Ledipasvir-sofosbuvir for treating chronic hepatitis C: A Single Technology Appraisal

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Praveen Thokala acted as the lead for this assessment. Emma Simpson summarised and critiqued the clinical effectiveness data reported by the company. Kath Dickinson critiqued the searches undertaken by the company. John Stevens critiqued the statistical analyses undertaken by the company. Praveen Thokala and Paul Tappenden critiqued the health economic analysis submitted by the company. Praveen Thokala undertook the additional analyses by the ERG. Dr Steve Ryder and Dr Phillip Harrison provided clinical advice to the ERG throughout the project. All authors were involved in drafting and commenting on the final document.

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LIST OF ABBREVIATIONS

AASLD	The American Association for the Study of Liver Diseases
AE	Adverse event
ALT	Alanine aminotransferase
ARV	Antiretroviral
BMI	Body mass index
BNF	British National Formulary
BOC	Boceprevir
CEAC	Cost-effectiveness acceptability curve
CHC	Chronic hepatitis C
CLDQ-HCV	Chronic Liver Disease Questionnaire-Hepatitis C virus
CPT	Child Pugh Turcotte
CS	Company's submission
CSR	Clinical study report
CUA	Cost-utility analysis
DARE	Database of Abstracts of Reviews of Effects
DCV	Daclatasvir
EASL	European Association for the Study of the Liver
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	Euroqol 5-Dimensions
ERG	Evidence Review Group
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full analysis set
FDC	Fixed dose combination
GT	Genotype
HAI	Histologic Activity Index
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRQoL	Health Related Quality of Life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IFN	Interferon
ITT	Intention-to-treat

IU	International unit
IWRS	Interactive web response system
IXRS	Interactive web and voice system
LDV	Ledipasvir
LLOQ	Lower limit of quantitation
NIAID	National Institute of Allergy and Infectious Diseases
NB	Net benefit
NEJM	New England Journal of Medicine
NHS	National Health Service
NHS-EED	NHS-Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NS5A	Non-structural protein 5A
PEG-IFN	Pegylated interferon
PI	Protease inhibitor
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality adjusted life year
QoL	Quality of life
RBV	Ribavirin
RCT	Randomised controlled trial
RNA	Ribonucleic acid
SAE	Serious adverse event
SD	Standard deviation
SF-36	Short Form Health Survey
SIGN	Scottish Intercollegiate Guidelines Network
SmPC	Summary of product characteristics
SMV	Simeprevir
SOF	Sofosbuvir
STR	Single tablet regimen
SVR	Sustained virologic response
TE	Treatment-experienced
TN	Treatment-naïve
TVR	Telaprevir
ULN	Upper limit of the normal range
WPAI: Hep C	Work Productivity and Activity Impairment: Hepatitis C

1. SUMMARY

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

The company's submission (CS) presents an evaluation of the clinical effectiveness and cost-effectiveness of ledipasvir-sofosbuvir (LDV/SOF) for the treatment of chronic hepatitis C (CHC). The decision problem addressed by the CS was not completely in line with the final scope issued by the National Institute for Health and Care Excellence (NICE) with respect to the population and intervention. In particular, the ledipasvir-sofosbuvir plus ribavirin (LDV/SOF+RBV) treatment duration for genotype 3 patients does not follow the wording of its marketing authorisation. In addition, the cost-effectiveness of telaprevir (TVR) and boceprevir (BOC) is evaluated in treatment-experienced patients with genotype 1/4 (GT1/4) infection, however neither product is licensed for the treatment of patients with genotype 4; this issue is highlighted in the footnotes to the results tables in the CS but is not discussed further.

The CS only presents the results for three subgroups (GT1, GT3 and GT4 patients); none of the analyses undertaken within the CS relate to patients with GT2, GT5 or GT6. The ERG notes that this is consistent with the wording of the EPAR, which only relates to GT1, GT3 and GT4 patients. The CS assumes that GT4 are similar to GT1 patients.

The company's model does not include the development of resistance to LDV/SOF; the CS states that resistance does not impact upon the cost-effectiveness of LDV/SOF i.e. it has no impact on costs or quality- adjusted life years (QALYs).

1.2 Summary of clinical effectiveness evidence submitted by the company

Ten trials of LDV/SOF were included in the CS. These were comprised of three Phase III trials and seven Phase II trials. Trials compared different durations of LDV/SOF, with and without ribavirin (RBV). There were no head-to-head trials comparing LDV/SOF with any of the comparators listed in the final NICE scope. The Phase III trials were designed to compare different durations of LDV/SOF with or without RBV, with only historical controls for comparison.

Data from the trials were mostly from populations with genotype 1 (GT1) disease, although some limited data were available for populations with genotypes 3 and 4. Treatment-naïve and treatment-experienced patients were represented within the trials. All ten trials reported sustained virologic response outcomes at 12-week post-treatment (SVR12). The Phase III trials provided data on resistance, health-related quality of life (HRQoL), and adverse events (AEs). One of the Phase II trials also contributed AE data.

For LDV/SOF treated patients, SVR12 rates ranged from 93% to 99% across all treatment arms for GT1 treatment-naïve patients. SVR12 rates of 93.1% to 99.4% were reported for subgroups of patients with GT1 treatment-naïve non-cirrhotic disease, whilst SVR rates of 94.1% to 100% were reported for subgroups of patients with compensated cirrhosis.

SVR12 rates for LDV/SOF treated GT1 treatment-experienced patients ranged from 94% to 99%. SVR rates ranging from 95.4% to 100% were reported for subgroups of GT1 treatment-experienced non-cirrhotic patients. Within subgroups of patients with compensated cirrhosis, reported SVR rates ranged from 81.8% to 100%

The most common AEs for LDV/SOF-treated patients were fatigue, headache, insomnia, and nausea. Across the treatment arms of the Phase III trials, 67% to 93% of patients experienced at least one AE. Of these, the majority were mild to moderate in severity.

Comparator data were not searched systematically as part of the submission, but were based on the company's previous NICE submission of sofosbuvir, with additional targeted searches. Network meta-analyses were not conducted.

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

It is unlikely that trials of LDV/SOF relevant to the final NICE scope were missed.

Although open-label, the three Phase III LDV/SOF trials were generally at low risk of bias. However, they were designed to compare different durations of LDV/SOF**.** There were no head-to-head trials comparing LDV/SOF against any of the comparators listed in the final NICE scope. Randomisation was stratified in the Phase III trials allowing investigation of subgroups. The Phase II trials had small sample sizes but provided data consistent with the Phase III trials.

SVR12 data were used. Historically, sustained virologic response at 24-weeks post-treatment (SVR24) has been used to measure patient response to therapy. However, research from clinical trials has indicated a high concordance between SVR12 and SVR24, and SVR12 is now considered an appropriate endpoint for regulatory approval. Thus, the ERG considered the use of SVR12 data to be appropriate.

The approach to searching the evidence base for comparator terms was not systematic. Comparator data (for SVR12) were provided by single arms of randomised controlled trials (RCTs), or non-RCTs. Although reported baseline characteristics appear similar between intervention and comparator trials, the possibility that other factors differed across trials cannot be ruled out.

1.4 Summary of cost-effectiveness submitted evidence by the company

The CS includes a systematic review of published economic evaluations of treatments for hepatitis C. The company's review was substantial, including 98 unique citations. The main body of the CS summarises the economic comparisons made for the intervention and comparators defined in the final NICE scope, including a list of studies in which the intervention was found to be dominant or cost-effective (acceptability criterion unspecified). One study which evaluated LDV/SOF was included in the company's review.

The company also submitted a health economic model to evaluate the cost-effectiveness of LDV/SOF+/-RBV against relevant comparators within patients with genotypes 1, 3 and 4. The company's model includes a total of twelve health states, including two death states, to represent the progression of liver disease and the costs and health benefits associated with curing the hepatitis C virus (HCV). All analyses adopt a lifetime horizon. The effectiveness of treatment is driven by SVR12 rates which are assumed to determine whether cure is achieved, whilst the cost-effectiveness of antiviral treatment is driven by the costs and benefits of the antiviral treatment and the avoidance of long-term costs and consequences associated with disease progression. Relative treatment benefits are modelled using naïve indirect comparisons between individual trial arms from multiple studies. The company's base case analysis includes separate economic comparisons for seven subgroups of patients: (i) genotype 1 treatment-naïve; (ii) genotype 4 treatment-naïve; (iii) genotype 1/4 treatment-experienced; (iv) genotype 3 treatment-naïve; (v) genotype 3 treatment-naïve with compensated cirrhosis; (vi) genotype 3 treatment-experienced IFN ineligible; and, (vii) genotype 3 treatment-experienced IFN-ineligible with compensated cirrhosis. The set of comparator therapies differs according to subgroup.

