharmacological treatments for CHC (TA106 and TA200). The model has a cycle length of one year.

In general the ERG considers that the modelling approach adopted in the submission is reasonable and is consistent with the sources of evidence used in its development.

4.2.2 Patient Group

The patient group included in the economic model is those with GT1 and GT4 HCV. This contrasts with the scope issued by NICE which identifies the population for this assessment as adults with chronic hepatitis C (without reference to genotype) and further identifies specific genotypes with reference to comparators identified in the scope (genotypes 1 to 6 for PegIFN+RBV, sofosbuvir+RBV±PegIFN and best supportive care). However this more restricted patient group is consistent with the draft SmPCs, included in the CS as Appendix 1, which state that “[t]he efficacy of Viekirax has not been established in patients with HCV genotypes 2, 3, 5 and 6; therefore Viekirax should not be used to treat patients infected with these genotypes” (pages 4 to 5).

The patient group is further divided by genotypes sub-types (GT1a and GT1b), stage of fibrosis (mild, moderate and cirrhosis), treatment history (naive or experienced) and eligibility for treatment with PegIFN. It is not clear whether the decision to sub-divide genotype 1 is driven by evidence of significant differences in efficacy or disease progression, or primarily due to the difference in treatment combination (3D alone for GT1b and 3D+RBV GT1a non-cirrhotic patients and for cirrhotic patients in both subgroups) and duration (24 weeks for GT1a cirrhotic patients versus 12 weeks for all others) for the intervention.

Baseline characteristics (starting age, weight, sex and fibrosis distribution) for the patient populations in the model are primarily derived from previous assessments conducted for NICE (see Table 71, page 251-252, and Table 100 page 282 to 286 of the CS) and do not appear to have been informed by baseline characteristics from the 3D or 2D trials (or from any of trials of the comparators). There is no discussion of the comparability of the assumed baseline population characteristics with the demographic or other characteristics of patients in identified clinical trials (from which efficacy or adverse event data were drawn to populate the model). The proportion of GT1 patients who are assumed to be GT1a is based on a published study of the prevalence of specific HCV genotypes in England and Wales.[39] Table 71 in the CS states the distribution of treatment-experienced patients across categories of prior null response, prior partial response or relapse from prior response was based on expert opinion. However Table 100 (page 282 to 286) of the CS states that the distribution of patients by prior treatment response was based on the NICE simeprevir STA. As noted above there is no discussion of the comparability of this assumed distribution against any of the identified clinical trials.

4.2.3 Interventions and comparators

The interventions included in the economic model are 3D with or without RBV for GT1 chronic hepatitis C and 2D with RBV for GT4 CHC. The recommended dose of ombitasvir/ parataprevir / ritonavir is two 12.5mg/ 75mg/ 50mg tablets once a day. For the 3D regimen 250mg dasabuvir twice a day is also taken. For GT1b patients with compensated cirrhosis and all GT1a patients 3D is taken in combination with weight-based dosage of RBV (taken twice a day). For all GT4 patients 2D is taken in combination with weight-based dosage of RBV (taken twice a day). See Table 32 for dosing details.

Treatment duration is 24 weeks for GT4 patients with compensated cirrhosis (2D+RBV) and for GT1a patients with compensated cirrhosis (3D+RBV). For all other groups treatment is for 12 weeks.

Table 32 Dosing details and treatment duration for 3D ± RBV and 2D+RBV (by genotype and stage of fibrosis)

Patient population	Treatment regimen	Duration
GT1a without cirrhosis	3D+RBV 1 tablet (12.5mg ombitasvir/ 75mg parataprevir / 50mg ritonavir) daily 1 tablet (250mg dasabuvir) twice daily 600mg ribavirin twice daily	12 weeks
GT1a with cirrhosis	3D+RBV 1 tablet (12.5mg ombitasvir/ 75mg parataprevir / 50mg ritonavir) daily 1 tablet (250mg dasabuvir) twice daily 600mg ribavirin twice daily	24 weeks
GT1b without cirrhosis	3D 1 tablet (12.5mg ombitasvir/ 75mg parataprevir / 50mg ritonavir) daily 1 tablet (250mg dasabuvir) twice daily	12 weeks
GT1b with cirrhosis	3D+RBV 1 tablet (12.5mg ombitasvir/ 75mg parataprevir / 50mg ritonavir) daily 1 tablet (250mg dasabuvir) twice daily 600mg ribavirin twice daily	12 weeks
GT4 without cirrhosis	2D+RBV 1 tablet (12.5mg ombitasvir/ 75mg parataprevir / 50mg ritonavir) daily 600mg ribavirin twice daily	12 weeks
GT4 with cirrhosis	2D+RBV 1 tablet (12.5mg ombitasvir/ 75mg parataprevir / 50mg ritonavir) daily 600mg ribavirin twice daily	24 weeks
Ribavirin dosage has been estimated by the ERG based on a patient body weight of 95kg		

A range of comparators were used, all of which are relevant to current UK practice (although relevance varies by genotype) and are included in the NICE scope. However the CS does not include all comparators that were listed in the scope. Specifically it excludes:

- Simeprevir+PegIFN+RBV for GT1 IFN-eligible patients, due to lack of publicly-available evidence on treatment outcome for GT1a patients with Q80K polymorphism, stratified by fibrosis stage (as required for the economic model);
- Sofosbuvir+RBV for GT1 IFN-ineligible patients, due to negative NICE recommendation;
- Sofosbuvir+simeprevir for GT1 IFN-ineligible patients, due to lack of evidence by fibrosis stage consistent with economic model;
- Simeprevir+PegIFN+RBV for non-cirrhotic GT4 IFN-eligible patients, lack of evidence by fibrosis stage consistent with economic model;
- Sofosbuvir+RBV for GT4 IFN-ineligible patients, due to negative NICE recommendation

- Sofosbuvir+simeprevir for GT4 IFN-ineligible patients.

For GT1 IFN-eligible patients, included comparators are telaprevir+PegIFN+RBV, boceprevir+PegIFN+RBV and PegIFN+RBV and are modelled in line with their respective marketing authorisations. The CS states (in section 2.7 page 45) that boceprevir+PegIFN+RBV and PegIFN+RBV are not widely used for HCV GT1 in current UK clinical practice. The implication (though not explicitly stated in the CS) of the statement (that boceprevir+PegIFN+RBV and PegIFN+RBV are not widely used for HCV GT1 in current UK clinical practice) is that telaprevir+PegIFN+RBV would be the current standard of care for the majority of protease inhibitor-tolerant GT1 HCV patients receiving anti-viral treatment in the UK. The ERG clinical advisors agree that PegIFN+RBV dual therapy would not be used in GT1 patients unless there was a reason not to include a protease inhibitor in the treatment regimen. However the ERG clinical advisors suggest that boceprevir would be used as frequently as telaprevir in GT1 patients. The CS includes both peginterferon alfa-2a (Pegasys, Roche Products Ltd) and peginterferon alfa-2b (ViraferonPeg, Merck, Sharp and Dohme Ltd) weighted by market share.

For GT1 IFN-ineligible patients, given the exclusion of sofosbuvir+RBV and sofosbuvir+simeprevir, the only included modelled comparator is best supportive care.

For GT4 non-cirrhotic IFN-eligible patients the included comparators are sofosbuvir +PegIFN+RBV and PegIFN+RBV which are modelled in line with their respective marketing authorisations. For G4 IFN-ineligible patients, given the exclusion of sofosbuvir+RBV and sofosbuvir+simeprevir, the only included comparator is best supportive care.

Superseded- see Erratum

4.2.4 Clinical Effectiveness

The key clinical event affected by anti-viral treatment in the economic model is the proportion of patients achieving SVR. This was obtained for each patient group by genotype from the corresponding 3D and 2D studies (summarised in Table 72, page 252 to 256 of the CS) and from individual trials of included comparators. Details of the SVR calculation and data sources are presented in Section 7.3.1 of the CS. Other outcomes obtained from the key trials are treatment duration (reported in Table 113 for 3D and 2D and in Table 114 for included comparators, pages 362 to 364 of the CS) and adverse events (reported in Table 75, page 256 of the CS for 3D and 2D and throughout section 7.3.1 of the CS for the included comparators). Ranges for the parameters used in deterministic sensitivity analyses are given in Table 125 (page 392) of the CS and for the probabilistic sensitivity analyses in Table 129 (pages 400 to 402) of the CS.

SVR

SVR is an accepted intermediate outcome relevant for assessing treatment efficacy in RCTs of anti-viral treatments in chronic HCV infection, where difficulties in designing, powering and ensuring adequate follow-up in the trial for final outcomes (such as advanced liver disease or liver-disease related death) render such trials infeasible. The CS briefly reviews evidence to support the use of SVR as a surrogate outcome (page 245 to 246) although it does not report evidence of systematic searching to identify this evidence nor does it evaluate the characteristics of SVR as a surrogate outcome. Clinical advice to the ERG indicated that SVR is regarded as a clinically relevant outcome and is accepted as the measure of successful outcome for patients receiving anti-viral treatment for chronic HCV infection. However patients with cirrhosis prior to SVR are believed to be at greater risk of liver cancer than those whose disease was mild or moderate before SVR. As a result patients who had progressed to cirrhosis prior to successful treatment require extended following up and monitoring for the development of liver cancer.

SVR enters the model as a baseline probability of response within the relevant treatment period. Different probabilities are used for patients with mild or moderate fibrosis and with cirrhosis at the start of treatment, depending on the level of reporting in included clinical trials. Where separate SVR estimates by level of fibrosis are not reported these have been imputed or the same response has been assumed for mild and moderate fibrosis. SVR estimates are presented for each combination of HCV genotype, treatment experience and interferon eligibility considered in the base case. These are summarised in Table 33 and Table 34 for G1 treatment-naive and treatment-experienced patients (including subgroups of treatment-experienced patients).

The CS does not provide a clear description of how each study providing these estimates was sourced, or any justification for the choice of studies. The ERG has checked the studies used to establish whether they are the most valid source of evidence on response to treatment, treatment duration and adverse events. The majority are phase III registration trials with large sample sizes, reporting outcomes of interest based on the required breakdown (GT1a and GT1b population, outcomes by stage of fibrosis) and are sourced from peer reviewed publications. All included estimates come from separate RCTs (except for telaprevir+PegIFN+RBV and PegIFN+RBV which have been extracted from the telaprevir RCTs used to power the 3D trials (see 3D trial protocols)) and no statistical adjustments have been attempted to take account of this. The CS acknowledges that this unadjusted

indirect comparison does not meet current methodological criteria for valid comparisons but argues that:

- the design of the 3D and 2D trials (without an active comparator arm) precludes the use of statistical methods such as network meta-analysis to derive a methodologically sound indirect comparison (see section 7.3.1, page 257 of the CS)
- by using fibrosis stage-specific outcomes, the modelling approach removes the major source of variation in response to treatment (for each group of patents defined by genotype and treatment-history) and therefore provides a valid comparison

The ERG therefore suggests caution is applied when interpreting these model outcomes based upon these data and that an alternative approach to the analysis could have considered deriving a consistent evidence network for comparators in the model and to then conduct a threshold analysis when introducing 3D and 2D into the model.

Table 33 Proportion of patients with SVR for 3D and comparators applied in the economic model: genotype 1, treatment-naïve, interferon-eligible population

Regimen	Genotype	Mild	Moderate	Compensated cirrhosis
3D	1[a]	0.972		0.951
	1a	0.960 ([redacted]/422)[b]		0.946 (53/56)[c]
	1b	1.000 (209/209)[d]		1.000 (22/22)[e]
Sofosbuvir+PegIFN+RBV[f]	1	0.917 (220/240)		0.807 (42/50)
Telaprevir+PegIFN+RBV[g]	1	0.813 (109/134)	0.716 (149/208)	0.619 (13/21)
Boceprevir+PegIFN+RBV[h]	1	0.658 (222/237)		0.3125 (5/16)
PegIFN+RBV[i]	1	0.455 (67/147)	0.435 (84/193)	0.333 (7/21)

[a] GT1 SVR for 3D estimated as weighted average (GT1a*0.688)+(GT1b*(1-0.688))
[b] estimated by simple pooling of number of patients with SVR & total patient population in SAPPHIRE I[23] and PEARL IV[25] trials. The CS reports SVR for mild and moderate fibrosis combined (and the economic analysis applies the same SVR mild and moderate fibrosis). The economic model reports SVR by each fibrosis stage for both SAPPHIRE I and PEARL IV trials, sourcing these data to the trial CSRs – separate SVRs for mild and moderate fibrosis, pooling data across the two trials, are mild = [redacted]/303 = 0.967 and moderate = [redacted]/119 = 0.941
[c] 24 week treatment arm from TURQUOISE II trial[17]
[d] PEARL III trial. [25] The economic model reports SVR by each fibrosis stage for PEARL III trial, sourcing these data to the trial CSR – separate SVRs for mild and moderate fibrosis are mild = [redacted] = 1.000 and moderate = [redacted] = 1.000
[e] GT1b 12 week treatment arm from TURQUOISE II trial[17]
[f] NEUTRINO trial.[40] Data from an updated subgroup analysis reported in the company submission for ID654 Single Technology Appraisal of Sofosbuvir (Page 98)[6]
[g] T12PR arm, ADVANCE RCT[28] Figure 2
[h] Arm 2 (RGT) SPRINT-2 RCT[41], Supplementary Figure S2A (NOTE PR48 SVR = 126/339 = 37% for non-cirrhotic; 6/13 = 46 for cirrhotic)
[i] PR arm, ADVANCE RCT[28] Figure 2

Table 34 Proportion of patients with SVR for 3D and comparators applied in the economic model: genotype 1, treatment-experienced (all types), interferon-eligible population

Regimen	Genotype	Mild	Moderate	Compensated cirrhosis
3D	1[a]	0.974		0.972
	1a	0.962		0.979
	1b	1.000		0.957
Telaprevir+PegIFN+RBV[f]	1	0.585	0.683	0.486
PegIFN+RBV[g]	1	0.140	0.173	0.143