The company's model suggests that for all seven subgroups, LDV/SOF is expected to be the most effective treatment option. Within the genotype 1 treatment-naïve subgroup, the incremental cost-effectiveness ratio (ICER) for LDV/SOF versus PEG-IFN2a+RBV (the next most effective non-dominated option) was estimated to be £7,985 per QALY gained. Within the genotype 4 treatment-naïve subgroup, the ICER for LDV/SOF versus PEG-IFN2a+RBV (the next most effective non-dominated option) was estimated to be £12,860 per QALY gained. Within the genotype 1/4 treatment-experienced subgroup, the ICER for LDV/SOF versus no treatment (the next most effective non-dominated option) was estimated to be £13,527 per QALY gained. Within the genotype 3 treatment-naïve subgroup, the ICER for LDV/SOF versus PEG-IFN2a+RBV (the next most effective non-dominated option) was estimated to be £26,491 per QALY gained. Within the genotype 3 treatment-naïve with compensated cirrhosis subgroup, the ICER for LDV/SOF+RBV versus SOF+PEG-IFN2a+RBV (the next most effective non-dominated option) was estimated to be £46,491 per QALY gained. Within the genotype 3 treatment-experienced IFN-ineligible subgroup, the ICER for

LDV/SOF+RBV versus no treatment was estimated to be £28,048 per QALY gained. Within the genotype 3 treatment-experienced IFN-ineligible cirrhotic subgroup, the ICER for LDV/SOF +RBV versus SOF+RBV was estimated to be £6,210 per QALY gained.

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

Whilst the company undertook a large systematic review of published cost-effectiveness evidence, the CS does not include discussion of the results of the individual studies of relevant interventions and comparators. There is very limited interpretation of the broader economic evidence available or what this means for the cost-effectiveness of LDV/SOF and competing treatments. The results of the published LDV/SOF study (McGinnis *et al*) are not discussed within the CS.

The ERG's critical appraisal of the company's economic evaluation highlighted a number of concerns. These include: (i) deviations from the final NICE scope; (ii) the exclusion of relevant health effects relating to disease transmission and re-infection from the model, (iii) the use of naïve indirect comparisons to inform estimates of effectiveness which may be subject to bias and confounding, (iv) the use of "blended comparisons" which take a weighted average of efficacy and treatment duration for LDV/SOF, (v) uncertainty regarding the HRQoL benefits of LDV/SOF whilst receiving treatment and (vi) discordance between some of the transition probabilities assumed within the company's model and those used within previous models to inform appraisals of other antiviral therapies for the treatment of HCV. In addition, the company's analysis of LDV/SOF+RBV in treatment-experienced patients with genotype 3 disease assumes a mean treatment duration of 15 weeks; this is inconsistent with the recommended 24-week duration stated within the European Public Assessment Report (EPAR) published by the European Medicines Agency (EMA).

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

1.6.1 Strengths

It is unlikely that trials of LDV/SOF, relevant to the final NICE scope, were missed.

The three Phase III LDV/SOF trials were generally of good quality, however these were designed to compare different durations of LDV/SOF with or without RBV, with only historical controls for comparison.

Clinical advisors to the ERG indicated that disease characteristics of trial populations were generally representative of current UK practice, but noted that the Phase III studies of LDV/SOF include a higher proportion of patients with GT1 infection, more patients of African/American origin and fewer patients of Asian origin.

Superseded – see erratum

The ERG considers the company's model structure to be broadly appropriate and in line with previous economic analyses of treatments for hepatitis C, although there are some potentially important omissions (see Section 1.6.2).

The ERG did not identify any major unequivocal programming errors within the company's submitted model.

1.6.2 Weaknesses and areas of uncertainty

The company's approach to searching the evidence base for comparator terms and AEs was not systematic.

There were no head-to-head trials comparing LDV/SOF with any of the comparators in the final NICE scope.

Comparator data (for SVR12) were provided by single arms of RCTs, or non-RCTs.

The company's health economic model uses naïve indirect comparisons to draw inferences on the relative effectiveness of LDV/SOF+/-RBV and other relevant comparators. This approach may be subject to bias and confounding. It would have been possible to undertake a formal network meta-analysis for the comparators listed in the final NICE scope; however, this was not done.

The ERG notes that some important health effects are missing from the health economic analysis, including the possibility of re-infection in individuals with hepatitis C and potential herd immunity effects across groups of individuals.

The company's model includes blended comparisons which take a weighted average of efficacy and treatment duration for LDV/SOF. The ERG has concerns that such blended comparisons may result in the inappropriate recommendation of some treatment options which are known to be efficient and other options which are known to be inefficient. The ERG urges caution in the interpretation of such comparisons.

The company's analysis of LDV/SOF+RBV in patients with genotype 3 disease is not in line with the recommended treatment duration published by the EMA.

These issues limit the credibility of the cost-effectiveness estimates presented within the CS.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook six sets of additional analyses to address issues identified within the company's health economic analysis:

Superseded – see erratum

1. Development of an ERG-preferred base case using "unblended" EMA-recommended treatment durations for LDV/SOF(+/-RBV)
2. Examination of alternative EMA-recommended treatment durations for LDV/SOF
3. Use of alternative transition probabilities based on the previous sofosbuvir STA model
4. Use of UK valued on-treatment utility increment derived by Wright *et al*
5. Use of shorter time horizons (5-years and 10-years) to dampen assumptions regarding no re-infection
6. Threshold analysis for SVR rates of the comparators

The ERG-preferred base case analysis suggests the following results. Within the genotype 1/4 treatment-naïve subgroup, in the non-cirrhotic population, the ICER for LDV/SOF versus SMV+PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £22,676 per QALY gained; within the cirrhotic population, the ICER for LDV/SOF versus SMV+SOF (the next most effective non-dominated option) is estimated to be £97,836 per QALY gained. Within the genotype 1/4 treatment-experienced subgroup, in the non-cirrhotic population, the ICER for LDV/SOF versus no treatment (the next most effective non-dominated option) is estimated to be £16,566 per QALY gained; within the cirrhotic population, the ICER for LDV/SOF versus SMV+SOF (the next most effective non-dominated option) is £92,704 per QALY gained. Within the genotype 3 treatment-naïve subgroup, in the non-cirrhotic population, the ICER for LDV/SOF versus PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £88,853 per QALY gained; within the cirrhotic population, the ICER for LDV/SOF versus SOF+PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £46,149 per QALY gained. Within the genotype 3 treatment-experienced subgroup, in the non-cirrhotic population, the ICER for LDV/SOF versus SOF+RBV (the next most effective non-dominated option) is estimated to be £131,654 per QALY gained; within the cirrhotic population, the ICER for LDV/SOF versus no treatment (the next most effective non-dominated option) is estimated to be £18,238 per QALY gained.

These analyses suggest that using the EMA-recommended treatment durations within an "unblended" analysis produces very different ICERs for the non-cirrhotic and cirrhotic subgroups. Within genotypes 1 and 4, the economic profile of LDV/SOF appears considerably more favourable for non-cirrhotic rather than cirrhotic subgroups. Within subgroups of patients with genotype 3 disease, however, the economic profile of LDV/SOF appears considerably more favourable for cirrhotic rather than non-cirrhotic subgroups. The ERG however urges caution in the interpretation of the results of the analyses in genotype 3 treatment-experienced patients as these are based on small patient numbers and use SVR4 data.

The use of alternative EMA-recommended treatment durations has a substantial impact upon the cost-effectiveness of LDV/SOF. Assuming an alternative treatment duration of 8 weeks LDV/SOF in the genotype 1/4 treatment-naïve non-cirrhotic subgroup, the ICER for LDV/SOF versus PEG-IFN2a+RBV (the next most effective non-dominated option) is reduced to £8,894 per QALY gained. Assuming an alternative treatment duration of 12 weeks LDV/SOF within the genotype 1/4 treatment-naïve cirrhotic population, the ICER for LDV/SOF versus no treatment (the next most effective non-dominated option) is reduced to £4,518 per QALY gained. In the treatment experienced GT1/4 non-cirrhotic subgroup, using an alternative treatment duration of 24 weeks for LDV/SOF, the ICER for LDV/SOF versus SMV+SOF is estimated to be £165,445 per QALY gained.

The ERG's additional analyses surrounding the company's transition probabilities and the HRQoL increment associated with achieving SVR also produce different ICERs, however the overall conclusions of the economic analysis remain unaffected.

The ERG's analyses which use shorter time horizons result in an increase in the ICERs for LDV/SOF (all of which are higher than £75,000 per QALY gained) compared to those estimated in the ERG-preferred base case analyses. This is unsurprising since the benefits are curtailed to a short time horizon yet the costs of treatment are incurred upfront.

The ERG's threshold analyses surrounding comparator SVR rates suggest that for the GT1/4 treatment naïve non-cirrhotic subgroup, the SVR rate for SMV+PEG-IFN2a+RBV (the next best non-dominated comparator) would need to increase by 3.4% (from 82% to 85.4%) in order for LDV/SOF to achieve an ICER of £30,000 per QALY gained. However, in the other subgroups the SVR rates of the comparators (the next best non-dominated options) would need to be lower than the company's current estimates in order for LDV/SOF to achieve an ICER of £30,000 per QALY gained.

The ERG notes that based on the company's analysis, the budget impact for the NHS will be substantial in the short-term. Clinical advisors to the ERG suggest that a treatment approach using a highly effective therapy has the possibility to eradicate HCV infection from the UK. Based on clinical advice received by the ERG, the patient numbers needed to treat in order to have a significant impact on disease prevalence is higher than the estimates reported within the CS[1] (around 6000-10000 per year).

Superseded – see erratum

2 BACKGROUND

This Evidence Review Group (ERG) report provides a review of the evidence submitted by the company in support of ledipasvir-sofosbuvir (LDV/SOF) for the treatment of chronic hepatitis C. It considers both the original submission from the company[1] received on the 22nd October 2014 and a subsequent response to clarification questions[2] on 28th November 2014. This chapter presents a brief commentary on the company's interpretation of the underlying health problem and the nature of current service provision.

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

The CS[1] provides a reasonable description of the underlying health problem, which is briefly summarised in this section. The CS describes the underlying health problem as chronic hepatitis C, caused by infection of the liver by the Hepatitis C virus (HCV). The CS states that 15–25% of acutely affected individuals will show a gradual decrease in virus levels but the remaining 75–85% will go on to develop chronic hepatitis C, which is defined as persistent, detectable serum HCV ribonucleic acid (RNA) for a period greater than 6 months. The CS states that untreated patients with chronic hepatitis C are at progressive risk of liver fibrosis, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC) and death, as well as extrahepatic diseases. The CS also states that chronic hepatitis C is the most common cause of liver cirrhosis and the most common indication for liver transplantation in Europe.

The CS[1] states that there are six major HCV RNA genotypes (GT1–6) and that sentinel surveillance data in England from 2009 to 2013 show GT1 (45%) and GT3 (45%) predominating, with other genotypes, including GT4, comprising just 10% of infections. The CS states that the choice of therapy, response to treatment and rate of disease progression is strongly influenced by HCV genotype.

The CS estimates that there are approximately 16,300 patients with chronic hepatitis C receiving care in England and Wales, of which 15,240 (94%) are infected with HCV GT1, GT3 or GT4, based upon a company-commissioned analysis of Public Health England sentinel survey data.

Clinical advisors to the ERG consider the description of the underlying health problem to be largely appropriate and relevant to the decision problem.

2.2 Critique of company's overview of current service provision

The CS[1] states that the aim of drug treatment is to cure the infection by eradicating the HCV virus. The CS states that decisions around the choice of treatments are influenced by HCV genotype, the stage of liver disease, based on the presence or absence of cirrhosis, and whether a patient has previously received treatment for the condition i.e. whether they are HCV treatment-naïve or treatment-experienced. The CS provides an overview of the current clinical pathway and relevant treatment options, based on the European Association for the Study of the Liver (EASL) recommendations on treatment of hepatitis C 2014 (April) guidelines,[3] the 2014 UK consensus guidelines on hepatitis C management and direct-acting anti-viral therapy[4] and current treatment options recommended by NICE (see CS[1] Section 2.5).

The CS[1] states that the current treatment options recommended by NICE include pegylated interferon (PEG-IFN), telaprevir (TVR), and boceprevir (BOC). The CS states that combination therapy with PEG-IFN alfa (2a or 2b) and RBV is recommended as a treatment option for adults with chronic hepatitis C, for patients with certain characteristics (see CS[1] Table 4). The CS also states that both BOC and TVR are recommended as an option for the treatment of genotype 1 HCV patients, in combination with PEG-IFN alfa and RBV.

The CS[1] also states that, of the new options that have been recently licensed (sofosbuvir [SOF], simeprevir [SMV], and daclatasvir [DCV]) and are currently under review by NICE, preliminary recommendations for SOF and SMV have been provided. The CS states that SOF+PEG-IFN+RBV has preliminary recommendations for use in HCV GT1 patients, HCV GT3 patients with cirrhosis and HCV GT3 treatment-experienced patients without cirrhosis. The CS also states that SMV+PEG-IFN+RBV has preliminary recommendations in GT1 patients, with the Appraisal Committee minded not to recommend its use in GT4 patients, and to not recommend SMV+SOF in GT1 or GT4 subgroups. The CS also states that, in genotypes of relevance to the LDV/SOF submission, SOF+RBV has a preliminary recommendation for use in GT3 patients with cirrhosis.

The CS[1] states that the single tablet regimen (STR) of LDV (90mg) and SOF (400mg) provides a simple, all oral, once-daily, IFN-, RBV- and PI-free treatment option for the majority of adult patients with GT1 and GT4 HCV, with improved efficacy and tolerability following 8-24 weeks of therapy. The company also asserts that, by adding RBV to the regimen, high cure rates can be achieved in patients with GT3 infection.

The ERG and their clinical advisors agree with the broad description of current clinical pathway and treatment options**.**

Superseded – see erratum

However, the ERG notes that the company's model assumes that 75% of the non-cirrhotic genotype 3 patients will receive 12 weeks LDV/SOF+RBV; this is not in line with the recommended treatment durations from the EMA.

Superseded – see erratum

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[1]

A summary of the decision problem as outlined in the final scope issued by NICE[5] and addressed in the CS[1] is presented in Table 1.

Table 1: Decision problem as outlined in the final scope issued by NICE[5] and addressed in the CS[1]

	Decision problem outlined in final scope issued by NICE[5]	**Decision problem addressed in the CS[1]**
Population	Adults with CHC • who have not had treatment for CHC before (treatment-naïve) • who have had treatment for CHC before (treatment-experienced)	The CS focusses solely on subgroups of patients with GT1, GT3 and GT4. Most of the data relate to patients with GT1 disease. The ERG notes that the wording of the EPAR[6] relates to patients with GT1, GT3 and GT4 disease.
Intervention	LDV/SOF with or without RBV	As per the final scope. The ERG notes issues concerning the use of blended comparisons for LDV/SOF and consider that the treatment duration adopted within the modelled GT3 treatment-experienced subgroup does not adhere to recommended treatment durations listed in the EPAR.[6]
Comparator(s)	• PEG-IFN+RBV (GT1–6) • TVR+PEG-IFN+RBV (GT1 only) • BOC+PEG-IFN+RBV (GT1 only) • SOF+RBV±PEG-IFN (GT1–6; subject to ongoing NICE appraisal ID654 • SMV+PEG-IFN+RBV (GT1 or GT4 subject to ongoing NICE appraisal ID668) • SMV+SOF (for patients with GT1 or GT4 disease and are ineligible for or intolerant to IFN treatment; subject to ongoing NICE appraisal ID668) • Best supportive care (watchful waiting; GT1–6)	Mostly in line with the final scope, albeit with some discrepancies (see Section 3.3). The company notes that "best supportive care" is defined as no treatment in their submission. The ERG notes that the wording of the EPAR relates to patients with GT1, GT3 and GT4 disease. TVR and BOC are included in the economic analysis of treatment-experienced patients with GT1/4 disease yet neither product is licensed for use in GT4 patients. IFN is not included as a treatment option for GT3 patients.
Outcomes	The outcome measures to be considered include: • SVR • Development of resistance to LDV/SOF • Mortality • Adverse effects of treatment • HRQoL	As per the final scope. The CS asserts that the development of resistance to LDV/SOF does not impact upon the cost-effectiveness of LDV/SOF i.e. it has no impact on cost or QALYs.

Superseded — see erratum

	Decision problem outlined in final scope issued by NICE[5]	Decision problem addressed in the CS[1]
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per the final scope. The company's submitted model evaluates costs and health gains from the perspective of the NHS and Personal Social Services (PSS) over a lifetime horizon.
Subgroups to be considered	If evidence allows the following subgroups will be considered: • Genotype • Co-infection with HIV • People with and without cirrhosis • People who have received treatment pre- and post-liver transplantation • Response to previous treatment (nonresponse, partial response, relapsed) • People who are intolerant to or ineligible for IFN-treatment If evidence allows the impact of treatment on reduced onward HCV transmission will be considered. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued in the context of the evidence that has underpinned the marketing authorisation	As per the final scope. The CS includes subgroup analyses relating to: • Genotype • People with and without cirrhosis • People who are intolerant to or ineligible for IFN treatment Separate subgroup analyses are not presented for patients who are co-infected with HIV, patients who have received treatment pre-/post-liver transplantation or patients with different response to previous treatment.
Special considerations, including issues related to equity or equality	CHC GT4 patients are characterised by a disproportionately higher number of patients from ethnic minorities and who are HCV/HIV co-infected	As per the final scope

BOC, boceprevir; CHC, chronic hepatitis C; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQoL, health related quality of life; LDV, ledipasvir; PEG-IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; TVR, telaprevir.

3.1 Population

The population described in the decision problem section of the CS[1] (pages 16 to 36) focuses solely on three subgroups (GT1, GT3 and GT4 patients). The CS states that there are very limited or no data for LDV/SOF in GT2, GT5 and GT6 patients. This overall population considered broadly reflects the final scope issued by NICE[5] which refers to *"adults with CHC, who have not had treatment for CHC before (treatment naïve) and who have had treatment for CHC before (treatment experienced)."*

3.2 Intervention

The CS[1] states that LDV is a HCV inhibitor targeting the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions. The CS states that SOF is a pan genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication and that SOF is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analogue triphosphate (GS 461203), which, when incorporated into HCV RNA by the NS5B polymerase, acts as a chain terminator. According to the CS,[1] GS 461203 (the active metabolite of SOF) is neither an inhibitor of human deoxyribonucleic acid (DNA) and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

LDV/SOF is administered in tablet form. Each tablet contains 90mg LDV and 400mg SOF. The cost of 28 day pack of LDV/SOF tablets is £12,993.33. The recommended dose is once daily with or without food. The company states that there is no requirement for response-guided therapy (RGT) with LDV/SOF and no tests or investigations are required in addition to current routine hepatitis tests.