[a] GT1 SVR for 3D estimated as weighted average (GT1a*0.688)+(GT1b*(1-0.688))
[b] SAPPHIRE II trial[24]
[c] 24 week treatment arm from TURQUOISE II trial[17]
[d] PEARL II trial[21]
[e] GT1b 12 week treatment arm from TURQUOISE II trial[17]
[f] T12/PR48 arm REALIZE RCT[30] Source for data in table is CHMP assessment report, Table 43
[g] PR48 arm REALIZE RCT[30]

For 3D and 2D the model uses data from the relevant clinical effectiveness trials reported in section 3.3. For GT1 treatment-naive patients, with mild or moderate fibrosis, the SVR data were taken from the SAPPHIRE I,[23] PEARL IV and PEARL III (both reported by Ferenci and colleagues[25]) trials, while for GT1 treatment-experienced patients with mild or moderate fibrosis the SVR data were taken from the SAPPHIRE II[24] and PEARL II[21] trials. Where there was more than one trial for a given genotype subgroup the results have been derived by simple pooling of the number of responders and total number of patients. The SVR data for both treatment-naive and treatment-experienced GT1 patients with compensated cirrhosis were taken from the TURQUOISE II trial.[17]

SVRs for GT1 treatment-naive patients receiving sofosbuvir+PegIFN+RBV were taken from the NEUTRINO trial.[40] This was a single-group, open-label study enrolling patients with genotype 1, 4, 5 or 6 HCV. The majority of patients in the trial were GT1 (69% (225/327) were GT1a and 20% (66/327) were GT1b), with almost all cirrhotic patients (52/54 96%) being infected with HCV GT1. The NEUTRINO trial was used as the basis for the clinical effectiveness data presented for this patient population in the company submission for the NICE STA of sofosbuvir (TA 330). SVRs were reported for some patient subgroups (overall SVRs for GT1a and GT1b patients and for all GT1 by stage of fibrosis), but were not reported both for genotype subgroups and by stage of fibrosis. As a result the CS needed to impute SVRs for these subgroups (see Table 76 and Table 77 in the CS, pages 258 and 259). The ERG has checked the SVRs reported in the CS against the original trial report (Lawitz and collages[40]) and the CS for sofosbuvir[6] and confirm that the data have been sourced from the CS for sofosbuvir (page 98).[6]

SVRs for GT1 treatment-naive patients receiving telaprevir+PegIFN+RBV and PegIFN+RBV, were taken from the ADVANCE RCT,[28] while those for GT1 treatment-experienced patients receiving telaprevir+PegIFN+RBV and PegIFN+RBV were taken from the REALIZE RCT.[30] These trials were used as the basis for the clinical effectiveness data for these patient populations in the CS for the NICE STA of telaprevir (TA 252). The ERG has checked the SVRs reported in the CS against original sources (ADVANCE RCT,[28] REALIZE RCT[30]) and the CS for telaprevir.[5] Neither of the telaprevir trials distinguished between GT1a and GT1b patients in their reporting of SVR by stage of fibrosis. Therefore SVRs for these genotype subgroups were imputed in the CS (see Tables 85, 86 and 90 in the CS, pages 265 to 270).

SVRs for GT1 treatment-naive patients receiving boceprevir+PegIFN+RBV were taken from the SPRINT-2 RCT.[41] SVRs for GT1 treatment-experienced patients, receiving boceprevir +PegIFN+RBV, were taken from the RESPOND-2 RCT.[42] Both of these trials were included in the clinical effectiveness data for this patient population in the company submission for the NICE STA of boceprevir[7] (TA 253). Neither trial publication reported SVR by stage of fibrosis populations for GT1a and the SVRs were imputed in the CS (see Tables 87 and 88 in the CS, pages 267 to 268 for treatment-naive patients and Tables 94 and 95 in the CS, pages 275 to 276 for treatment-experienced patients).The CS does not include boceprevir+PegIFN+RBV in the economic analysis for the overall population of treatment-experienced patients as the RESPOND-2 RCT included only prior partial responders and prior relapsers.

The ERG has checked the SVRs reported in the CS against original sources (SPRINT-2 RCT[41] RESPOND-2 RCT [42]) and the CS for boceprevir.[7] However the SVRs used in the CS for boceprevir[7] were derived from a meta-analysis of boceprevir trials (which was not reported in the main body of the CS for boceprevir[7] and is not available on the NICE website for the appraisal).

Section 4.2.3 of this report discussed the comparators included in the company's model indicating that some data may be available to allow simeprevir+PegIFN+RBV to be included. As stated in the CS, the same level of information (number of trial participants and number experiencing SVR) is not reported for the Q80K negative population in the simeprevir trials, as is reported for other included comparators. However the mixed treatment comparison (MTC) outputs for the Q80K negative population are available in the simeprevir CS[43] Table 30 (page 83) and Table 85 (page 145). The MTC results report odds ratios, with 95% credible intervals, for three treatment regimens (telaprevir, boceprevir and simeprevir each in

combination with PegIFN+RBV) compared with PegIFN+RBV. The ERG has estimated fibrosis-stage specific SVRs for simeprevir using the PegIFN+RBV SVRs from the ADVANCE RCT[28] (which are used in the CS model) and the odds ratio for simeprevir relative to PegIFN+RBV (4.83) reported in the CS for simeprevir[28] (see Table 35).

Table 35 SVRs for comparator regimes applied in the economic model, in company submissions for comparator regimes and ERG estimate of SVR with simeprevir+PegIFN+RBV (using MTC output from simeprevir CS[28]): genotype 1, treatment-naive, interferon-eligible population

Regimen	Fibrosis Stage	Model	Telaprevir CS[a]	Boceprevir CS[b]	Simeprevir CS[c]	Simeprevir CS ORs[d]
PegIFN+ RBV	Mild	0.455	0.455	0.42	0.519	0.455
	Mod	0.435	0.435	0.42		0.435
	Severe	0.333	0.333	0.385	0.354	0.333
Telaprevir+ PegIFN+ RBV	Mild	0.813	0.813	NA	0.804	0.760
	Mod	0.716	0.716			0.745
	Severe	0.619	0.619		0.675	0.654
Boceprevir+ PegIFN+ RBV	Mild	0.658	NA	0.677	0.763	0.714
	Mod	0.658		0.677		0.697
	Severe	0.313		0.417	0.621	0.599
Simeprevir+ PegIFN+ RBV	Mild	NA		NA	0.839	0.801
	Mod					0.788
	Severe				0.726	0.707

Notes:
[a] data taken directly from ADVANCE trial[28]
[b] data taken from meta-analysis of identified trials. Appendix 15 to the boceprevir CS (reporting the meta analysis) is not available with the CS[7] on the NICE website.
[c] SVR for PegIFN+RBV using mean of SVR by stage in studies included in MTC reported in pages 63 to 91 of the simeprevir CS.[43] SVR for other regimens are not reported in the simeprevir CS and have been estimated for this report by the ERG using the SVR by stage for PegIFN+RBV and odds ratios for other regimens reported in Table 85 (page 145) of the Simpeprevir CS[43]. Simeprevir CS used different definition of mild/ moderate and severe compared to other CS included here (see text)
[d] SVRs in this column have been estimated by the ERG using PegIFN+RBV SVRs by stage applied in the current model (see column 3 of this table, headed "Model") and applying the regimen-specific odds ratios reported in Table 85 (page 145) of the Simeprevir CS[43]

None of the trials of 2D undertaken in GT4 patients included cirrhotic patients and as a result the economic model only includes patients with mild and moderate HCV. For GT4 treatment-naive and treatment-experienced patients, the SVRs used in the model for treatment with 2D have been derived using data for relevant subgroups in the PEARL I trial (see Table 36). The SVR for sofosbuvir+PegIFN+RBV in GT4 treatment-naive, interferon-eligible patients, is based on a subgroup analysis reported in the CS for sofosbuvir.[6] The SVR for PegIFN+RBV in GT4 treatment-naive, interferon-eligible patients, uses data from one arm (PegIFN α-2a) of a trial comparing PegIFN α-2a and PegIFN α-2b in GT4 patients.[44] The CS doesn't discuss the appropriateness of this source, other than to state that a previous meta-analysis

has suggested that PegIFN α-2a is associated with superior outcomes in GT4 patients. The CS does not report whether specific targeted searches were undertaken for evidence on effectiveness of treatments in this patient population.

As with the GT1 population the evidence entering the model for GT4 is taken from single-armed studies or from single arms of randomised trials. The CS has not presented any information on the baseline characteristics of patients entering these trials, nor have they discussed the comparability of the identified trials.

Table 36 Proportion of patients with SVR for 2D and comparators applied in the economic model: genotype 4, treatment-naïve, interferon-eligible population

Regimen	Genotype	Mild	Moderate	CC
treatment-naïve, interferon-eligible population				
2D [a]	4	1.000 (42/42)		NA
Sofosbuvir+PegIFN+RBV [b]	4	1.000 (27/27)		0 (0/1)
PegIFN+RBV [c]	4	0.706 (77/109)		NA
treatment-experienced, interferon-eligible population				
2D [d]	4	1.000 (49/49)		NA

[a] PEARL I trial[22]
[b] NEUTRINO trial . Source Sofosbuvir CS (Sub-group analysis of SVR 12 page 98)
[c] Kamal and colleagues[44]. PegIFN α-2a arm in trial of PegIFN α-2a vs PegIFN α-2b
[d] PEARL I trial.[22] SVR was 100% for each patient experience sub-group in the PEARL I trial (prior null responder, 23/23; prior partial responder 9/9; prior relapse 17/17)

Interferon-ineligible

The CS does not state explicitly where the efficacy data for the interferon-ineligible sub-groups have been derived from, nor do they discuss the appropriateness of applying a natural history model that was developed and populated for evaluating interferon-containing regimes to an interferon-ineligible population. Examination of the electronic model makes it clear that the same SVR estimates are used for both interferon-eligible and interferon-ineligible populations. The ERG feels that this assumption should have been highlighted in the CS and that some justification is needed to support this assumption. Without this discussion and justification the ERG feel that the results of this analysis should be interpreted with caution.

Treatment duration

Treatment duration (discussed in Section 7.5 of the CS) is a major determinant of intervention cost (discussed further in section 4.2.6 of this report). The economic model uses average treatment durations, derived using data on discontinuations reported in each of the included trials, in order to estimate the drug acquisition costs and monitoring costs whilst on

treatment (see Section 7.5.1 pages 361 to 364 of the CS, Tables 113 and 114 report trial-based treatment durations for intervention and comparators).

The average treatment duration is calculated as the weighted average of the indicated treatment duration for each treatment multiplied by the proportion completing the trial plus half the indicated treatment duration multiplied by the proportion not completing the trial. This approach seems reasonable for 3D and 2D. However, the ERG is concerned that these trial-based estimates may not fully capture treatment-futility stopping rules for PegIFN-based treatment regimens or response-guided treatment durations indicated for patients treated with telaprevir and boceprevir.

For telaprevir, the approach taken to estimating treatment duration appears not to have taken account of patients discontinuing study drugs (either telaprevir alone or all treatment) during the first twelve weeks of treatment (referred to as the “telaprevir (or placebo) phase”) for which data are reported by Jacobson and colleagues,[28] but is based on overall discontinuations reported at the end of the trial. The publication reporting the SPRINT-2 trial[41] used to populate the model with clinical data for boceprevir reports less information on discontinuations and would not provide a suitable basis for similar adjustments to modelled treatment duration.

Model transition probabilities

As discussed previously, SVR is an intermediate outcome and is related to survival in the model using transition probabilities for disease progression. Transition probabilities for natural history of progressive liver disease used in the model are summarised in Table 37. The model assumes the same probabilities for all HCV genotypes.

Table 37 Natural history transition probabilities used in the economic model (extracted from Table 100 in CS)

Transition Probability	Base Case Value	Source
Disease progression		
Mild to Moderate	0.025	Wright and colleagues,[4] Grieve and colleagues,[45] Shepherd and colleagues,[37] Hartwell and colleagues[1]
Moderate to CC	0.037	
Recovered, no HCV, History of Severe Fibrosis to HCC	0.012	Cardoso and colleagues[46]
CC to DCC	0.039	Fattovich and colleagues,[47] Wright and colleagues,[4] Grieve and colleagues,[45] Shepherd and colleagues,[37] Hartwell and colleagues[1]
CC to HCC (First Year)	0.014	
DCC to HCC (First Year)	0.014	
Liver Transplant		
DCC to Liver Transplant (First Year)	0.020	Wright and colleagues,[4] Grieve and colleagues,[45] Shepherd and colleagues,[37] Hartwell and colleagues,[1] Siebert and colleagues[48]
HCC to Liver Transplant (First Year)	0.020	Wright and colleagues,[4] Hartwell and colleagues[1]
Liver-related Mortality		
DCC to Liver Death	0.130	Fattovich and colleagues,[47] Wright and colleagues,[4] Grieve and colleagues,[45] Shepherd and colleagues,[37] Hartwell and colleagues[1]
Liver Transplant to Liver Death	0.150	Hartwell and colleagues, [1] Grieve and colleagues[45]
After Liver Transplant to Liver Death	0.057	Shepherd colleagues,[37] Hartwell and colleagues[1], Bennett and colleagues[49]
HCC First Year to Liver Death	0.430	Fattovich and colleagues,[47] Wright and colleagues,[4] Shepherd and colleagues,[37] Hartwell and colleagues[1]
HCC Subsequent Year to Liver Death	0.430	
Viral reinfection		
Viral reinfection	0.010	Expert opinion

The majority of the transition probabilities applied within the natural history model of progressive liver disease have been sourced from the long-term model developed alongside the UK Mild Hepatitis C trial[4] or to models developed to inform previous NICE appraisals (TA106 and TA200, Shepherd colleagues,[37] Hartwell and colleagues[1]) or both. The majority of these were originally sourced from a natural history study reported by Fattovich and

colleagues.[47] The model developed for the CS contains two updates compared with models reported in previous appraisals.[3 2] These are:

- that patients undergoing an SVR from the compensated cirrhosis state remain at higher risk of HCC than those who underwent SVR from the mild or moderate CHC states the general population who have not experienced CHC. This transition probability was sourced to a study published by Cardoso and colleagues.[46] As with previous models the CS assumes that those who undergo SVR from the mild or moderate CHC states face the same risk of HCC as the general population who have not experienced CHC;
- that patients who undergo SVR are at risk of re-infection with CHC (at a constant probability of 0.01), based on expert opinion.

The ERG have identified a recent large study (Bruno and colleagues[50]) of the incidence of HCC in cirrhotic patients, with and without SVR. This study included only patients with cirrhosis, whereas Cardoso and colleagues included both patients staged at F3 and F4. In addition the duration of follow up and sample size was larger in the study reported by Bruno and colleagues. The ERG suggest this may be a better source for populating the model with these transition probabilities and test the impact of using these data, on the cost effectiveness results, in additional analyses.

Adverse events

The health effects of adverse events associated with each of the regimens are included in the economic model as incidences. The adverse events included in the model are: anaemia, neutropenia, thrombocytopenia, rash and depression. The adverse event incidences are drawn from the same sources as the SVRs (see Table 38). The CS is not explicit regarding the grade of included adverse events included in the model.

Superseded- see Erratum

Table 38 Summary of sources of adverse event data used in economic model by patient population and treatment regimen

Regimen	Genotype	Source
GT1 treatment-naive patients		
3D	1a	SAPPHIRE I[23] and PEARL IV[25] trials for patients with mild or moderate fibrosis. TURQUOISE II trial[17] for patients with compensated cirrhosis [a b]
	1b	PEARL III trial trials for patients with mild or moderate fibrosis. TURQUOISE II trial[17] for patients with compensated cirrhosis [a b]
Sofosbuvir+PegIFN+RBV	1	NEUTRINO trial.[40 a c]
Telaprevir+PegIFN+RBV	1	ADVANCE RCT[28], ILLUMINATE RCT[51 a d]
Boceprevir+PegIFN+RBV	1	SPRINT-2 RCT[41 a]
PegIFN+RBV	1	ADVANCE RCT[28], ILLUMINATE RCT[51 a d]
GT1 treatment-experienced patients		
3D	1a	SAPPHIRE II trial[24] trial for patients with mild or moderate fibrosis. TURQUOISE II trial[17] for patients with compensated cirrhosis [a b]
	1b	PEARL II trial[21] trial for patients with mild or moderate fibrosis. TURQUOISE II trial[17] for patients with compensated cirrhosis [a b]
Telaprevir+PegIFN+RBV	1	REALIZE RCT[30], Kauffman and colleagues[51 d]
PegIFN+RBV	1	REALIZE RCT[30], Kauffman and colleagues[51]
Boceprevir+PegIFN+RBV	1	RESPOND-2 RCT[42 e]
GT4 treatment-naive patients		
2D	4	PEARL I trial[22 a]
Sofosbuvir+PegIFN+RBV	4	NEUTRINO trial.[40 a c]
PegIFN+RBV	4	Use values reported for GT1 in ADVANCE RCT[28], ILLUMINATE RCT[51 a d]
GT4 treatment-experienced patients		
2D	4	Use values reported for GT4 treatment-naive from PEARL I trial[22]

[a] Includes Grade 3 and 4 adverse events for neutropenia and thrombocytopenia. Not explicit regarding grade/ severity of other adverse events
[b] assume value of zero for depression, where this adverse event was not reported
[c] Adverse events reported for all genotypes – not specific to GT1 or GT4
[d] This source appears to be a report of a conference presentation, including copies of slides from the presentation. Proportion of patients with neutropenia and thrombocytopenia in two telaprevir trial arms were combined in this report. CS has imputed adverse events based on the proportion of patients in the relevant arm of the trial
[e] thrombocytopenia not reported – CS assumed value of zero

4.2.5 Patient outcomes

The economic model incorporates the effect of treatment on HRQoL as utilities associated with the different health states in the model (reported in Table 100, page 285 to 286 of the CS) and accounts for the adverse impact of treatment by applying treatment-specific utility decrements (reported in Tables 109, 110, 111 and 112 on pages 354 to 357 of the CS). The description of the use of HRQoL data in the model is presented in section 7.4.9 of the CS (pages 355 to 358). The measurement of health benefits in the model is consistent with previous models undertaken in HCV (see Table 39).

The CS briefly reviews evidence on key determinants of HRQoL in chronic HCV patients (using information on HRQoL (EQ-5D) and fibrosis level from the Mild Hepatitis C Trial[4]) indicating that HRQoL declines with increasing degree of liver fibrosis, but that chronic HCV is also associated extra-hepatic symptoms including depression, fatigue and sexual dysfunction. [52;53] The CS also presents EQ-5D-5L data (with utilities derived using the UK cross-walk to EQ-5D-3L) collected during their own clinical trials (baseline and end-of treatment values for each trial (by degree of fibrosis at baseline) reported in Table 104 and 105, pages 294 to 296). The CS indicates that the baseline and end-of treatment utility values were used to estimate on-treatment utility decrements. It is not clear whether this end-of–treatment assessment refers to scheduled or actual end-of-treatment – if it is the former, then the on-treatment disutility is likely to be under-estimated as observations would be missing for patients who prematurely discontinued (including those who discontinued due to adverse events). The CS states (on the top of page 295) that no imputation was performed for missing values, but does not report how many values were missing for each trial.

The CS reports a systematic search for HRQoL studies reporting utility for health states included in the model. Searches were conducted as an update of the review reported by Hartwell and colleagues,[1] using MEDLINE (and MEDLINE in-process), EMBASE, NHS EED and EconLit with a start date of 1st January 2009. The eligibility criteria for the review appear reasonable to the ERG. The searches identified 1,036 references (894 after de-duplication) of which 839 were excluded on the basis of title and abstract and 18 were excluded on the basis of full-text assessment. Of the remaining 37 studies, 31 studies were excluded from further consideration as they were not primary studies but sourced utility values from literature published prior to 2009. None of the remaining studies were considered suitable as sources for updating utilities in the model. Four had questionable applicability to the UK (studies from Asia, Brazil and Canada), while the remaining three studies did not report utilities by relevant health states or included patients on opioids. The CS concludes on the basis of this review that there are no significant sources of utility data for use in the model published since the UK Mild Hepatitis C trial[4] (see page 352 of CS).

Health state utilities applied in the model are reported in Table 39. These were derived using patient responses to EQ-5D in the UK Mild Hepatitis C trial[4] and valued using the UK general population tariff.[54]

Table 39 Baseline health state utilities and sources

Health-state	Utility	Source
Mild HCV	0.77	Wright et al 2006[4]
Moderate HCV	0.66	Wright et al 2006[4]
Compensated cirrhosis	0.55	Wright et al 2006[4]
Recovered (no HCV, history of mild fibrosis)	0.82	Calculated – add 0.05 to utility for mild HCV
Recovered (no HCV, history of moderate fibrosis)	0.71	Calculated – add 0.05 to utility for moderate HCV
Recovered (no HCV, history of compensated cirrhosis)	0.60	Calculated – add 0.05 to utility for CC
Decompensated cirrhosis	0.45	Wright et al 2006[4]
Hepatocellular carcinoma	0.45	Wright et al 2006[4]
Liver transplant	0.45	Wright et al 2006[4]
Post-liver transplant	0.67	Wright et al 2006[4]

Method and values for estimating post-SVR utility derived from Wright et al 2006[4]

Superseded- see Erratum

On-treatment utility decrements are applied to the state-specific utilities while patients are in treatment-eligible health states, for the duration of treatment – as a result these treatment-specific utility decrements are only applied during the first year (first cycle) of the model. On-treatment disutilities for comparator technologies were extracted from previous company submissions to NICE (where available),[6 5 7] with different utility decrements applied for treatment-naïve or treatment-experienced patients. These are summarised in Table 109 of the CS (page 354).

On-treatment disutilities for 3D and 2D are reported in Table 110 (page 354-355) of the CS. Separate values by fibrosis stage, genotype sub-group, previous treatment experience and duration of treatment are reported in Table 110, and in Table 111 (page 356) of the CS. The CS does not discuss the reasoning behind estimating different disutilities for each fibrosis stage or genotype sub-group or appear to consider the clinical meaningfulness or statistical plausibility of the differences identified. Furthermore the CS does not discuss the plausibility of including positive values (i.e. an assumption which appears to apply for a number of the groups that patients are better on-treatment than off it) – for example GT1b patients with mild and moderate fibrosis have positive utility decrements while on-treatment as do GT4 patients with mild and moderate fibrosis. The ERG is concerned that the utility decrements

used in the CS have been derived as the difference between baseline and end-of-treatment utility scores, and do not appear to have taken any account of improvement in HRQoL that may have occurred as a result of patients' response to treatment. This would render these values of questionable validity as measures of on-treatment disutility (related to the side effects of treatment) and risks double-counting the HRQoL gain associated with SVR. Basing the disutility measure on responses at end of treatment is likely to miss patients who have discontinued treatment due adverse effects of treatment, although this is less likely to be a significant problem for 3D and 2D since few patients discontinued treatment in the trials. As a result the ERG feel that the disutilities applied in the model for 3D and 2D are likely to be under-estimates.

4.2.6 Resource use

The CS reports systematic searches for relevant resource data in section 7.5.3 of the CS (pages 365 to 376). Searches were conducted as an update of the review reported by Hartwell and colleagues,[1] using MEDLINE (and MEDLINE in-process), EMBASE, NHS EED and EconLit with a start date of 1st January 2009 and an end date of 2nd April 2014 (full details are presented in Appendix 13 of the CS). The eligibility criteria for the review appear reasonable to the ERG. The search was conducted approximately eight months prior to the submission of the CS and the ERG suggests it may have been appropriate to conduct update searches prior to submission. The ERG conducted an update search, but found no new studies that would have been included in the review. The searches identified 1,386 references (1,109 after de-duplication) of which 1,093 were excluded on basis of title and abstract and 8 were excluded on the basis of full-text assessment. The remaining 8 studies (including two publications arising from the review undertaken by Hartwell and colleagues[1;55]) were summarised in two tables (CS Table 116 for cost-effectiveness studies and CS Table 117 for resource use studies). However the CS does not present a quality assessment of these publications or any discussion of their relevance to the decision problem, other than a column in Table 116 headed "Applicability", with an explanatory note that this was assessed according to study setting, perspective, population and interventions. It is not clear what this assessment would add, given that the eligibility criteria listed in Table 115 of the CS state that included studies had to be based on a population of adults with GT1 HCV (excluding chronic hepatitis B co-infection and substance dependent or illegal drug users), including only the specified intervention or comparators, and would have a UK perspective.

The CS states in section 7.5.6 (pages 389 to 390) that health state costs were based on two sources[1;56] without offering substantial justification for use of these sources. The first reference (Hartwell and colleagues[1]) was used to derive health state costs for mild chronic HCV, decompensated cirrhosis, hepatocellular carcinoma and liver transplant health states. These costs were uprated to 2102/13 prices using the HCHS Pay and Prices Index.[57] The second reference (Backx and colleagues[56]) was not reviewed in any detail. Its use in the model is justified in the CS as "a more recent and relevant source than Hartwell et al". Health state costs for moderate fibrosis, compensated cirrhosis and the recovered (SVR) states are all taken from this second source.

The CS does not explicitly state assumptions over dosing, frequency, or location of treatments that underlie the acquisition costs of the intervention or comparators. Table 118 in the CS documents derivations of assumed cost per day for all the component medications including intervention or comparator treatment regimes. However the CS does not provide summary estimates (per day, per week or per treatment course) for any of the included treatment regimes. It is particularly unclear regarding the dosage of RBV included in any treatment regimen (including the 3D and 2D regimens where appropriate). Table 40 indicates the ERG's understanding of the dosing included in the model and typical treatment durations as indicated in the SmPCs for comparator interventions. Although no explicit assumptions were provided for the resource use, the doses used in the model (in terms of dose per day or per week) appear to be consistent with those in the trials providing evidence of clinical effectiveness.

Table 40 Dosage of comparator treatments included in the model

Sofosbuvir+PegIFN+RBV	**Sofosbuvir**	**PegIFN**	**RBV**
Standard dosing	400mg per day for 12 weeks	1 per week for 12 weeks	1200mg per day for 12 weeks
Boceprevir+PegIFN+RBV	**Boceprevir**	**PegIFN**	**RBV**
Standard dosing	2400mg per week (weeks 5 to 48)	1 per week for 48 weeks	1200mg per day for 48 weeks
Response guided (treatment-naïve) [a]	2400mg per week (weeks 5 to 28)	1 per week for 28 weeks	1200mg per day for 28 weeks
Response guided (previously-treated) [b]	2400mg per week (weeks 5 to 36)	1 per week for 48 weeks	1200mg per day for 48 weeks
Telaprevir+PegIFN+RBV	**Telaprevir**	**PegIFN**	**RBV**
Standard dosing	2250mg per week (weeks 1 to12)	1 per week for 48 weeks	1200mg per day for 48 weeks
Non-cirrhotic treatment-naïve/ prior relapsers [c]	2250mg per week (weeks 1 to12)	1 per week for 24 weeks	1200mg per day for 24 weeks

[a] Treatment-naïve patients, who do not have cirrhosis, are eligible for response-guided treatment with Boceprevir+PegIFN+RBV if they have undetectable HCV RNA at week 8 and week 24. Response-guided treatment involves reducing duration of treatment to 28 weeks.
[b] Treatment-experienced patients, who do not have cirrhosis, are eligible for response-guided treatment with Boceprevir+PegIFN+RBV if they have undetectable HCV RNA at week 8 and week 24. Response-guided treatment involves stopping boceprevir at week 36 but continuing PegIFN+RBV to week 48.
[c] Treatment-naïve patients and those who relapsed following response to prior treatment, who do not have cirrhosis, are eligible for response-guided treatment with Telaprevir+PegIFN+RBV if they have undetectable HCV RNA at weeks 4 and 12. Response-guided treatment involves reducing duration of treatment with PegIFN+RBV to 24 weeks.

The ERG is concerned about the approach taken to estimating drug acquisition costs in the CS. As noted above, the CS provides estimates of drug acquisition costs per day – even in cases, such as PegIFN, where the drug is administered weekly. The ERG is concerned that this approach may give rise to some unrealistic assumptions regarding drug wastage. The model estimates of medication consumption are derived from a combination of the estimated daily consumption and the average duration of treatment reported from the trial. However it is likely that patients will be provided with supplies of medication at each secondary attendance for monitoring – as a result patient consumption patterns are more likely to reflect the pattern of routine monitoring visits than a continuous distribution over time (as implied by the approach taken in the CS).