LDV/SOF was granted marketing authorisation on 18th November 2014. LDV/SOF is indicated for the treatment of chronic hepatitis C virus (HCV) in adults and is recommended in treatment-naïve and treatment-experienced cirrhotic and non-cirrhotic genotype 1 and 4 patients.[6] The recommended treatment duration is either 12 or 24 weeks depending on prior treatment history and cirrhosis status. Eight weeks of LDV/SOF treatment may be considered in non-cirrhotic treatment-naïve genotype 1 patients.[6] In genotype 3 patients with cirrhosis and/or prior treatment failure, LDV/SOF should be used in combination with RBV for 24 weeks.[6]

It should be noted that the treatment durations used in the company's economic analysis are based on anticipated use of LDV/SOF regimens as the CS was made prior to the regulatory approval in UK. As such, the LDV/SOF treatment described for the GT3 subgroup in the company's economic model does not correspond to its licensed indication. Furthermore, the CS makes use of "blended" comparisons of LDV/SOF, which involves taking a weighted average of the effectiveness of different LDV/SOF treatment options given over different durations based on the expected proportion of patients who would receive each (see Chapter 5).

Superseded – see erratum

3.3 Comparators

The company included the following comparators in their decision problem:

- PEG-IFN+RBV (GT1–6)
- TVR+PEG-IFN+RBV (GT1 only)
- BOC+PEG-IFN+RBV (GT1 only)
- SOF+RBV±PEG-IFN (GT1–6; subject to ongoing NICE appraisal ID654)
- SMV+PEG-IFN+RBV (GT1 or GT4 subject to ongoing NICE appraisal ID668)
- SMV+SOF (for patients with GT1 or GT4 disease and are ineligible for or intolerant to IFN treatment; subject to ongoing NICE appraisal ID668)
- Best supportive care (watchful waiting; GT1–6)

The comparators defined in the decision problem broadly match the final scope specified by NICE. However, there are some discrepancies. TVR and BOC are included in the economic analysis of GT1/4 treatment-experienced patients however neither product is licensed for use in GT4 patients. This issue is highlighted in the footnotes to the results tables within the CS but is not discussed further with respect to the results for individual genotypes. "Best supportive care" is defined as no treatment in the CS. It should be noted that the CS only presents the results for three subgroups (GT1, GT3 and GT4 patients); no analyses undertaken by the company relate to GT2, GT5 or GT6 patients. Within the treatment-experienced GT3 subgroup, IFN-based treatments are not included as comparators.

The clinical advisors to the ERG indicated that daclatasvir in combination with SOF may also be an appropriate comparator in GT3 patients; this option was not however specified in the final NICE scope[5] and is not considered within the company's health economic analysis.

3.4 Outcomes

The CS[1] includes the following outcomes, all of which are specified in the final NICE scope:[5]

- SVR
- Mortality
- Adverse effects of treatment
- HRQoL

The CS does not include one of the outcomes specified in the NICE scope,[5] that is, the development of resistance to LDV/SOF, stating that this outcome does not impact upon the cost-effectiveness of LDV/SOF i.e. it has no impact on either expected costs or health gains. However, the CS does include some discussion of the development of resistance to LDV/SOF (see CS[1] Section 6.10). The CS states that LDV/SOF has a high barrier to the development of treatment-resistant mutations and the analyses

of Phase III studies showed that, of [redacted] patients experiencing relapse, none had resistance to SOF, [redacted] did not have resistance to LDV at virologic failure and single-class resistance to LDV was observed in the remaining [redacted]

The ERG also notes that SVR4 data were used for the economic analysis of GT3 patients; clinical advice received by the ERG suggests that this end point may be an unreliable marker for SVR12 and SVR24.

3.5 Economic analysis

The company submitted an executable health economic model to evaluate the incremental cost-effectiveness of LDV/SOF versus a range of comparators in patients with chronic hepatitis C. The model estimates cost-effectiveness in terms of the incremental cost per QALY gained over a lifetime horizon from the perspective of the NHS and PSS. Issues relating to the model are discussed in detail in Section 5.4.

3.6 Other relevant factors

The decision problem addressed by the CS[1] includes consideration of the following subgroups, all of which were specified in the final NICE scope:[5]

- Genotype
- People with and without cirrhosis
- People who are intolerant to or ineligible for IFN-treatment

Separate subgroup analyses are not presented for patients who are co-infected with HIV, patients who have received treatment pre-/post-liver transplantation or patients with different response to previous treatment.

In terms of equity considerations, the CS states that the CHC GT4 patients are characterised by a higher proportion of patients from ethnic minorities and patients who are HCV/HIV co-infected.

4. CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the clinical effectiveness evidence for LDV/SOF and relevant comparators contained within the CS.[1]

4.1 Critique of the methods of review and critique of included trials

4.1.1 Searches

The search strategy was newly developed for the purposes of this appraisal and was not based on any previously published search strategies, although the CS[1] states that the search strategies are similar to those conducted for the sofosbuvir appraisal. The searches were conducted on 2nd September 2014; no update searches were required as the evidence base was considered to be sufficiently up-to-date. The following databases were searched:

- MEDLINE/MEDLINE (R) In-Process
- Embase
- The Cochrane Library

The company's search strategy was comprised of terms for the intervention only (no comparator terms). The issue of comparator terms is addressed in more detail in the critique which follows. Results were from the inception of each database to the date the searches were performed (2nd September 2014). The results were not limited to English language studies.

In addition to the database searches, the proceedings of two conferences were also searched:

- The American Association for the Study of Liver Diseases (AASLD, 2013)
- European Association for the Study of the Liver (EASL, 2014)

Critique

Overall, there are some major gaps in the reporting of the company's searches which made it difficult for the ERG to determine their suitability for this appraisal. Comparator terms were not included in the clinical effectiveness searches, and it is not clear from the CS how comparator evidence was identified. Having sought clarification on this matter (see clarification response[2] question B7), it is clear that comparator evidence was identified as part of the previous appraisal for sofosbuvir. Due to restrictions on time, targeted searches were performed, and for the current appraisal (LDV/SOF for treating chronic hepatitis C), Summary of Product Characteristics (SmPCs) were used by the company as a means of identifying additional studies and comparators of interest. This is not considered by the ERG to be the most systematic approach to identifying relevant data on comparator drugs and adverse events, and further details, including search strategies, would ideally have been provided in the CS to enable the ERG to make an informed critique.

Brief mention of ongoing trials is provided within the CS[1] (page 17), although it is not clear how this information was compiled. A search of the intervention terms in ClinicalTrials.gov by the ERG identified 35 studies, and clarification was sought from the company as to whether any of these are due to report data within the next 12 months. Following clarification, the company provided this information. A detailed breakdown of the 35 studies is provided in Appendix 1.

The CS states that the proceedings of two conferences were searched for a limited date span only (see above for details). Clarification was sought on why the conferences 'Digestive Disease week' and 'Asian Pacific Association for the Study of the Liver' were not searched. In their response (see clarification response[2] question A4) the company stated that *"Digestive Disease Week was not searched as the focus was on liver-specific congresses and this conference extends to gastroenterology, hepatology, endoscopy and gastrointestinal surgery. APASL was not searched as it was deemed likely that abstracts, and the patient populations described therein, would be biased towards Asian populations. Thus, identified abstracts would be of limited relevance for this submission."* The ERG was satisfied with this response.

4.1.2 Study selection and data extraction

4.1.2.1 Study selection for LDV/SOF trials

Study selection inclusion criteria for clinical effectiveness data (see CS[1] Table 8, page 45) match the decision problem set out within the final NICE scope[5] in terms of the population and the intervention.

The population comprised patients with chronic hepatitis C. This included treatment-naïve patients, that is, those who have not previously received treatment for chronic hepatitis C, and treatment-experienced patients, that is, those who have previously received treatment for chronic hepatitis C. Study selection exclusion criteria listed in Table 8 of the CS[1] indicate that studies would be excluded for not having hepatitis C in "relevant genotypes", however the company's clarification response[2] stated that no studies were excluded on the basis of genotype (see clarification response[2] question B3). It was the case that study arms could be excluded on the basis of genotype (for ELECTRON-2, GT6 patients were excluded from the CS, see CS[1] page 102). The study selection criteria do not specify adult patients, however this was specified in the decision problem (see CS[1] Section 5), and for all included trials the populations related to patients aged 18 or over.

The intervention was defined as LDV/SOF. The inclusion and exclusion criteria in Table 8 of the CS specify LDV as the intervention, and Section 6.2.7 states that studies would have been excluded from the review if they did not include LDV and SOF in combination. Dose is not specified in the study selection criteria, however included trials used the licensed dose (as stated on page 11 of the CS[1]) of 90mg LDV and 400mg SOF. All included trials had at least one treatment arm which reflects the

EMA-recommended[6] recommended treatment duration of LDV/SOF for the population investigated.

Comparator terms were not used as an exclusion criterion for the search of LDV/SOF trials, which was appropriate given the lack of head-to-head trials comparing LDV/SOF with any of the comparators in the final NICE scope.[5]

Only trials reporting sustained virologic response (SVR) were included in the company's review. From the final NICE scope,[5] the outcomes to be considered were: SVR; development of resistance to LDV/SOF; mortality; adverse effects of treatment, and; HRQoL. This could mean that trials with other relevant outcomes might have been excluded. However, the company's response to clarification[2] (question B1) indicates that the only articles (n=6) excluded on the basis of outcomes (see CS[1] Figure 3) were publications of included trials with insufficient data reported. This means that no trials were excluded solely for not reporting SVR.

Study design was not limited to RCTs. This was appropriate given the absence of head-to-head trials comparing LDV/SOF with any of the comparators in the final NICE scope [5].

Two reviewers conducted study selection (see CS[1] page 44); this is in line with good practice. The study selection process was provided in a flow diagram of study selection (see CS[1] Figure 3) that indicates that 22 citations were included. Of these, three citations were of two trials, Wyles *et al* and Thompson *et al*[7-9] that were later excluded because, while investigating LDV, none of the trial arms included LDV in combination with SOF (see CS[1] Section 6.2.7 and clarification response[2] question B2).

From the systematic review, seven LDV/SOF trials (ION-1, ION-2, ION-3, LONESTAR, ELECTRON, SYNERGY, ELECTRON-2) were included in the CS; these were reported across 19 publications (see clarification response[2] question B2). Additionally, three trials (ERADICATE, SOLAR-1, SIRIUS) that were unpublished at the time of the search were identified for inclusion from the company's LDV/SOF clinical trial programme (clarification response[2] question B2).

Other trials identified from the company's LDV/SOF clinical trial programme (see clarification response[2] question B2), were GS-US-337-1119 (French GT4/5 study), GS-US-337-0115 (ION-4), GS-US-337-0113 (Japanese Phase III), and GS-US-337-0124 (SOLAR-2) (see clarification response[2] question B3). Three of these four trials were excluded as no data were available at time of submission (French GT4/5 study, ION-4, SOLAR-2). The Japanese Phase III study was excluded as the CS considered the Japanese population to be different to the population demographics of the UK (see clarification response[2] question B3). The population in the Japanese study[10] had a higher proportion of IL28B CC, a lower mean body mass index (BMI) and a higher percentage of GT1b compared with

included studies. Excluding this study would be unlikely to impact on the results. For treatment-naïve or treatment-experienced patients with GT1, following 12 weeks of treatment with LDV/SOF with or without RBV, SVR12 rates ranged from 96% to 100%.

Ten LDV/SOF trials were included in the CS, comprising three Phase III trials (ION-1, ION-2, ION-3) and seven Phase II trials (LONESTAR, ELECTRON, SYNERGY, ELECTRON-2, ERADICATE, SOLAR-1, SIRIUS).

For the Phase III trials, data from all treatment arms were reported in the CS, including arms that did not reflect the recommended treatment duration of LDV/SOF for the population investigated.[6]

Not all of the arms of all the Phase II trials were included in the CS.[1] ELECTRON-2 provided data from four groups. Data from the other eleven arms of the trials were not included in the CS as data were not available at the time of submission (treatment-experienced GT3 patients with no cirrhosis or compensated cirrhosis) or were excluded for relating to patients with GT6 disease (treatment-naïve and treatment-experienced, HCV GT6), or having unlicensed drugs. The SYNERGY trial was still recruiting at the time of submission and was designed with nine experimental groups. Treatment arms with unlicensed drugs (GS-9669 or GS-9451) were excluded from the CS,[1] leaving three potentially relevant treatment arms. At the time of submission, two treatment arms had available data: GT1 prior SOF failure patients, and GT1 treatment-naïve patients, both of which were assigned to LDV/SOF for 12 weeks.

The ELECTRON study[11] was conducted in six parts, with 22 patient groups planned (although not all groups were enrolled), of which five provided data on LDV/SOF. However for comparator treatment data, an arm from ELECTRON was used; SOF+PEG-IFN+RBV 12 weeks treatment in GT2/3 patients (see CS[1] Table 38).

4.1.2.2 Study selection for comparator trials

Searches for comparator data were not conducted systematically (see Section 4.1.1). The company's response to clarification[2] (question B6) provides some detail concerning how comparator studies were selected. The company had previously provided a submission to NICE for the appraisal of SOF.[12] Data from the searches from the SOF submission[12] were used to identify comparator data for the LDV/SOF submission.

For GT1 and GT3 treatment-naïve patients for PEG+RBV, BOC, TVR, and SOF, comparator data were based on the systematic review in the SOF submission[12] (see clarification response[2] question B6). The systematic review used searches of publications from 2002 to September 2013 (see

Superseded – see erratum

clarification response[2] question B7). The search was not updated, although targeted searches were used to identify additional studies.

For GT1 treatment-experienced patients (see clarification response[2] question B6), the SOF submission[12] had not provided a systematic review, but had conducted targeted searches for comparator trials.

4.1.2.3 Data extraction

Appendix 10.2.7 of the CS briefly describes the data extraction process. Items to be extracted were not listed in CS Appendix 10.2.7, however relevant study characteristic details were described for the LDV/SOF trials; these are detailed in Section 6 of the CS.[1] Data were extracted by two reviewers independently (see CS[1] page 44); the ERG considers this to reflect good practice. For each trial, data from multiple publications were compiled to avoid double-counting of patients; the ERG also considers this to be good practice.

Data in the CS from ION-1 and ION-3 differ slightly from the New England Journal of Medicine (NEJM) publications,[13,14] but this was explained by the NEJM results being published at an earlier timepoint (see CS[1] pages 78 and 83). As the CS data were more recent, these have been used in this ERG report. ION-2 data presented in the CS were consistent with the NEJM publication.[15]

4.1.3 Quality assessment

4.1.3.1 Quality assessment of Phase III LDV/SOF trials

Appendix 10.3 of the CS[1] provided quality assessment for the included Phase III LDV/SOF trials; this information is summarised in Table 21 of the CS. It was not clear if quality assessment was conducted by one or two reviewers. The quality assessment criteria used were taken from the NICE suggested format based on the Centre for Reviews and Dissemination (CRD);[16] this is appropriate for the critical appraisal of the Phase III trials.

ION-1[13] and ION-3[14] recruited treatment-naïve populations, whereas ION-2[15] recruited a treatment-experienced population. Therefore, ION-2 is presented after the other ION trials throughout the CS and also throughout this ERG report.

Table 2 includes a summary of the company's assessment of study quality (adapted from the CS[1] Table 21, page 77) and equivalent assessment undertaken by the ERG. For the majority of items, there was agreement between CS and ERG in terms of the assessment of quality.

Table 2: CS and ERG assessment of quality of included Phase III LDV/SOF trials

ION-1		**ION-3**		**ION-2**	
CS	**ERG**	**CS**	**ERG**	**CS**	**ERG**
Was randomisation carried out appropriately?					
Yes	Yes	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?					
N/A	Yes	N/A	Yes	N/A	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?					
Yes	Yes	Yes	Yes	There were no significant differences among the treatment groups except for age (*p*=0.02).	Mostly, except for age
Were the care providers, participants and outcome assessors blind to treatment allocation?					
Study was open-label. Post-treatment HCV RNA results were blinded to the investigator and sponsor.	No, except outcome assessors for HCV RNA	Study was open-label. Post-treatment HCV RNA results were blinded to the investigator.	No, except outcome assessors for HCV RNA	Study was open-label. Post-treatment HCV RNA results were blinded to the investigator.	No, except outcome assessors for HCV RNA
Were there any unexpected imbalances in drop-outs between groups?					
No	No	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?					
No	HRQoL not published at time of CS	No	HRQoL not published at time of CS	No	HRQoL not published at time of CS
Did the analysis include an intention-to-treat analysis?					
No. The analyses assessed the patients that were randomised and received at least one dose of study drug (FAS). Appropriate methods were used to account for missing data	No, FAS	No. The analyses assessed the patients that were randomised and received at least one dose of study drug (FAS). Appropriate methods were used to account for missing data	FAS planned, but all patients dosed, so ITT in practice	No. The analyses assessed the patients that were randomised and received at least one dose of study drug (FAS). Appropriate methods were used to account for missing data	No, FAS

CS – company's submission; ERG – Evidence Review Group; HCV – hepatitis C virus; RNA ribonucleic acid; FAS – full analysis set; HRQoL – health-related quality of life; ITT – intention to treat

Randomisation and blinding

Note that randomisation here refers to the LDV/SOF groups within trials, and does not apply to the comparator of protease inhibitor (PI) treated patients, for whom historical controls were used.

The generation of randomisation sequences was adequate for all three Phase III trials. Patients were randomised in a 1:1:1:1 (ION-1, ION-2), or 1:1:1 (ION-3) ratio using an interactive web and voice system (IXRS, ION-1) or interactive web response system (IWRS, ION-3, ION-2), and randomisation was stratified for all three trials. In ION-1, randomisation was stratified by genotype and presence or absence of cirrhosis. ION-3 stratified randomisation by genotype. In ION-2, randomisation was stratified by genotype, the presence or absence of cirrhosis, and response to prior HCV therapy (relapse or virologic breakthrough versus no response).

The CS assessed allocation concealment for all three Phase III trials as "not applicable" as each study was open-label. However, allocation concealment refers to whether or not treatment allocation could be predicted before or during enrolment. This assesses whether the trial was prone to selection bias. Allocation concealment was considered adequate by the ERG as allocation was centralised by IXRS (ION-1) or IWRS (ION-3, ION-2).