Resources used for on-treatment monitoring were taken from Shepherd and colleagues.[37] The CS reports that these assumptions were validated by an advisory board (described in section 7.3.5 of the CS, page 282) as were additional assumptions regarding monitoring in shortened PegIFN-containing regimes and in PegIFN-free regimes.

Resource use for management of adverse events were based on assumptions reported by Thorlund and colleagues[58] in a budget impact analysis of boceprevir and telaprevir for treatment of GT1 HCV infection. This reference was identified in the resource use searches reported in section 7.5.3 of the CS. While limited information from the study is tabulated in the CS there is no reported assessment of the quality or relevance of this source. The CS further states that assumptions for costing depression treatment and monitoring were based on NICE GC90: Depression in adults.[59]

4.2.7 Costs

Costings for the model were estimated using an NHS and PSS perspective and include drug acquisition costs, monitoring costs, disease progression (health state) costs and adverse event costs.

Drug acquisition costs

Unit costs for 3D and 2D included in the CS (see Table 118, page 377 to 378 of the CS) are attributed to the company as data on file. Since submission of the CS the same prices for 3D and 2D have been reported in MIMS[60] and are summarised here in Table 41 along with the comparator unit costs, also sourced from MIMS.[60] The cost of a 56 tablet packet of ombitasvir/ parataprevir /ritonavir (equivalent to four weeks supply) is £10,733.33. The cost of a 56 tablet packet of dasabuvir (equivalent to four weeks supply) is £933.33, making the total cost of 12 weeks treatment with 3D come to £34,999.98 and 12 weeks treatment with 2D costs £33,164.13. The additional cost of RBV where this is required is approximately £1,000 over 12 weeks. The CS presents these estimates in Table 21 (page 32) without including the additional costs of RBV.

Table 41 Cost per week of component treatments of intervention and comparators

	Cost per pack (£)	Quantity / pack	Unit dose	Frequency	Cost / week (£)
2D (Viekirax)	10,733.33	56	125/75/50mg	2 per day	2,683.33
3D (Exviera)	933.33	56	250 mg	2 per day	233.33
Sofosbuvir	11,660.98	28	400 mg	1 per day	2,915.25
Simeprevir	1,866.50	7	150mg	1 per day	1,866.50
Boceprevir	2,800.00	336	200mg	12 per day	700.00
Telaprevir	1,866.50	42	375	6 per day	1,866.50
PegIFN (Pegasys)	497.60	4	180µg/ 0.5ml	1 per week	124.40
PegIFN (VirferonPeg)	199.38	1	150µg prefilled pen	1 per week	199.38
RBV (Copegus)	92.50	42	200 mg	6 per day	92.50
RBV (Rebetol)	160.69	84	200 mg	6 per day	80.35

Source: MIMS, Feb 2015[61]

The CS does not provide estimates of the total drug acquisition costs for comparator treatments. Table 42 below reports estimated drug acquisition costs over the standard treatment for all interventions and comparators included in the model.

Table 42 Drug acquisition costs

	Genotype	Fibrosis stage	Tx naïve/ experienced	Treatment duration (weeks)	Ombitasvir/ paritaprevir/ ritonavir	Dasabuvir	Ribavirin (1200mg/day)	Total cost
3D+RBV	GT1a	Non-cirrhotic	either	12	32,199.99	2,799.99	964.14	35,964.12
3D+RBV	GT1a	Cirrhotic	either	24	64,399.98	5,599.98	1,928.28	71,928.24
3D	GT1b	Non-cirrhotic	either	12	32,199.99	2,799.99		34,999.98
3D+RBV	GT1b	Cirrhotic	either	12	32,199.99	2,799.99	964.14	35,964.12
2D+RBV	GT4	Non-cirrhotic	either	12	32,199.99		964.14	33,164.13
2D+RBV	GT4	Cirrhotic	either	24	64,399.98		1,928.28	66,328.26
					Sofosbuvir	PegIFN	RBV	Total cost
Sofosbuvir+ PegIFN+RBV	GT1, GT4	Non-cirrhotic	either	12	34,983	1,493	1,110	37,586
Sofosbuvir+ PegIFN+RBV	GT1, GT4	Non-cirrhotic	either	12	34,983	2,393	964	38,340
					Boceprevir	PegIFN	RBV	Total cost
Boceprevir+ PegIFN+RBV	Any	Any	either	48	30,800	5,971	4,440	41,211
Response-guided treatment	Any	Non-cirrhotic	Naïve	28	16,800	3,483	2,590	22,873
Response-guided treatment	Any	Non-cirrhotic	Experienced	48	22,400	5,971	4,440	32,811
					Telaprevir	PegIFN	RBV	Total cost
Telaprevir+ PegIFN+RBV	Any	Any	either	48	22,398	5,971	4,440	32,809
Telaprevir+ PegIFN+RBV	Any	Non-cirrhotic	Naïve	24	22,398	2,986	2,220	27,604
Telaprevir+ PegIFN+RBV	Any	Non-cirrhotic	Prior relapser	24	22,398	2,986	2,220	27,604
						PegIFN	RBV	Total cost
PegIFN+RBV	GT1,GT4	Any	either	48		5,971	4,440	10,411
PegIFN+RBV	GT1,GT4	Any	either	48		9,570	3,857	13,427

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Monitoring costs

Resource use for monitoring patients on PegIFN-containing regimes was taken from protocols developed and reported by Shepherd and colleagues.[37] Unit costs applied to these resource estimates were taken directly from Shepherd and colleagues (inflated to 2012/13 costs using the HCHS Pay and Prices Index[57]) for biochemical and pathology tests or while unit costs for staff time were taken from the Unit Cost of Community Care.[57]

Health state costs

Health state costs were sourced from two references identified in the systematic searches reported in section 7.5.3 of the CS. As stated previously, the CS does not provide any discussion of the quality of these sources or offer any substantial justification for using these sources.

Table 43 Key health state costs

Health state	Cost (£) (2012/13 prices)	Source
SVR from mild chronic HCV	58	Backx and colleagues [56]
SVR from moderate chronic HCV	58	Backx and colleagues [56]
SVR from CC	586	Backx and colleagues [56]
Mild chronic HCV	160	Hartwell and colleagues[1]
Moderate chronic HCV	589	Backx and colleagues [56]
Compensated cirrhosis	914	Backx and colleagues [56]
Decompensated cirrhosis	12,333	Hartwell and colleagues[1]
HCC	10,990	Hartwell and colleagues[1]
Liver transplant	49,749	Hartwell and colleagues[1]
Post-liver transplant	1,873	Hartwell and colleagues[1]

Adverse event costs

Adverse event costs applied in the model include the costs of drugs used to treat adverse events, costs of out-patient visits and appointments in primary care. These are presented in Table 124 on page 390 to 391 of the CS. Resource use assumptions and unit costs for treatment of anaemia and rash were taken directly from the reference by Thorlund and colleagues[58] while resource use assumptions and unit costs for treatment of depression were taken from NICE clinical guideline GC 90. Resource use assumptions and unit costs for

treatment of neutropenia and thrombocytopaenia were taken from the company submission for the Sofosbuvir STA.[6]

4.2.8 Consistency/ Model validation

The ERG has examined the submitted electronic model for internal and external consistency and accuracy. Random checking has been done for some of the key equations of the model although this has not been a comprehensive 'checking' process of all cells in the model.

Internal consistency

The CS contains limited information on assessment of the model's technical and internal validation. While the CS suggests that a process of checking the model for potential programming errors was followed, no detail is provided on how this was undertaken. Similarly, while the CS states that "routine tests" were conducted yielding "expected results", no detail is provided on what those might have been, what the expected results might be nor on any remedial action that might have been required should any anomalies be detected. The CS also states that an independent modelling team at an academic institution conducted further validation checks.

External consistency

The CS reports limited assessment of the external consistency of the model outputs, comparing the cumulative compensated cirrhosis estimates at a single point in time (20 years) predicted by the model if all patients had mild disease at baseline and were not treated, against a range of estimates reported in the literature. The cumulative compensated cirrhosis estimate at 30 years is also compared against the estimate reported by Wright and colleagues.[4]

The CS does not appear to have attempted to compare the cost, QALY or cost effectiveness estimates for comparators output by their model against results reported in the literature or in previous NICE appraisals. For example, it does not compare the results obtained for comparators from their model against the cost effectiveness results identified and reviewed in section 7.1.2 of the CS.

4.2.9 Assessment of Uncertainty

One-way sensitivity analyses

The CS reports the results of nine deterministic sensitivity analyses (DSA). These include:

- four DSA for GT1 treatment-naive IFN-eligible patients: one for each comparator (Sofosbuvir+PegIFN+RBV, telaprevir+PegIFN+RBV, boceprevir+PegIFN+RBV, PegIFN+RBV) compared with ombitasvir/paritaprevir/ritonavir
- two DSA for GT1 treatment-experienced IFN-eligible patients: one for each comparator (telaprevir +PegIFN+RBV, PegIFN+RBV) compared with ombitasvir/paritaprevir/ritonavir
- two DSA for GT4 treatment-naive IFN-eligible patients: one for each comparator (Sofosbuvir+PegIFN+RBV, PegIFN+RBV) compared with ombitasvir/paritaprevir/ritonavir
- one DSA for GT4 treatment-experienced IFN-eligible patients: for best supportive compared with ombitasvir/paritaprevir/ritonavir

The parameters of 49 one-way sensitivity analyses, which are common to all comparisons, are presented in Table 128 (page 397 to 398) of the CS. While the majority of the DSA are truly one-way analyses (varying one parameter value, while holding all others constant), some involve varying at least two inputs simultaneously (for example treatment-related attributes such as SVR or rate of AE are varied for both intervention and comparator in a single DSA). Methodological assumptions (such as alternative choice of discount rate) and variation in baseline assumptions (such as mean cohort age and distribution across stage of fibrosis) have not been included in the DSA, but are included in scenario analyses reported in the CS.

The ranges applied in the DSA are clearly stated in Table 128 and are based on a mixture of statistically derived measures of variation (such as standard errors or 95% confidence intervals) and arbitrarily defined ranges (±20%for utilities or ±50% for costs). No justification is provided for adopting particular limits when using arbitrary ranges in the DSA. Table 128 reports that SVRs and AE rates are varied using ±1.96 SD of base values. It is not clear from the CS whether this variation is based on standard deviation (as implied by the SD notation) or a standard error (which would be more appropriate if considering variation according to a 95% confidence interval. It is also unclear from the CS where the SD has been calculated from as tables reporting the SVRs used in the model report number of responders and total number of

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patients. Given these data are available it might have been more appropriate to draw the DSA limits for SVRs from beta distributions, parameterised using the numbers of responders and non-responders in the included trials. Results of the DSAs are presented as tornado diagrams (section 7.7.7, Figures 29 to 37, pages 413 to 422 of the CS).

Health state utilities (in particular for the recovered health state with history of mild or moderate fibrosis) appear to be influential on the cost effectiveness estimates across all DSA. Overall variation in certain of the utility values was more influential on cost effectiveness results than was variation in SVR.

Variation in SVR seemed to more influential in the DSA comparisons of 3D with telaprevir+PegIFN+RBV and in the comparison of 2D with sofosbuvir+PegIFN+RBV.

The CS does not provide a narrative overview or discussion alongside each DSA or for each genotype-treatment history comparison, but offers a summary and conclusion in Section 7.7.10 stating that the incremental cost/QALY results [are] most sensitive to utility values for progressive disease states and their associated recovered states.

Scenario Analysis

The MS reports the results of twenty one scenario analyses examining the impact on the ICER (relative to a common baseline, such as PegIFN+RBV for GT1 treatment-naive IFN-eligible patients). The scenario analyses are presented as tabulations (up to four tables for each scenario, resulting in a total of 39 tables) with no accompany narrative or discussion. As a result it very difficult to interpret what the scenario analyses show. Since a number of the scenario analysis involve varying individual or groups of input parameters between pre-defined ranges the ERG feel that some of these analyses would be better presented graphically, as with the tornado diagrams for the DSA. It might also be easier to interpret the scenario analyses if the CS indicated some form of priority for the analyses – for example, which of the three scenario analyses using different efficacy estimates for PegIFN+RBV (14-16) might represent the most reasonable alternative to the base case

The CS does not provide a summary or conclusion at the end of Section 7.7.9 (page 425 to 435 of the CS), which presents the scenario parameters included in the scenario analyses and

Superseded- see Erratum

tabulation of results, nor does it makes any reference to the output of the scenario analyses in Section 7.7.10 (page 436 of the CS) headed “What are the main findings of each of the sensitivity analyses?”

Probabilistic Sensitivity Analysis

The CS reports results from four PSA: one for each patient population defined by genotype and prior treatment history, considered in the base case (see Section 7.7.8, page 422 to 425 of the CS). Each PSA is based on 500 iterations of the model and takes approximately three and a half minutes to run on a computer with 3.4 GHz quad core processor and 16 Gb memory. For a full analysis, including multiple CEACs the analysis runs for approximately fourteen minutes. The CS does not discuss or provide a rationale for the decision to run 500 simulations for the PSA. For each patient population the CS presents multiple CEACs, for ceiling ratio values between £0 and £100,000 per QALY gained, and reports willingness-to-pay ranges over which 3D or 2D or selected comparators are deemed cost effective. The mean costs, QALYs and ICER arising from the PSA runs are not reported.

Distributions used in PSA for natural history transition probabilities, health state costs, monitoring costs, AE treatment costs and health state utilities are given in Table 129 (page 400 to 402) of the CS. Text in section 7.6.3 (page 398 to 402) of the CS states that SVRs and adverse event rates were sampled from beta distributions that were parameterised using percentage SVR/AE, and the estimated standard error.

The ERG re-ran the PSA to derive the mean costs, QALYs and ICER arising from the PSA runs to compare with the deterministic base case results (see Table 44 for GT1, treatment-naive, interferon-eligible patients and Table 45 for GT1, treatment-experienced, interferon-eligible patients).