The three ION trials were not blinded, but outcome assessment for post-treatment HCV RNA results were blinded to the investigator in all three trials (ION-1, ION-3, ION-2) and additionally to the sponsor in ION-1. Other outcome data were not blinded, thus leading to a risk of bias, particularly for subjective outcomes such as HRQoL. The company's response to clarification question B4 states that for open-label trials *"There is no likely impact of the study design on the objective, laboratory-determined, efficacy parameter (HCV RNA)."*[2]

Balance between groups

Note that balance between groups here refers to the LDV/SOF groups within trials, and does not apply to the comparator of PI-treated patients, for whom historical controls were used.

Within each of the Phase III trials, baseline demographic and prognostic characteristics did not differ significantly between groups, with one exception. In the ION-2 trial, there was a significant difference in age between the groups (p=0.02). Patients treated with 12-weeks LDV/SOF+RBV were older than in other treatment arms, mean age 57 (range 27-75).[15] Patients treated with 24-weeks LDV/SOF+RBV were younger than in other treatment arms, mean age 55 (range 28-70).[15] In the ION-1 trial,[13] the two treatment arms with RBV had higher proportions of patients with the CC allele of IL28B than the other treatment arms, but this did not reach statistical significance (p=0.063).[17]

Superseded – see erratum

Within each of the three trials, the frequency of assessments for endpoints was the same for each treatment group.

The number of drop-outs (Table 3) was small in the ION trials.

Table 3: Dropouts in the ION studies (adapted from CS[1] Appendix 10.3)

ION-1	ION-3	ION-2
LDV/SOF 12 weeks Lost to follow-up: 2 *LDV/SOF+RBV 12 weeks* Lost to follow-up: 4 Withdrew consent: 2 *LDV/SOF 24 weeks* Lost to follow-up: 2 Withdrew consent: 1 Discontinued due to AEs: 4 *LDV/SOF+RBV 24 weeks* Lost to follow-up: 2 Discontinued due to AEs: 6	*LDV/SOF 8 weeks* Lost to follow-up: 1 Withdrew consent: 1 *LDV/SOF+RBV 8 weeks* Lost to follow-up: 5 Withdrew consent: 1 Discontinued due to AEs: 1 *LDV/SOF 12 weeks* Lost to follow-up: 7 Discontinued due to AEs:2	*LDV/SOF 24 weeks* Withdrew consent: 1 0 drop-outs from other groups

LDV/SOF – ledipasvir/sofosbuvir

Outcomes and ITT analysis

HRQoL outcomes were not published at time of submission, and were not listed on ClinicalTrials.gov[18] however they were reported in the submission (see CS[1] Tables 23, 26 and 30).

For the efficacy analyses, all patients were analysed in the treatment arm to which they were randomly allocated. Each of the three included Phase III trials provided data from a full analysis set (FAS, see CS[1] page 68), which is a modified ITT analysis, including only randomised patients who received at least one dose of the study drug. For the ION-3 trial, all patients received at least one dose of the study drug. For SVR and HRQoL outcomes, missing data were imputed, meaning these analyses were ITT analyses.

For all three included Phase III trials, no patient received treatment for which they were not allocated. The safety analysis sets consisted of the same patients as the efficacy analyses, that is, the FAS of only randomised patients who received at least one dose of the study drug.

For the three included Phase III trials, missing data were imputed only for HCV RNA and HRQoL outcomes. According to page 71 of the CS,[1] *"For categorical HCV RNA data, if a data point was missing and was preceded and followed by values that were a success (<LLOQ TND and/or <LLOQ detected) then the missing data point was termed a bracketed success; otherwise the data point was termed a bracketed failure (≥LLOQ detected). Patients with missing data due to premature*

discontinuation of the study had missing data imputed up to the time of their last dose (if last dose was on-treatment). If study day associated with the last dose was ≥the lower bound of a visit window, and the value at visit was missing, then the value was imputed. If the study day associated with the last dose was <the lower bound of the visit window, then the on-treatment value at that visit remained missing. If HCV RNA values after the last dose of study drug were missing, the patient was considered a treatment failure for SVR outcomes. However, patients who achieved SVR12 and had no further HCV RNA measurements were counted as having achieved SVR24 due to the high correlation between SVR12 and SVR24. For continuous HCV RNA efficacy data, missing values in a visit window which were bracketed by values that were a success were set to 24 IU/mL. No other imputations were performed for continuous data. For HRQL data, missing data at on-treatment visits and post-treatment week 4 visit were not imputed. The last post-treatment observation carried forward was used for imputation of missing data at post-treatment visits after post-treatment week 4."

The three Phase III trials did not have comparator treatment arms. Historical controls were used to compare LDV/SOF treatment with TVR or BOC treatment (see CS[1] Table 17).

For treatment-naïve patients, trial data were used for TVR from the ADVANCE study[19] and BOC from the SPRINT2 study.[20] These studies provided approximate SVR rates of 70% for non-cirrhotic patients, and 44% for cirrhotic patients.

For ION-1, adjustment for the expected rate of 20% cirrhotic patients produced an estimated SVR rate of 65% for controls. There was no recalculation based on actual rates of cirrhotic patients enrolled.

Actual rates of cirrhosis in the four treatment arms of ION-1 ranged from 15 to 17%. This was only a small difference from the expected rate.

For ION-3, only non-cirrhotic patients were enrolled, but the control SVR rate was estimated as 65% (rather than 70%) based on the assumption that a minimum of 8% of the ION-3 patients would be IFN-ineligible and that these patients had an assumed 5% response rate. Actual rates of IFN ineligible patients in the three treatment groups of ION-3 ranged from 6% to 7%.

For both the ION-1 and ION-3 trials, the comparator rate used was 60% (rather than 65%) based on a reported *"5% trade-off in efficacy exchanged for an improved safety profile and shorter treatment duration"* (see CS[1] Table 17). The ERG believes that a more rigorous approach would have involved using the 65% figure, and investigating safety separately.

For ION-2, control data for treatment-experienced patients were derived from the REALIZE study[21] of TVR, and the RESPOND-2 study[22] of BOC. According to clinical advice received by the ERG, TVR and BOC are the protease inhibitors used in current UK practice. These studies provided approximate SVR rates of 69% for non-cirrhotic patients and 50% for cirrhotic patients. Adjustment for an expected rate of 20% cirrhotic patients produced an estimate of 65% SVR rate for controls. The actual rate of cirrhosis in ION-2 was 20% in all four treatment arms.

Based on assumptions of 50% of ION-2 patients having failed PI+PEG-IFN+RBV treatment, the control SVR rate was estimated as 35%, assuming only 5% of these patients achieved SVR. Clinical advice received by the ERG suggests that in current UK practice, it would be unusual for a patient failing one PI to be given another PI regimen. Actual rates of prior treatment with a PI regimen in ION-2 ranged from 46% to 61% across the four treatment groups; there was no recalculation to adjust the control rate accordingly.

For ION-2, the comparator rate used was 25%, based on *"allowing for a further 10% trade-off in efficacy exchanged for an improved safety profile and shorter treatment duration."*

Based on these assumed control rates, sample size was determined to be adequately powered to detect superiority of LDV/SOF (based on null hypothesis) using a two-sided one-sample binomial test at a significance level of 0.0125. For ION-1, a sample size of 200 patients in each treatment group was calculated to provide over 91% power to detect ≥13% improvement in SVR12 rate from historical controls. For ION-3, a sample size of 200 patients in each treatment group was calculated to provide over 90% power to detect ≥30% improvement in SVR12 rate. For ION-2, a sample size of 100 patients in each treatment group was calculated to provide over 99% power to detect ≥45% improvement in SVR12 rate.

The ERG notes that there are limitations with the use of historical controls. This is particularly true of cases whereby there are changes in the definition of, or diagnostic methods used to detect, the condition under consideration. This is however unlikely to be an issue for hepatitis C.[12] Based on clinical expert advice received by the ERG, the use of historical controls in this context was considered to be reasonable. There can also be a problem with treatment pathways differing between patient groups, although in this case it would not be an issue for treatment-naïve patients. By using historical controls, the intervention and control groups are not randomised, and therefore may differ in demographic and prognostic characteristics. These concerns should be borne in mind when interpreting the results of the ION studies presented within the CS.[1]

Baseline characteristics for the trials used as historical controls, ADVANCE, SPRINT2, REALIZE, RESPOND-2, are detailed in Section 4.3 of this ERG report and Tables 39 and 40 of the CS.[1]

The ERG notes that the historical control SVR rates were not the same as those used to inform the effectiveness estimates of comparators in the company's health economic analysis (see CS[1] Section 7). The ADVANCE, SPRINT2, REALIZE, RESPOND-2 trials were used, but considered separately by comparator regimens, and additional trials were used to inform estimates for TVR treatment in GT1 treatment-naïve patients (ILLUMINATE and C211).[21] SVR rates used in the company's health economic analysis are discussed further in Section 5.2.3.2.

4.1.3.2 Quality assessment of Phase II LDV/SOF trials

Quality assessment of Phase II trials was provided in the company's clarification response[2] (question B4). The quality assessment criteria used by the company were taken from those suggested by NICE which in turn are based on criteria from the CRD.[16] The ERG considers the use of these criteria to be appropriate for the critical appraisal of controlled trials. This was not the best choice of assessment tool for the ERADICATE trial which included only one treatment arm. As most of the Phase II trials were ongoing, it was not deemed appropriate by the ERG to ask if the authors measured more outcomes than they reported.