Table 44 ERG replication of PSA reported in CS for GT1, treatment-naive, interferon-eligible. Mean total cost and QALY estimates by regimen

Regimen	Total cost		Total QALYs	
	Mean	Median (percentile-based 95% CI)	Mean	Median (percentile-based 95% CI)
Best supportive care	19,632	19,393 (14,435 - 26,591)	12.82	12.87 (11.51 - 13.99)
PegIFN+RBV	22,768	22,593 (19,262 - 27,386)	13.82	13.86 (12.48 - 14.96)
Boceprevir+ PegIFN +RBV	32,069	31,939 (29,259 - 35,990)	14.31	14.35 (13.01 - 15.45)
Telaprevir+ PegIFN +RBV	35,836	35,756 (33,483 - 39,136)	14.64	14.68 (13.32 - 15.81)
3D	43,581	43,416 (41,641 - 46,409)	15.29	15.35 (14.00 - 16.54)
Sofosbuvir+ PegIFN +RBV	44,293	44,158 (42,243 - 47,264)	15.09	15.14 (13.78 - 16.27)

Table 45 ERG replication of PSA reported in CS for GT1, treatment-experienced, interferon-eligible. Mean total cost and QALY estimates by regimen

Regimen	Total cost		Total QALYs	
	Mean	Median (percentile-based 95% CI)	Mean	Median (percentile-based 95% CI)
Best supportive care	24,264	23,999 (16,869 - 33,185)	10.9	10.86 (9.86 - 12.03)
PegIFN+RBV	30,151	29,997 (23,566 - 38,131)	11.16	11.15 (10.13 - 12.27)
Telaprevir+ PegIFN +RBV	42,579	42,469 (38,393 - 47,400)	12.21	12.21 (11.10 - 13.25)
3D	51,727	51,510 (48,330 - 55,777)	13.31	13.35 (12.01 - 14.36)

The results of the probabilistic evaluation of the model are consistent with the deterministic base case for GT1, treatment-naive and treatment-experienced, interferon-eligible patients presented in Tables 137 and 138 (page 411) of the CS (summarised in Table 29 of this report). Mean costs are slightly lower than total costs in the deterministic base case, while mean QALYs are slightly higher than in the deterministic base case. The rank order of interventions (in terms of increasing effectiveness) is the same and ICERs calculated at the mean cost and QALYs, from the probabilistic analysis, are similar to those reported in the base case analysis (see Table 46).

Table 46 ERG replication of PSA for GT1 interferon-eligible patients. ICERs calculated at mean cost and QALYs and mean ICERs compared with PegIFN+RBV

Regimen	Treatment-naive		Treatment-experienced	
	ICER at mean cost and QALYs	Mean ICER	ICER at mean cost and QALYs	Mean ICER
PegIFN+RBV	NA	NA	NA	NA
Boceprevir+ PegIFN +RBV	18,430	19,554	NA	NA
Telaprevir+ PegIFN +RBV	15,929	16,541	11,895	12,660
3D	14,039	14,364	10,033	10,614
Sofosbuvir+ PegIFN +RBV	16,776	17,176	NA	NA

Table 47 and Table 48 report the results of the PSA for GT4, treatment-naive, interferon-eligible and GT4, treatment-experienced, interferon-eligible patients, respectively. As with GT1 patients, the results of the probabilistic evaluation of the model are consistent with the deterministic base case for non-cirrhotic, interferon-eligible, GT4 patients presented in Tables 139 and 140 (pages 411 to 412) of the CS (summarised in Table 29 of this report). Mean costs are slightly lower than total costs in the deterministic base case, while mean QALYs are slightly higher than in the deterministic base case. The rank order of interventions (in terms of increasing effectiveness) is the same and ICERs calculated at the mean cost and QALYs, from the probabilistic analysis, are similar to those reported in the base case analysis (see Table 49).

Table 47 ERG replication of PSA reported in CS for GT4, treatment-naive, interferon-eligible. Mean total cost and QALY estimates by regimen

Regimen	Total cost		Total QALYs	
	Mean	Median (percentile-based 95% CI)	Mean	Median (percentile-based 95% CI)
Best supportive care	16,946	16,840 (12,770 - 22,101)	13.40	13.40 (12.23 - 14.60)
PegIFN+RBV	19,104	18,937 (17,103 - 21,681)	15.04	15.02 (13.80 - 16.35)
3D	36,386	36,288 (35,001 - 38,481)	15.87	15.86 (14.57 - 17.25)
Sofosbuvir+ PegIFN+RBV	41,127	41,026 (39,734 - 43,250)	15.83	15.83 (14.53 - 17.21)

Table 48 ERG replication of PSA reported in CS for GT4, treatment-experienced, interferon-eligible. Mean total cost and QALY estimates by regimen

Regimen	Total cost		Total QALYs	
	Mean	Median (percentile-based 95% CI)	Mean	Median (percentile-based 95% CI)
Best supportive care	16,148	15,974 (12,135 - 21,488)	12.62	12.60 (11.55 - 13.64)
3D	36,504	36,409 (35,214 - 38,307)	14.84	14.86 (13.67 - 15.97)

Table 49 ERG replication of PSA for non-cirrhotic GT4 interferon-eligible patients. ICERs calculated at mean cost and QALYs and mean ICERs

Regimen	Treatment-naive[a]		Treatment-experienced[b]	
	ICER at mean cost and QALYs	Mean ICER	ICER at mean cost and QALYs	Mean ICER
3D	20,947	21,468	9,164	9,363
Sofosbuvir+ PegIFN +RBV	27,928	28,657	NA	NA

[a] ICERs for treatment-naive patients are calculated for each regimen compared with PegIFN+RBV
[b] ICERs for treatment-naive patients are calculated for each regimen compared with best supportive care

The ERG is concerned with the approach taken to including SVR for patients with mild and moderate fibrosis in the model when trials have only reported the SVR proportion for the population combined. When the SVR proportion has been included for the combined population the model uses the combined population for calculating the standard error – which gives an incorrectly small confidence interval, hence will underestimate the amount of variability around these estimates in the PSA. While this is likely to have a small influence it would be expected under-estimate the degree of variability in the model. The ERG assesses the impact of this in the additional analyses.

The CS, and the associated economic model, makes no allowance for the methodological uncertainty underlying the approach adopted to comparing alternative treatment using unadjusted indirect comparisons. Uncertainty included in the probabilistic model only accounts for statistical uncertainty in the derivation of the individual SVR and adverse event rate estimates. It would be appropriate to incorporate some additional measure of uncertainty to take account of this – although it is not clear how this might best be achieved. The ERG suggests an alternative approach to reduce this methodological uncertainty in the majority of the comparisons in the model would be to:

- conduct a network meta-analysis for comparators included in the model
- conduct an external validation of this model using cost effectiveness results reported in previous NICE appraisals and in the published literature
- introduce 3D and 2D into this model, using observed data from the relevant trials and allow for an additional degree of methodological uncertainty arising from the use of an unadjusted indirect comparison for this intervention.

The ERG further notes that the MALACHITE trials including 3D in a head-to-head comparison with telaprevir+PegIFN+RBV provide direct evidence, for non-cirrhotic patients. Including the results of these trials in the analysis would allow a limited cost effectiveness analysis to be conducted using head-to-head comparative data, and would also provide the links required to include 3D in a network meta-analysis which could include the majority of comparators identified in the NICE scope. The ERG investigates the feasibility of these options in the additional analyses presented in this report.

The CS does not report any overall summary from the PSA other than to present multiple CEAC charts derived from probabilistic evaluations of the model for each population of interferon-eligible patient and to state the WTP ranges where 3D or 2D would be the optimal choice.

4.2.10 Comment on validity of results with reference to methodology used

The economic model captures most of the important aspects of the disease pathway. The model extrapolates intermediate outcomes to final outcomes in a consistent manner, drawing upon standard sources from the literature, and has updated transition probabilities within the natural history model where more appropriate sources have become available. The CS has briefly reviewed the literature and provided a justification for extrapolating final from intermediate outcomes.

A number of imputations or assumptions have been required to populate the model, including imputation of SVR by stage of fibrosis, by genotype sub-groups or for other sub-groups of larger populations (such null and partial responders and relapse following previous treatment among the treatment-experienced population). In some cases this has relied on data from very small sub-groups of patient populations and conducting analyses for which the original studies were not powered. In addition the economic model has not taken account of the additional uncertainty that these imputations have introduced.

The major concern regarding the analyses undertaken in the model and presented in the CS is the use of unadjusted indirect comparison. The CS provides a justification for not conducting indirect comparisons based on a network of evidence (given the design of the 3D and 2D trials). However the analysis conducted within the model makes no additional allowance for the uncertainty introduced by conducting this form of comparison.

4.3 Additional work undertaken by the ERG

The ERG undertook additional work to:

a) include SVR data from head-to-head comparisons of 3D and telaprevir+PegIFN+RBV

b) re-run PSA using fibrosis stage-specific SVRs (mild and moderate fibrosis stages) from 3D trials rather values pooled across fibrosis stages

c) re-run the base case analysis adjusting effectiveness of boceprevir+PegIFN+RBV

d) re-run the base case analysis including simeprevir+PegIFN+RBV

e) re-run base case analysis (for non-cirrhotic patients) using an adjusted indirect comparison – to include PegIFN+RBV and boceprevir+PegIFN+RBV in addition to 3D and telaprevir+PegIFN+RBV

f) conduct a threshold analysis on relative effectiveness (SVR) for 3D and 2D

g) present a scenario using an alternative estimate of the risk of HCC for those patients who underwent SVR from the compensated cirrhosis health state

h) present a scenario using an alternative estimate for the risk of HCC for those in the compensated cirrhosis health state

i) combine scenario g) and h)

a) analysis using head-to-head data on SVR for 3D vs telaprevir+PegIFN+RBV using data from the MALACHITE trials

The ERG undertook additional analysis using data on SVR for 3D vs telaprevir+PegIFN+RBV from the MALACHITE I and MALACHITE II trials (head-to-head, randomised, open-label trials comparing 3D with or without RBV with telaprevir+PegIFN+RBV in non-cirrhotic GT1 treatment-naïve and treatment-experienced patients), provided by the company in response to the ERG and NICE request for clarification (response A9.2). The trials are on-going and did not form part of the evidence in the original CS and were not included in the company's electronic model. However the company response states that primary endpoint data were released at the end of December 2014 and are planned for presentation at EASL in April 2015.

Since the trials excluded cirrhotic patients, the results from these analyses are not directly comparable to the base case results from the model, reported in the CS for patients at all stages of fibrosis (mild, moderate CHC and cirrhosis). However the model includes an option to restrict the base case to non-cirrhotic patients only.

The ERG re-ran the base case analysis for non-cirrhotic patients using data from the CS unadjusted indirect comparison of 3D versus telaprevir+PegIFN+RBV and using the SVRs reported from the MALACHITE trials (see Table 50 and Table 51 for the results of the deterministic analyses). The results of the two pairs of analyses are very similar, reflecting the similarity in SVRs reported in the MALACHITE trials for 3D and telaprevir+PegIFN+RBV and the SVRs used to populate the model in the company's base case.

Table 50 ERG analysis using SVRs from MALACHITE I trial: GT1 non-cirrhotic treatment-naive, interferon-eligible patients

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Original model SVRs (unadjusted indirect comparison)					
Telaprevir+ PegIFN+RBV	33,748	15.16	NA	NA	NA
3D	39,556	15.77	5,808	0.61	9,521
MALACHITE I SVRs (direct comparison)					
Telaprevir+ PegIFN +RBV	33,799	15.14	NA	NA	NA
3D	39,553	15.77	5,754	0.62	9,212

Table 51 ERG analysis using SVRs from MALACHITE II trial: GT1 treatment-experienced, interferon-eligible patients

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Original model SVRs (unadjusted indirect comparison)					
Telaprevir+ PegIFN +RBV	35,402	13.90	NA	NA	NA
3D	39,173	14.78	3,771	0.88	4,287
MALACHITE II SVRs (direct comparison)					
Telaprevir+ PegIFN +RBV	35,397	13.93	NA	NA	NA
3D	38,959	14.81	3,562	0.88	4,036

The total costs, incremental costs and ICERs in this analysis are noticeably lower than in the base case analysis. This arises from two significant differences between the two analyses:

- as noted above the MALCHITE trials did not recruit cirrhotic patients. Costs in non-cirrhotic patients are likely to be lower since these patients are more likely to respond to treatment than are cirrhotic patients. Moreover, in a population that is not cirrhotic at baseline, fewer patients would be expected to progress to more advanced stages of liver disease over a given period of time. 3D costs will also be lower given that GT1a patients with cirrhosis are treated with 24 weeks of 3D, rather than 12 weeks;
- the incremental costs and ICERs for 3D in the base case analysis were derived from comparison with PegIFN+RBV, whereas in this analysis the incremental costs and ICERs for 3D were derived from comparison with telaprevir+PegIFN+RBV.

Table 52 below reports the drug acquisition costs, adverse events costs and health state costs for 3D and telaprevir+PegIFN+RBV in the base case and in this head-to-head comparison.

Table 52 ERG comparison of costs in base case and non-cirrhotic GT1 population

Regimen	Regimen cost	Adverse event costs	Health state costs
GT1 Treatment-naïve base case population			
telaprevir+PegIFN+RBV	25,499	425	9,963
3D	37,771	41	5,813
GT1 Treatment-naïve non-cirrhotic population			
telaprevir+PegIFN+RBV	25,499	425	7,875
3D	35,392	34	4,127
GT1 Treatment-experienced base case population			
telaprevir+PegIFN+RBV	26,487	397	15,762
3D	43,012	53	8,816
GT1 Treatment-experienced non-cirrhotic population			
telaprevir+PegIFN+RBV	26,487	397	8,518
3D	35,404	28	3,741

The company clarification responses did not report treatment duration, discontinuations or incidence of adverse events in the MALACHITE trials. As a result the model used in these analyses is populated with data from the ADVANCE and REALIZE trials for telaprevir+PegIFN+RBV and from the SAPPHIRE I, PEARL IV and TURQUOISE II trials for 3D, as in the CS base case analysis. As a consequence this analysis, while using the only available head-to-head data for 3D versus a comparator used in current standard practice, should be regarded as exploratory.

b) Re-run PSA using fibrosis stage-specific SVRs (mild and moderate fibrosis stages) from 3D trials rather than pooled values

The PSA reported in the CS used a pooled estimate (across the mild and moderate stages) for the SVR for GT1 treatment-naïve patients treated with 3D. The distribution sampled in the PSA was parameterised using the combined population for both the mild and moderate fibrosis states, which would tend to underestimate the amount of variability around these estimates in the PSA. The ERG noted that the model contained unpublished data from the CSRs for the SAPPHIRE I, PEARL IV and PEARL III studies, which reported the total number of mild and moderate patients and the numbers achieving SVR. These data can be selected for use in the model (using a drop-down menu). The PSA was re-run with these data selected and the results

are reported in Table 53. As anticipated, this had minimal impact on the cost effectiveness results in the PSA.

Table 53 ERG replication of PSA reported in CS for GT1, treatment-naive, interferon-eligible. Mean total cost and QALY estimates by regimen

Regimen	Total cost		Total QALYs	
	Mean	Median (percentile-based 95% CI)	Mean	Median (percentile-based 95% CI)
BSC	19,729	19,471 (14,506 - 26,057)	12.76	12.76 (11.54 - 13.95)
Sofosbuvir+ PegIFN +RBV	44,369	44,244 (42,374 - 47,373)	15.03	15.03 (13.75 - 16.28)
Telaprevir+ PegIFN +RBV	35,947	35,835 (33,557 - 39,374)	14.57	14.57 (13.36 - 15.79)
PegIFN +RBV	22,900	22,729 (19,396 - 27,508)	13.75	13.75 (12.52 - 14.89)
Boceprevir+ PegIFN +RBV	32,142	32,001 (29,201 - 35,957)	14.25	14.25 (13.06 - 15.43)
3D	43,686	43,476 (41,696 - 46,618)	15.23	15.24 (13.94 - 16.51)

c) Re-run base case analysis adjusting effectiveness of boceprevir+PegIFN+RBV

The ERG noted that the SVR for PegIFN+RBV in the SPRINT-2 trial,[28] from which the SVR for boceprevir+PegIFN+RBV used in the model was taken, was lower than that reported for PegIFN+RBV in the ADVANCE trial, [28] the source for SVRs used in the model for telaprevir+PegIFN+RBV and PegIFN+RBV. Since the model was populated on the basis of an unadjusted indirect comparison, this is likely to underestimate the effectiveness of boceprevir+PegIFN+RBV relative to PegIFN+RBV. The ERG compared the odds ratio for SVR with boceprevir+PegIFN+RBV compared with PegIFN+RBV based on the SPRINT-2 trial data (2.85) with the odds ratio implied by the data entered into the model (boceprevir+PegIFN+RBV from the SPRINT-2 trial compared with PegIFN+RBV ADVANCE trial, odds ratio=2.22).

To investigate the impact of this potential under-estimation the ERG calculated an SVR using the odds ratio derived from the SPRINT-2 trial data and the stage-specific SVRs for PegIFN+RBV from the ADVANCE trial (see Table 54).

Table 54 ERG analysis c) adjustment of SVR for boceprevir+PegIFN+RBV compared with SVR for PegIFN+RBV in ADVANCE trial[28]

Regimen	Fibrosis Stage	Model	Estimated using overall SVR odds ratio [c]
PegIFN+RBV	Mild	0.455 [a]	NA
	Moderate	0.435 [a]	
	Compensated cirrhosis	0.333 [a]	
Telaprevir+ PegIFN+RBV	Mild	0.813 [a]	0.760
	Moderate	0.716 [a]	0.745
	Compensated cirrhosis	0.619 [a]	0.654
Boceprevir+PegIFN+RBV	Mild	0.658 [b]	0.705
	Moderate	0.658 [b]	0.687
	Compensated cirrhosis	0.313 [b]	0.587

Notes:
[a] data taken directly from ADVANCE trial[28]
[b] data taken directly from Response Guided Treatment arm of SPRINT-2 RCT[41]
[c] SVRs in this column have been estimated by the ERG using PegIFN+RBV SVRs by stage applied in the current model (see column 3 of this table, headed "Model") and applying the following regimen-specific odds ratios (3.785 for telparevir+PegIFN+RBV vs PegIFN+RBV derived from overall response in ADVANCE RCT[28] 271/363 vs 158/361 and 2.847 for boceprevir+PegIFN+RBV vs PegIFN+RBV derived from overall response in Response Guided Treatment arm of SPRINT-2 RCT[41] 137/363 vs 233/368)

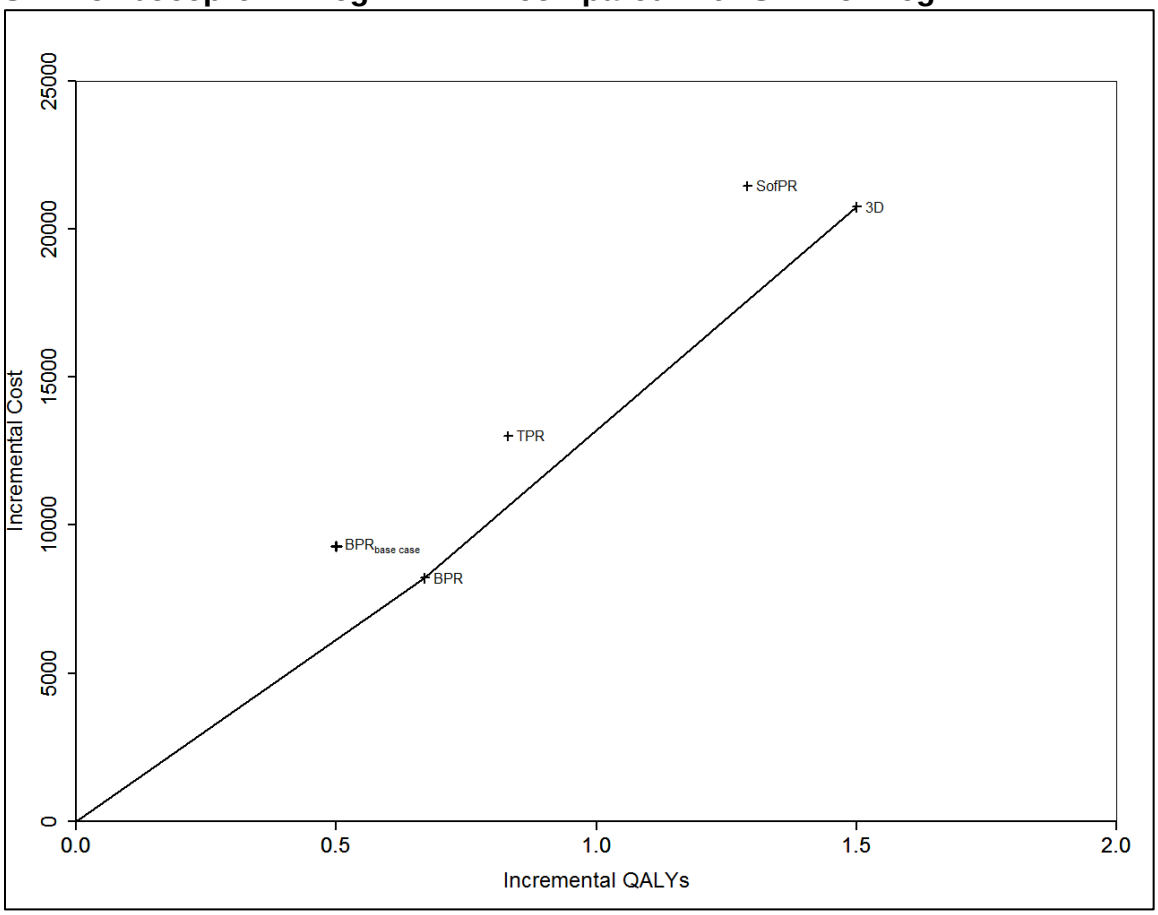
When these SVRs are included in the economic model the total costs for boceprevir+PegIFN+RBV are slightly reduced and the total QALYs slightly increased, to the extent that boceprevir+PegIFN+RBV is no longer extendedly dominated by 3D. The effect of this is that the ICER for 3D (now compared with boceprevir+PegIFN+RBV rather than PegIFN+RBV, which was the only non-dominated or non-extendedly-dominated comparator in the base case analysis) increases slightly from £13,864 in the base case analysis to £15,206 after adjusted the effectiveness of boceprevir+PegIFN+RBV in the indirect comparison (see Table 55).

Table 55 ERG analysis c) Cost effectiveness results for GT1 treatment-naive patients after adjustment of SVR for boceprevir+PegIFN+RBV compared with SVR for PegIFN+RBV

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PegIFN+RBV	22,872	13.72	NA	NA	NA
Boceprevir + PegIFN+RBV	31,085	14.39	£8,213	0.67	12,219
Telaprevir + PegIFN+RBV	35,887	14.55	Extended dominance		
3D	43,624	15.21	12,539	0.82	15,206
Sofosbuvir + PegIFN+RBV	44,337	15.01	Dominated		

The effect of this exploratory analysis is illustrated in Figure 2**.**

Figure 2 ERG analysis c) Base case cost effectiveness and effect of adjustment of SVR for boceprevir+PegIFN+RBV compared with SVR for PegIFN+RBV



d) re-run base case analysis including simeprevir+PegIFN+RBV

The company provided a justification for not including simeprevir+PegIFN+RBV in the model due to a lack of publicly available data on SVR by fibrosis stage, for patients who are Q80K negative, consistent with the data used to populate the model for other comparators. The ERG accept that these data are not available and that the CS could not undertake a robust cost effectiveness analysis without having access to these data. The ERG also note that the electronic model for the CS can be set to include simeprevir+PegIFN+RBV, using SVR data for the overall population Q80K negative and Q80K positive in the QUEST I[62] and QUEST II[63] trials.

The ERG reviewed the CS for simeprevir[43] and noted that, while the input data for the MTC reported in the CS for simeprevir were withheld, the odds ratio for SVR compared with PegIFN+RBV in the Q80K negative population is reported. The ERG have undertaken an exploratory analysis, similar to that presented for boceprevir+PegIFN+RBV (ERG additional analysis c) using the odds ratio for SVR with simeprevir+PegIFN+RBV compared with PegIFN+RBV and the stage-specific SVRs for PegIFN+RBV from the ADVANCE trial (reported in Table 35, in section 4.2.4 of this report).

The ERG updated the SVRs for simeprevir+PegIFN+RBV in the model and derived total cost and QALYs for this comparator as presented in Table 56. All other values in the table are as reported in the CS base case for this population.

Table 56 ERG analysis d) Cost effectiveness results for GT1 treatment-naive patients including simeprevir+PegIFN+RBV

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PegIFN+RBV	22,872	13.72	NA	NA	NA
Boceprevir + PegIFN+RBV	32,147	14.22	Extended dominance		
Telaprevir + PegIFN+RBV	35,887	14.55			
Simeprevir + PegIFN+RBV	36,304	14.69	13,432	0.97	13,786
3D	43,624	15.21	7,320	0.52	14,010
Sofosbuvir + PegIFN+RBV	44,337	15.01	Dominated		
Include note on what results are using overall data from trial (included in model) Simeprevir + PegIFN+RBV incremental costs 36,934 incremental QALYs 14.62					

Including simeprevir+PegIFN+RBV in the analysis, on the basis of the odds ratio reported in the CS for simeprevir has a small effect on the ICER for 3D, since simeprevir+PegIFN+RBV is not extendedly dominated (unlike telaprevir+PegIFN+RBV and boceprevir+PegIFN+RBV). The incremental cost and incremental QALYs for 3D are therefore calculated by comparison with simeprevir+PegIFN+RBV rather than PegIFN+RBV (in the base case).

e) re-run base case analysis (for non-cirrhotic patients) using adjusted indirect comparison

The ERG developed an exploratory adjusted indirect comparison, including PegIFN+RBV, telaprevir+ PegIFN+RBV, boceprevir PegIFN+RBV and 3D using SVRs for non-cirrhotic patients from the ADVANCE[28], SPRINT-2[41] and MALACHITE I trials. The method adopted was to estimate odds ratios for each regimen compared with PegIFN+RBV and was estimated using fixed effect logistic regression,[64] using the R software package[65] (glm). Table 57 shows the odds ratios for SVR, compared with PegIFN+RBV, and SVRs estimated for each regimen using the SVR for PegIFN+RBV from the ADVANCE[28] and the odds ratio from the meta-analysis.

Table 57 ERG analysis e) Odds ratios for SVR and estimated SVRs from ERG adjusted indirect comparison

Regimen	Odds ratio vs PegIFN+RBV (95% CI)		SVR
PegIFN+RBV	1.000		0.4441
TEL+PegIFN+RBV	3.844	(2.774 to 5.327)	0.7544
BOC+PegIFN+RBV	3.263	(2.382 to 4.472)	0.7228
3D	48.055	(12.885 to 179.222)	0.9746

Table 58 reports the base case cost effectiveness results for this patient population and using the SVRs derived using the adjusted indirect comparison. In the base case analysis, using SVRs from the unadjusted indirect comparison, both telaprevir+ PegIFN+RBV, boceprevir PegIFN+RBV are extendedly dominated by 3D and the ICER reported in the model is £13,297 per QALY gained. In the analysis using SVRs from the adjusted indirect comparison boceprevir PegIFN+RBV is not extendedly dominated. As a result the ICER for 3D is higher than in the base case (increasing to £15,477) and is estimated compared with boceprevir PegIFN+RBV, rather than PegIFN+RBV (in the base case).