Not all arms of all Phase II trials were included in the CS.[1] ELECTRON-2 provided data from four arms, two of which were randomised (GT3a patients), two of which were not (GT1).[23] The ELECTRON study had both randomised and non-randomised arms that were included in the CS. Treatment-experienced GT1 patients with cirrhosis were randomised into two groups: LDV/SOF or LDV/SOF+RBV for 12 weeks. The other three included LDV/SOF groups were not randomised: GT1 treatment-naive patients; GT1 treatment-experienced patients, and; GT1 patients with an inherited bleeding disorder. For SYNERGY, two arms provided results in the CS,[1] from a study with several treatment groups.

Table 4 includes a summary of the company's and the ERG's quality assessment of the included Phase II LDV/SOF trials.

Superseded — see erratum

Table 4: CS and ERG assessment of quality of included Phase II LDV/SOF trials

ELECTRON-2[23;24]		SOLAR-1[25]		ELECTRON[26]		LONESTAR[27]		SIRIUS[28]		SYNERGY[29]		ERADICATE[30]	
CS	**ERG**	**CS**	**ERG**	**CS**	**ERG**	**CS**	**ERG**	**CS**	**ERG**	**CS**	**ERG**	**CS**	**ERG**
Was randomisation carried out appropriately?													
Yes for GT3 arms. GT1 not randomised	Unclear Only GT3 TN arms randomised, method of sequence generation NR	Yes	Yes - IWRS	Yes for randomised arms	Yes for randomised arms. Computer generated sequence	Yes	Yes computer generated sequence	Yes	Yes computer generated sequence	N/A	N/A	N/A	N/A
Was the concealment of treatment allocation adequate?													
N/A	Unclear method of allocation NR	N/A	Yes - IWRS	N/A	Yes, for randomised arms there was central allocation	N/A	Yes, central allocation	Yes	Yes, IWRS	N/A	N/A	N/A	N/A
Were the groups similar at the outset of the study in terms of prognostic factors?													
Yes for GT3. GT1 not randomised, baseline characteristics not discussed	Yes for randomised arms. Other arms not discussed	Yes	Yes (based on CS clarification response, unclear from publication)	Yes for randomised arms Other arms not randomised, baseline characteristics not discussed	Yes for randomised arms Other arms not discussed	Yes	Yes	Yes	Yes (based on CS clarification response, unclear from publication)	N/A groups not compared as different genotypes	Groups included in CS not compared	N/A	N/A One treatment arm, patients discussed in two groups according to HIV treatment
Were the care providers, participants and outcome assessors blind to treatment allocation?													
Open-label	No Open-label	Open-label	No Open-label	Open-label	No Open-label	Open-label	No Open-label	Yes	Yes, Double-blind	Open-label	No Open-label	Open-label	No Open-label
Were there any unexpected imbalances in drop-outs between groups?													

ELECTRON-2[23;24]		SOLAR-1[25]		ELECTRON[26]		LONESTAR[27]		SIRIUS[28]		SYNERGY[29]		ERADICATE[30]	
CS	**ERG**	**CS**	**ERG**	**CS**	**ERG**	**CS**	**ERG**	**CS**	**ERG**	**CS**	**ERG**	**CS**	**ERG**
No	no	No, as expected higher on-treatment discontinuation rates in patients receiving the 24 week duration	no	No	no	No	no	No	No (1 patient discontinued)	N/A Groups not compared as different genotypes	Groups included in CS not compared	No	N/A
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?													
No, patients that were randomised and received at least one dose of study drug (FAS)	No, FAS	No, patients that were randomised and received at least one dose of study drug (FAS)	FAS planned (limited SVR12 data available at time of CS)	No, patients that were randomised and received at least one dose of study drug (FAS)	FAS but all patients dosed and followed up (so ITT for groups included in CS)	No, patients that were randomised and received at least one dose of study drug (FAS)	FAS, but all randomised patients included in analysis	No, patients that were randomised and received at least one dose of study drug (FAS)	No, FAS, one patient that discontinued due to AE (on placebo) was excluded from analysis	Yes (one patient had not reached SVR12 time point at CS but will be included in analysis)	Not currently, but ITT planned	Yes	FAS but all enrolled patients dosed and followed up, so ITT

CS – company's submission; ERG – Evidence Review Group; ITT – intention to treat; FAS – full analysis set; IWRS - interactive web response system; SVR – sustained virologic response; HIV – human immunodeficiency virus

4.1.3.3 Quality assessment of trials providing SVR data in comparator drug regimens

Quality assessment of trials that were used for comparator data was provided in the company's response to clarification[2] (question B8). The quality assessment criteria used were taken from the NICE suggested format based on criteria produced by the CRD;[16] this is appropriate for the critical appraisal of controlled trials. The use of these criteria was not however the best choice of assessment tool for the NEUTRINO trial which was a single cohort trial, or for the PROTON trial for which only the single cohort (cohort B) part of the trial was applicable to the CS.[31]

Eighteen trials provided SVR data for comparator drug regimens. Study characteristics are presented in Section 4.3 of this ERG report.

Nine trials provided SVR data for comparator drug regimens in GT1 treatment-naïve patients. NEUTRINO (SPC[32] and Lawitz *et al* 2013[33]) provided data on SOF+PEG-IFN+/RBV. Two studies provided data on SMV+PEG-IFN+RBV: QUEST (C208) (SPC[34] and Jacobsen 2014[35]); and QUEST 2 (C216) (SPC[34] and Manns 2014[36]). Poordad *et al*, 2013[20] provided data on BOC+PEG-IFN+RBV. Three studies provided data on TVR+PEG-IFN+RBV: ADVANCE (Study 108; Jacobson *et al*, 2011[19], SPC[21]); ILLUMINATE (Study 111) (SPC[21]); and Study C211 (SPC[21]). IDEAL[37] provided data on PEG-IFN+RBV. COSMOS (SPC,[34] Lawitz *et al* 2014,[38]) provided data on SMV+SOF in GT1 treatment-naïve patients and also in GT1 treatment-experienced patients.

Five trials (including COSMOS as mentioned above) provided SVR data for comparator drug regimens in GT1 treatment-experienced patients. RESPOND-2[22] provided data on BOC+PEG-IFN+RBV. Two trials provided data on SMV+PEG-IFN+RBV: PROMISE (HPC3007) (SPC[34] and Forns *et al* 2014[39]); and ASPIRE (C206) (SPC[34]). REALIZE (Study C216 (SPC[21]) provided data on two treatment regimens: PEG-IFN+RBV and TVR+PEG-IFN+RBV.

Five trials provided SVR data for comparator drug regimens in GT3 treatment-naïve patients. FISSION (SPC[32] and Lawitz *et al*, 2013[33]) provided data on PEG-IFN+RBV. VALENCE (SPC[32] and Zeuzem *et al*, 2014[40]) provided data on SOF+RBV in GT3 treatment-naïve patients and also in GT3 treatment-experienced patients. Both ELECTRON (SPC[32] and Gane 2013[41]) and PROTON (SPC[32], Lawitz, 2013[31] and clinical study report [CSR][42]) provided data on SOF+PEG-IFN+RBV. The CS also used the treatment arm SOF+PEG-IFN+RBV from LONESTAR-2 for data on cirrhotic patients in the GT3 treatment-naïve analysis even though the study was conducted in GT3 treatment-experienced patients, with the CS explaining this as otherwise no data would be available for cirrhotic patients in this treatment regimen (see CS[1] page 123).

VALENCE[32,40] (as mentioned above) was the only study that provided data for GT3 treatment-experienced patients.

The ELECTRON study was the same study as included for LDV/SOF trials, but a different part of this study was used for the comparator. Quality assessment for the ELECTRON study is reported in Section 4.1.3.2 with the other Phase II LDV/SOF trials. The quality assessment for the other seventeen comparator trials is shown in Tables 5-7; this information was taken from the company's response to clarification[2] (question B8).