Table 58 ERG analysis e) Cost effectiveness results for non-cirrhotic GT1 treatment-naive patients using SVRs from adjusted indirect comparison

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Original model SVRs (unadjusted indirect comparison)					
PegIFN +RBV	20,483	14.33	NA	NA	NA
Boceprevir+ PegIFN +RBV	29,404	14.90			
Telaprevir+ PegIFN +RBV	33,799	15.14			
3D	39,553	15.77	19,070	1.43	13,297
Using SVRs based on adjusted indirect comparison					
PegIFN +RBV	20,437	14.33	NA	NA	NA
Boceprevir+ PegIFN +RBV	28,511	15.06	8,074	0.73	11,112
Telaprevir+ PegIFN +RBV	33,583	15.15	Extended dominance		
3D	39,524	15.77	11,013	0.71	15,477

These results should be regarded with caution as they are based on limited trial evidence – only one trial has been included for each comparison. In addition the odds ratios for SVR compared with PegIFN+RBV have been derived using the overall SVRs reported for the trials and have not been broken down by genotype subgroup or stage of fibrosis. It should also be borne in mind that these results are only based on non-cirrhotic, and as a result only cover part of the population covered by the decision problem for this appraisal.

f) re-run base case analysis as threshold analysis on effectiveness of 3D and 2D

The ERG conducted a threshold analysis for 3D reducing the effectiveness (in terms of SVR) for each fibrosis stage until comparators were no longer excluded by extended dominance and until 3D was excluded by dominance. The same proportionate reduction (1% increments) was applied to the SVRs for mild, moderate and patients with compensated cirrhosis. The results of this analysis are reported in Table 59 and in Figure 3.

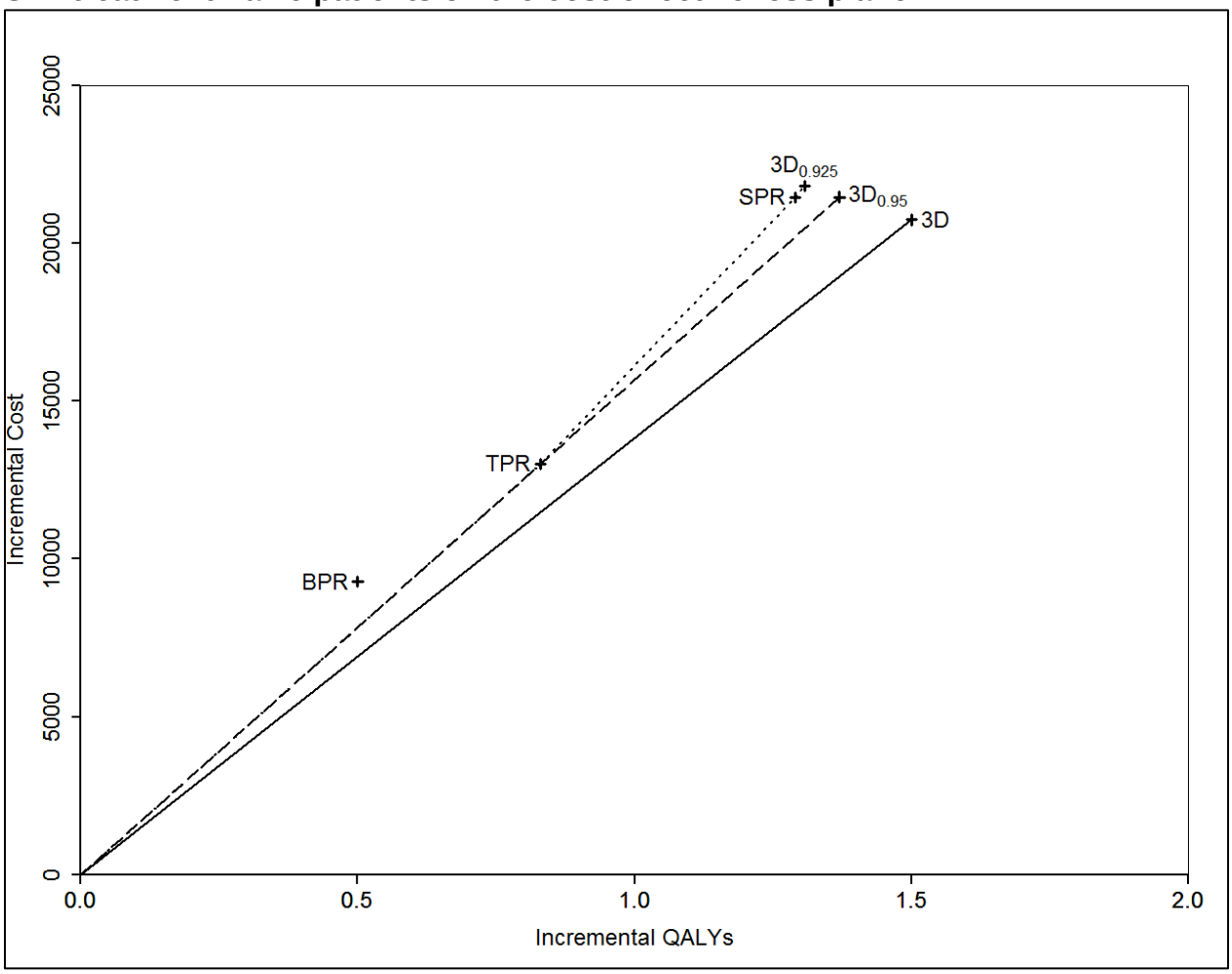
Table 59 ERG analysis f) Threshold analysis on effectiveness (SVR) with 3D in GT1 treatment-naive patients

					SVR		
Relative effectiveness	Regimen	Incremental cost	Incremental QALYs	ICER (£ per QALY gained)	Mild CHC	Moderate CHC	Compensated cirrhosis
1.00	3D	20,752	1.50	13,864	0.972	0.972	0.963
0.95	Telaprevir+ PegIFN +RBV no longer excluded by extended dominance Sofosbuvir+ PegIFN +RBV no longer dominated by 3D, but still excluded by extended dominance						
	Telaprevir+ PegIFN +RBV	13,014	0.83	15,602			
	3D	8,462	0.54	15,758	0.924	0.924	0.915
0.925	Sofosbuvir + PegIFN +RBV no longer excluded by extended dominance						
	Telaprevir+ PegIFN +RBV	13,014	0.83	15,602			
	Sofosbuvir+ PegIFN +RBV	8,451	0.46	18,471			
	3D	373	0.017	22,417	0.899	0.899	0.891
0.92	Telaprevir+ PegIFN +RBV	13,014	0.83	15,602			
	Sofosbuvir+ PegIFN +RBV	8,451	0.46	18,471			
	3D	445	0.004	109,535	0.895	0.895	0.886
0.91	3D dominated by Sofosbuvir + PegIFN +RBV				0.885	0.885	0.876

When the effectiveness of 3D is reduced to 95% of the base case SVR values, it no longer dominates sofosbuvir+ PegIFN +RBV and no longer extendedly dominates telaprevir+PegIFN +RBV. As a result the ICER for 3D further increases with each proportionate reduction in effectiveness and is measured relative to telaprevir+PegIFN+RBV. When effectiveness of 3D is reduced to 92.5%, sofosbuvir+PegIFN+RBV is no longer excluded by extended dominance leading to more marked increases in the ICER for 3D, which is now determined by comparison with sofosbuvir+PegIFN +RBV. When the effectiveness of 3D is reduced below 92% 3D is dominated by sofosbuvir+ PegIFN +RBV, being more costly and less effective.

Three points are shown for 3D in Figure 3 – these correspond to the incremental cost and QALY combinations (versus PegIFN+RBV) at three levels of effectiveness. The point marked 3D is the incremental cost and QALY combination for the base case (relative effectiveness =1). The other two points (marked $3D_{0.95}$ and $3D_{0.925}$) relate to the incremental cost and QALY combinations at relative effectiveness of 95% and 92.5% respectively.

Figure 3 ERG analysis f) Threshold analysis on effectiveness (SVR) with 3D in GT1 treatment-naive patients on the cost-effectiveness plane



A similar analysis was undertaken for the GT1 treatment-experienced population. The effect of varying the effectiveness is less marked, because sofosbuvir+PegIFN+RBV is not included in the analysis. In this analysis telaprevir+PegIFN+RBV stops being extendedly dominated when the effectiveness of 3D is reduced below 92%.

g) scenario using an alternative source for the risk of HCC in patients who experienced SVR from the compensated cirrhosis state

The ERG identified a recent study (Bruno and colleagues[50]) of the incidence of HCC in cirrhotic patients, with and without SVR. The ERG compared this with the study reported by Cardoso and colleagues[46] and note that, while Bruno and colleagues included only patients with cirrhosis, Cardoso and colleagues included both patients staged at F3 and F4. Since the duration of

follow up and sample size was larger in the study reported by Bruno and colleagues the ERG suggest this may be a better source for populating the model with these transition probabilities. The transition probability derived from the study by Bruno and colleagues is 0.00658, compared with 0.0123 which was applied in the CS. As this implies a lower risk of HCC in patients who experienced SVR from the compensated cirrhosis CC state, this change would be expected to reduce total costs, increase total QALYs and may result in more favourable ICERs.

Table 60 reports the cost effectiveness results after updating the risk of HCC in GT1 patients who underwent SVR from the compensated cirrhosis state (this additional analysis was only undertaken in GT1 patients as the model for GT4 patients did not include those who were cirrhotic at baseline). This change has minimal effect on the cost effectiveness results.

Table 60 ERG analysis g) cost effectiveness results using risk of HCC for patients who had cirrhosis prior to SVR from Bruno and colleagues

Base-case results for GT1, treatment-naïve, interferon eligible patients

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PegIFN+RBV	22,840	13.74	NA	NA	NA
Boceprevir + PegIFN+RBV	32,117	14.24	9,277	0.50	Extended dominance
Telaprevir + PegIFN+RBV	35,828	14.60	12,987	0.85	Extended dominance
3D	43,533	15.28	20,692	1.54	13,421
Sofosbuvir + PegIFN+RBV	44,260	15.07	21,420	1.33	Dominated

Base-case results for GT1, treatment-experienced (overall) interferon eligible patients

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PegIFN+RBV	30,082	11.09	NA	NA	NA
Telaprevir + PegIFN+RBV	42,489	12.20	12,408	1.10	Extended dominance
3D	51,569	13.38	21,487	2.29	9,390

h) scenario using an alternative source for the risk of HCC for patients with compensated cirrhosis

Bruno and colleagues also presented an estimated of the risk of HCC in patients with compensated cirrhosis. The transition probability derived from the study by Bruno and colleagues is 0.021, compared with 0.014 which was applied in the CS. As this implies a greater

risk of HCC for patients with compensated cirrhosis CC state, this change would be expected to increase total costs, reduce total QALYs and may result in less favourable ICERs.

Table 61 reports the cost effectiveness results after updating the risk of HCC in GT1 patients who underwent SVR from the compensated cirrhosis state (this additional analysis was only undertaken in GT1 patients as the model for GT4 patients did not include those who were cirrhotic at baseline). As anticipated the effect of this change is increase total costs, reduce total QALYs. However the effect is very slight and has minimal impact on the cost effectiveness results.

Table 61 ERG analysis h) cost effectiveness results using risk of HCC for patients with cirrhosis from Bruno and colleagues

Base-case results for GT1, treatment-naïve, interferon eligible patients

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PegIFN+RBV	22,744	13.64	NA	NA	NA
Boceprevir + PegIFN+RBV	32,041	14.16	9,297	0.52	Extended dominance
Telaprevir + PegIFN+RBV	35,814	14.50	13,071	0.87	Extended dominance
3D	43,609	15.20	20,865	1.56	13,390
Sofosbuvir + PegIFN+RBV	44,302	14.98	21,558	1.34	Dominated

Base-case results for GT1, treatment-experienced (overall) interferon eligible patients

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PegIFN+RBV	29,873	10.92	NA	NA	NA
Telaprevir + PegIFN+RBV	42,498	12.01	12,625	1.10	Extended dominance
3D	51,862	13.16	21,989	2.25	9,777

i) combine g) and h)

The final scenario related to risk of HCC in patients who experienced SVR from the compensated cirrhosis state and for those who do not experience SVR (and therefore remain in the compensated cirrhosis state) was to apply both these updated transition probabilities in the model. Since the risk of HCC for who had experienced SVR was reduced (compared with the base case transition probability) while the risk of HCC for patients who remain in the compensated cirrhosis state was increased (compared with the base case transition probability)

it was not clear what effect these combined changes would have on the cost effectiveness results.

Table 62 reports the cost effectiveness results after updating both transition probabilities in the model. The net effect of these two changes was to slightly reduce both total costs and total QALYs. However the effect is very slight and has minimal impact on the cost effectiveness results.

Table 62 ERG analysis i) cost effectiveness results, combining ERG scenario g) and ERG scenario h)

Base-case results for GT1, treatment-naïve, interferon eligible patients

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PegIFN+RBV	22,712	13.66	NA	NA	NA
Boceprevir + PegIFN+RBV	32,011	14.18	9,299	0.52	Extended dominance
Telaprevir + PegIFN+RBV	35,755	14.55	13,043	0.89	Extended dominance
3D	43,517	15.27	20,805	1.60	13,390
Sofosbuvir + PegIFN+RBV	44,225	15.04	21,513	1.38	Dominated

Base-case results for GT1, treatment-experienced (overall) interferon eligible patients

Regimen	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
PegIFN+RBV	29,827	10.94	NA	NA	NA
Telaprevir + PegIFN+RBV	42,341	12.11	12,514	1.17	10,739
3D	51,548	13.36	21,721	2.42	8,991

4.4 Summary of uncertainties and issues

There is a lack of head to head RCTs comparing 3D and 2D with alternative anti-viral treatments. The clinical effectiveness section of the CS presents an unadjusted indirect comparison of 3D with historical controls derived from clinical trials of telaprevir. The unadjusted indirect comparison is extended for the economic evaluation where data for comparators in the model have been drawn from single arms identified clinical trials. While the CS has sourced evidence from appropriate phase III registration trials the use of unadjusted indirect comparisons does not meet current methodological standards. The company has justified this approach as arising from the design of the 3D and 2D trials and have attempted to maximise the

validity of the comparison by sourcing input data for the model by stage of fibrosis (which has been shown to be a major determinant of response to interferon treatment). The ERG has attempted to assess the sensitivity of the cost effectiveness results to alternative approaches to conducting the indirect comparisons. However the data to support more methodologically robust indirect comparisons are generally lacking for some comparators within the NICE scope. The ERG feel the cost effectiveness results reported in the CS should be approached with caution.

The CS has presented analyses of both interferon-eligible and interferon-ineligible patients using the same estimates for effectiveness of 3D and 2D in both populations, but the assumption of equal effectiveness for both populations is not discussed in the CS. The ERG suggest that this assumptions requires clear justification before the results of this analysis can be assessed properly. Moreover the ERG question whether the economic model adopted for the CS (which was developed for evaluation of interferon-based treatment regimes and is populated with natural history data that has largely been derived in interferon-eligible populations) is appropriate for an interferon-ineligible population.

5 End of life

Not applicable.

6 Innovation

The company considers that the 3D regimen and 2D regimen for patients with GT1 and GT4, respectively, offer a stepped change in the treatment of CHC as 2D and 3D are both completely orally administered, interferon-free regimens. The company argues that in comparison to the current standards of care, which all require administration of interferon, 3D and 2D provide patients with a shortened treatment duration, while also offering better efficacy and improved safety.

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The company's clinical effectiveness systematic review identified six phase 3 trials and one phase 2 trial that provided results from individual trial arms or subgroups that met the licensed indications for 3D in treating people with HCV sub-genotypes GT1a and GT1b. The company additionally identified a Phase 2 trial of GT1 patients, which did not meet the licensed indications, because the dose of dasabuvir used in the trial was lower than in the licence. Five trials compared different 3D regimens to each other and to a planned historical telaprevir comparator. Only two trials, which compared 3D regimens with placebo, provided evidence that was directly relevant to the decision problem and NICE's scope in terms of having a relevant, randomised comparator (i.e. placebo may approximate best supportive care). However, these studies did not measure SVR outcomes in the placebo arm, so SVR data from these trials were also from individual trial arms. Only one trial was identified of 2D regimens in patients with HCV GT4. This compared different 2D regimens, with two of the three arms presented in the CS providing data relevant to the licensed indication. No data were presented for the 2D + RBV 24 weeks regimen for people with HCV GT4 with cirrhosis.

One of the main issues with the clinical effectiveness data presented in the CS is the lack of comparison to relevant comparators listed in the scope, including the current standards of care for GT1 patients (boceprevir + PegIFN+RBV and telaprevir + PegIFN+RBV, other than by historical comparison to telaprevir regimens) and GT4 patients (PegIFN + RBV), as well as sofosbuvir and simeprevir regimens preliminarily approved for HCV GT1 and GT4 patients by NICE. This means that no robust, randomised comparisons for SVR12 outcomes from 3D or 2D regimens against the comparators listed in the decision problem are available to inform the economic model. Although the ERG acknowledges that the SVR rates associated with 3D and 2D are likely to be high, the ERG considers the evidence presented in the results section of the clinical effectiveness review may be subject to bias due to the data being derived from what are essentially observational studies (individual trial arms and subgroups).

Superseded- see Erratum

7.2 Summary of cost effectiveness issues

The MS includes evidence on the cost-effectiveness of 3D (with or without RBV) and 2D (with RBV) compared with current standard care in patients infected with either GT1 or GT4 CHC. The model structure and methods adopted for the economic evaluation are reasonable and generally appropriate.

The ERG has identified weaknesses in the data used to model treatment effectiveness, with the lack of evidence of comparative clinical effectiveness being considered the most important. This means that no robust, randomised comparisons for SVR12 outcomes from 3D or 2D regimens against the comparators listed in the decision problem are available to inform the economic model. While additional analyses have been presented by the ERG, the evidence presented by CS for clinical effectiveness may be subject to bias and the chance of systematic error is considered uncertain.

The CS presented analyses of both interferon-eligible and interferon-ineligible patients based on an assumption of equal effectiveness for both populations. This assumption is not discussed in the CS. The terms interferon-eligible and interferon-ineligible are not defined in the CS and in some cases the terms interferon-intolerant and interferon-ineligible are used together, without clarifying what differences there might be between the two definitions. In addition the ERG question whether an economic model that was developed for evaluation of interferon-based treatment regimes and which is populated with natural history data largely been derived in interferon-eligible patient populations is appropriate for evaluating treatment in interferon-ineligible populations.

8 REFERENCES

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9 APPENDICES

9.1 Trial arms where treatment is outside the licensed indication for either some or all of the participants with HCV GT1

SVR 12

The three trials enrolling HCV GT1, treatment naive, non-cirrhotic patients (SAPPHIRE I,[23] PEARL IV, PEARL III) included trial arms where treatment was outside the licensed indication for either all patients enrolled in the trial arm or for one of the two subgroups of HCV GT1 subtypes (GT1a and GT1b) enrolled. These results are presented for information in Table 63. The lowest SVR12 obtained was 80.0% in the TURQUOISE II trial among prior null responders to PEGIFN+RBV with HCV GT1a and compensated cirrhosis treated with 3D+RBV for 12 weeks (the licensed treatment for this group would be 3D+RBV for 24 weeks) and all other SVR12 rates in Table 63 were above 88.6%).

Table 63: SVR12 outcome from trial arms or subgroups where treatment is outside the licensed indication for either some or all of the participants

Trial & Details	Group or subgroup	n/N SVR12	% SVR12	95% CI	Telaprevir comparator % SVR12 (95% CI)
Genotype 1, treatment naive, non-cirrhotic (CS Table 38 p. 153, Table 49 p. 173, Table 47 p. 170)					
SAPPHIRE I[23] GT1 3D+RBV vs placebo 12wk	Overall (GT1a + GT1b) 3D+RBV 12wk	456/473	96.4	94.7 to 98.1	78 (75 to 80)
	GT1b 3D+RBV 12wk	148/151	98.0	95.8 to 100	80 (75 to 84)
PEARL IV GT1a 3D+RBV vs 3D 12wk	GT1a 3D 12wk	185/205	90.2	86.2 to 94.3	80 (75 to 84)
PEARL III GT1b 3D+RBV vs 3D	Overall (GT1b) 3D+RBV 12wk	209/210	99.5	98.6 to 100.0	80 (75 to 84)
Genotype 1, treatment experienced, non-cirrhotic (CS Table 40 p. 158, Table 45 p. 168)					
SAPPHIRE II GT1 3D+RBV vs placebo 12wk	Overall (GT1a + GT1b) 3D+RBV 12wk	286/297	96.3	94.1, 98.4	65 (60 to 70)
	GT1b 3D+RBV 12wk	119/123	96.7	93.6 to 99.9	71 (64 to 77)
	Prior null responder	56/59	94.9	89.3 to 100.0	
	Prior partial	28/28	100	100.0 to	

	responder			100.0	
	Prior relapser	35/36	97.2	91.9 to 100.0	
PEARL II GT1b 3D+RBV vs 3D	Overall (GT1b) 3D+RBV 12wk	86/88	97.7	94.6 to 100.0	69 (62 to 75)
	Prior null responder	30/31	96.8	90.6 to 100.0	
	Prior partial responder	24/25	96.0	88.3 to 100.0	
	Prior relapser	32/32	100	89.3 to 100.0	
Genotype 1, treatment naive & treatment experienced, non-cirrhotic on stable opioid replacement therapy (CS Table 53 p. 178)					
M14-103[27] Single arm study	GT1 3D+RBV 12 wks	37/38	97.4	92.3 to 100	not reported
Genotype 1, treatment naive & treatment experienced, compensated cirrhosis (CS Table 42 p. 163)					
TURQUOISE II GT1 3D+RBV 12 wks vs 24 wks	Overall (GT1a + GT1b) 3D+RBV 12wk	191/208	91.8	87.6 to 96.1	47 (41 to 54)
	GT1a 3D+RBV 12wk	124/140	88.6	83.3 to 93.8	
	Tx Naive	59/64	92.2		
	Prior null responder	40/50	80.0		
	Prior partial responder	11/11	100		
	Prior relapser	14/15	93.3		
	Overall (GT1a + GT1b) 3D+RBV 24wk	166/172	96.5	93.4 to 99.6	47 (41 to 54)
	GT1b 3D+RBV 24wk	51/51	100	100.0 to 100.0	
	Tx Naive	18/18	100		
	Prior null responder	20/20	100		
	Prior partial responder	3/3	100		
	Prior relapser	10/10	100		

Meta-analysis of SVR12 from all active trial arms (including licensed and unlicensed treatment regimens))

The 2091 participants represented by the full trial populations of the 7 included studies [SAPPHIRE I,[23] PEARL IV, PEARL III (treatment naive, non-cirrhotic); SAPPHIRE II,[24] PEARL II (treatment experienced, non-cirrhotic), TURQUOISE II (treatment naive & treatment experienced, compensated cirrhosis) and the single arm study M14-103[27] (treatment naive & treatment experienced, non-cirrhotic on stable opioid replacement therapy) were included in a single arm meta-analysis. This yielded an overall pooled estimate for SVR12 from a random effects model of 96.4% (95% CI 94.2 to 97.8).

Summary of SVR24 results

Trial arms where treatment is outside the licensed indication

SVR24 was the primary outcome for the phase II dose-finding AVIATOR study[26] which did not report SVR12. The ERG believes that none of the 14 treatment arms meet the licensed indication because, even in those arms where ombitasvir, paritaprevir and ritonavir are provided at the licensed doses (arms E, G and L) the dasabuvir dose in this study was 400mg twice daily which is greater than the 250mg twice daily specified in the licensed 3D regimen. SVR24 rates in the AVIATOR study[26] ranged from 82.9% (arm B) to 100% (arm N) (Table 64). Table 65 shows subgroup analyses of SVR24 by HCV GT1 sub-genotype (i.e. GT1a and GT1b) for arms E, G and L of the AVIATOR trial, which the company provided to the ERG during the appraisal in response to the ERG's clarifications request (clarification point A15).

Table 64: SVR24 outcome from trial arms of the AVIATOR study[26]

Cohort	Arm	Drug combination (total daily dose[a])					Treatment duration (weeks)	SVR 24	
		Par mg	Rit mg	Om mg	Das mg	RBV		n/N	% (95% CI)
Treatment naïve patients non-cirrhotic (N=438) 68% have HCV GT1a[b]	Unlicensed treatment duration & dasabuvir dose								
	A	150	100	25	800	✓	8	70/80	87.5 (78-94)
	Absence of ombitasvir from regimen & dasabuvir dose outside 3D licence								
	B	150	100	none	800	✓	12	34/41	82.9 (68-93)
	No dasabuvir in regimen and paritaprevir dose outside 3D licence								
	C	100	100	25	None	✓	12	33/39	84.6 (69-94)
	No dasabuvir in regimen and paritaprevir dose outside 3D licence								
	D	200	100	25	None	✓	12	37/40	92.5 (80-98)
	Dasabuvir dose outside 3D license								
	E	150	100	25	800	none	12	70/79	88.6 (79-95)
	Paritaprevir & dasabuvir doses outside 3D license								
	F	100	100	25	800	✓	12	38/39	97.4 (87-100)
	Dasabuvir dose outside 3D license								
	G	150	100	25	800	✓	12	38/40	95.0 (83-99)
	Unlicensed treatment duration, paritaprevir & dasabuvir doses								
	H	100	100	25	800	✓	24	37/40	92.5 (80-98)
	Unlicensed treatment duration & dasabuvir dose								
	I	150	100	25	800	✓	24	36/40	90.0 (76-97)
Prior null responders non-cirrhotic (N=133) 61% have HCV GT1a	No dasabuvir in regimen and paritaprevir dose outside 3D licence								
	J	200	100	25	None	✓	12	40/45	88.9 (76-96)
	Paritaprevir & dasabuvir doses outside 3D license								
	K	100	100	25	800	✓	12	21/23	91.3 (72-99)
	Dasabuvir dose outside 3D license								
	L	150	100	25	800	✓	12	21/22	95.5 (77-100)
	Unlicensed treatment duration, paritaprevir & dasabuvir doses								
	M	100	100	25	800	✓	24	21/23	91.3 (72-99)
	Unlicensed treatment duration & dasabuvir dose								
	N	150	100	25	800		24	20/20	100 (83-100)

Data from CS Table 51 p. 176
Par - paritaprevir; Rit - ritonavir; Om - ombitasvir; Das - dasabuvir; RBV - ribavirin
[a] Paritaprevir, ritonavir, and ombitasvir taken once daily. The dasabuvir dose is the daily total but this is achieved via twice daily administration (i.e. 250mg twice daily as per 3D license to achieve 500mg total daily dose, or 400mg twice daily as per AVIATOR trial to achieve 800mg total daily dose)
[b] Licensed treatment for HCV GT1a is 3D + RBV for 12 weeks and licensed treatment for HCV GT1b is 3D for 12 weeks. The licensed 3D regimen is once daily paritaprevir 150 mg, ritonavir 100mg, ombitasvir 25 mg and twice daily dasabuvir 250mg.

Table 65: SVR24 rates for arms E, G and L from AVIATOR stratified by sub-genotype

AVIATOR trial arm (treatment regimen)	Genotype 1a	Genotype 1b
Tx naïve - Arm E (3D)	[redacted]	[redacted]
Tx naive - Arm G (3D + RBV)	[redacted]	[redacted]
Null responders - Arm L (3D + RBV)	[redacted]	[redacted]

Data from company clarification response A15 Table 13

9.2 Trial arms where treatment is outside the licensed indication for either some or all of the participants with HCV GT4

PEARL I included several trial arms where treatment was outside the licensed indication. Those that were outside the licensed indication because the participants had HCV GT1b were not included in the CS as 2D is not the appropriate regimen for these patients. One arm where treatment was outside the licensed indication was reported in the CS. Participants were treatment naive and received 2D without RBV. SVR12 was achieved by 90.9% (Table 66).

Table 66: SVR12 outcome from trial arm where treatment does not match licensed indication, GT4

Trial & Details	Group or subgroup	n/N SVR12	% SVR12	95% CI	Telaprevir comparator % SVR12 (95% CI)
Genotype 4, treatment naive & treatment experienced, non-cirrhotic (CS Table 56 p. 184)					
PEARL I 2D+RBV vs 2D (TxN) 2D+RBV (TxExp)	Tx Naive 2D 12 wks	40/44	90.9%	78.3 to 97.5	not reported

TxExp = treatment experienced; TxN = treatment naive.