Note that quality assessment is provided to illustrate trial quality only. Randomisation and similarity between groups applies only to groups within each trial. It does not apply to comparisons between LDV/SOF and comparator regimen trials in the health economic analysis presented within the CS.[1]

Table 5: Company's quality assessment of simeprivir and boceprivir trials (adapted from clarification response[2] question B8 Table 12)

Simeprevir										**Boceprevir**			
QUEST1[35,43]		**QUEST2[36;43]**		**PROMISE[34;43]**		**ASPIRE[34;43]**		**COSMOS[38]**		**Poordad *et al* SPRINT-2 P05216[20;44]**		**Bacon et al 2011 RESPOND-2 P05101[22;44]**	
CS	**ERG**	**CS**	**ERG**	**CS**	**ERG**	**CS**	**ERG**	**CS**	**ERG**	**CS**	**ERG**	**CS**	**ERG**
Was randomisation carried out appropriately?													
Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?													
Yes	Yes IWRS/IVRS	Yes	Yes IWRS/IVRS	Yes	Yes	Not clear	Yes IWRS/IVRS	N/A	Yes IWRS/IVRS	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?													
Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	Mostly yes, except for Gln80Lys (Q80K) polymorphism.	Yes	Yes	Yes	Mostly yes, except for high viral load.
Were the care providers, participants and outcome assessors blind to treatment allocation?													
Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes for investigator and patients. HCV RNA monitor unblinded.[43]	No	No	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop- outs between groups?													
No	No	No	Yes. Higher discontinuations in PR arm	No	Yes. More withdrawal placebo+PR than simeprevir+PR	No	No	No	No	No	Unclear	No	Unclear
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?													
Yes	No, FAS	Yes	No, FAS	Yes	No, FAS	Yes	No, FAS (one patient only randomised not dosed)	Yes	No, FAS	Yes	No, FAS	Yes	No, FAS

CS – company's submission; ERG – Evidence Review Group; PR = peg-interferon-2a and ribavirin; IWRS - interactive web response system; IWRS - interactive web response system

Table 6: Company's quality assessment of telaprevir and peginterferon+ribavirin trials (adapted from clarification response[2] question B8 Table 13)

Telaprevir		**Telaprevir and Peginterferon+ribavirin**		**Telaprevir**				**Peginterferon+ribavirin**		**Peginterferon+ribavirin and sofosbuvir**	
ADVANCE[19,45]		**REALIZE[21;45]**		**ILLUMINATE[21]**		**C211[21]**		**IDEAL[37]**		**FISSION[33]**	
CS	**ERG**	**CS**	**ERG**	**CS**	**ERG**	**CS**	**ERG**	**CS**	**ERG**	**CS**	**ERG**
Was randomisation carried out appropriately?											
Yes	Yes	Not clear	Unclear randomisation list constructed through random permuted blocks	Not clear	Unclear	Not clear	Unclear	Yes	Yes	Yes	Unclear how sequence generated
Was the concealment of treatment allocation adequate?											
Yes	Yes	Yes	Yes	N/A	Unclear	N/A	Unclear	Yes	Yes IVRS	N/A	Yes, central allocation
Were the groups similar at the outset of the study in terms of prognostic factors?											
Yes	Mostly, apart from BMI sig (*p*-0.02) higher in TVR/PR than placebo/PR	Yes	Yes	Not clear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?											
Not clear	Unclear – blinded until weeks 28, but HCV RNA assessor unblinded	Yes	Yes	No	No	No	No	Yes	Yes	N/A	No, open label
Were there any unexpected imbalances in drop- outs between groups?											
Yes	Yes	Yes	Yes	No	Unclear	Not clear	Unclear	No	No (large numbers of dropouts in all groups)	No	no
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?											
Yes	No, FAS patients who had received at least one dose of the study drug (n=7 fewer than ITT)	Yes	No, FAS patients who had received at least one dose of the study drug (n=1 less than ITT)	Yes	Unclear	Yes	Yes	Unclear	No, FAS	Yes	No, FAS patients who had received at least one dose of the study drug (499 of 527 randomised)

CS – company's submission; ERG – Evidence Review Group; FAS – full analysis set; TVR – telaprevir; RNA – ribonucleic acid; HCV – hepatitis C virus; BMI – body mass index

Table 7: Company's quality assessment of sosfbuvir trials (adapted from clarification response[2] question B8 Table 14, FISSION in table above)

GS-US-334-0110 (NEUTRINO, single cohort study)[12;33]		GS-US-334-0133 (VALENCE)[12,40]		P7077-0422 (PROTON,[31] single cohort (cohort B) (RCT part of study but not licensed SOF regimens)		GS-US-334-0151 (LONESTAR-2,[32;46] non-random)	
CS	**ERG**	**CS**	**ERG**	**CS**	**ERG**	**CS**	**ERG**
Was randomisation carried out appropriately?							
N/A	N/A	Yes	Yes	N/A	N/A	N/A	N/A
Was the concealment of treatment allocation adequate?							
N/A	N/A	Yes	Yes, IWRS (randomisation broken during trial)	N/A	N/A	N/A	N/A
Were the groups similar at the outset of the study in terms of prognostic factors?							
N/A	N/A	Yes	Yes	Yes	N/A	Yes	N/A
Were the care providers, participants and outcome assessors blind to treatment allocation?							
N/A	N/A, open label	Yes	No (initially blinded, unblinded when randomisation broken)	N/A	N/A, open label	N/A	N/A
Were there any unexpected imbalances in drop- outs between groups?							
N/A	N/A	No	Yes, placebo arm terminated by sponsor	No	N/A	No	N/A
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?							
Yes	No, FAS (one patient enrolled but not treated)	Yes	No, randomisation broken	Yes	Yes	Yes	Yes

CS – company's submission; ERG – Evidence Review Group; IWRS - interactive web response system; FAS – full analysis set; N/A – not applicable

4.2 Clinical effectiveness trials of LDV/SOF

No RCTs or other head-to-head trials were identified that compared LDV/SOF with comparators listed in the final NICE scope.[5] The ERG believes that no RCTs of LDV/SOF were missed by the CS and that no other head-to-head trials with reported clinical effectiveness data available were excluded from the CS. Ongoing trials are mentioned on page 17 of the CS;[1] these studies are detailed in Appendix 1 of this report.

The CS included ten trials of LDV/SOF. These comprised three Phase III trials and seven Phase II trials. Quality assessment of the LDV/SOF trials is reported in Section 4.1.3.

The three Phase III trials, and the ELECTRON-2 GT3 treatment-naïve LDV/SOF+RBV treated group, were the only trials used to provide LDV/SOF SVR data within the company's health economic analysis (see Section 5.2.3). However, data for the comparator treatment SOF+PEG-IFN+RBV in GT3 treatment-naïve patients were taken from the ELECTRON study.

4.2.1 Study characteristics of LDV/SOF trials included in the review

Effectiveness data were taken from three Phase III trials (ION-1, ION-3, ION-2) and seven Phase II trials (ELECTRON, ELECTRON-2, LONESTAR, SYNERGY, SIRIUS, ERADICATE, SOLAR-1).
For the three Phase III trials, LDV/SOF was administered orally once daily as a single tablet containing a fixed dose combination (FDC) of 90 mg of LDV and 400 mg of SOF (LDV/SOF). This was also the case for most of the included Phase II trials, however ELECTRON included a treatment arm where LDV and SOF were administered as single agents (LDV+SOF). For treatment arms including RBV, this was administered orally twice daily, at a dose of 1,000 mg daily in patients with a body weight <75 kg, or 1,200 mg daily in patients with a body weight ≥75kg. All included trials had at least one treatment arm which included the EMA-recommended treatment duration of LDV/SOF, for the population investigated, detailed in the EPAR.[6]

Five of the Phase II studies were considered to provide supporting data for the Phase III studies (ELECTRON, ELECTRON-2, LONESTAR, SYNERGY, SIRIUS). Two of the Phase II studies were conducted in specific populations that were not represented in the Phase III studies: in ERADICATE, the population was co-infected with HIV; in SOLAR-1, the population had decompensated liver cirrhosis, or had undergone liver transplant.

Study characteristics of included LDV/SOF trials are shown in Table 8.

The three Phase III studies (ION-1, ION-3, ION-2), and two of the Phase II studies (ELECTRON and LONESTAR) had been completed at the time of submission, whereas five Phase II studies were

ongoing (ELECTRON-2, SYNERGY, SIRIUS, ERADICATE, SOLAR-1). All studies were open-label with the exception of SYRIUS which was double-blind. SYNERGY and ERADICATE were sponsored by the National Institute of Allergy and Infectious Diseases (NIAID); the remaining studies were sponsored by Gilead Sciences.

The three Phase III trials were multicentre studies. ION-1 had some centres in Europe, including seven in England, as well as sites in the United States of America. ION-3 and ION-2 had sites only in the USA. For the three Phase III trials, follow-up was 24 weeks post-treatment. For the outcome of SVR, all patients underwent assessment at 12 weeks post-treatment, and patients with HCV RNA<LLOQ (25 IU/mL) at post-treatment week 12 had to complete post-treatment week 24 assessments unless confirmed viral relapse occurred.

Superseded – see erratum

Table 8: Characteristics of LDV/SOF trials providing clinical effectiveness data in the CS[1]

Trial identifiers	Study design	Population	Intervention(s) Sample size / N randomised or allocated	Primary outcome(s)[18]
ION-1[13;17] **GS-US-337-0102** **NCT01701401**	Phase III randomised multicentre, open-label	GT1 Treatment-naïve No cirrhosis or compensated cirrhosis	LDV/SOF for 12 weeks (n=214) LDV/SOF+RBV for 12 weeks (n=217) (12 weeks RBV not licensed) LDV/SOF for 24 weeks (n=217) LDV/SOF+RBV for 24 weeks (n=217) (n=870 randomised, 5 of these not treated – allocated group unclear from patient flow chart)	SVR12 Discontinuation due to AEs
ION-3[14;11] **GS-US-337-0108** **NCT01851330**	Phase III randomised multicentre, open-label	GT1 Treatment-naïve No cirrhosis	LDV/SOF for 8 weeks (n=215) LDV/SOF+RBV for 8 weeks (n=216) (not licensed) LDV/SOF for 12 weeks (n=216)	SVR12 Discontinuation due to AEs
ION-2[15;17] **GS-US-337-0109** **NCT01768286**	Phase III randomised multicentre, open-label	GT1 Treatment-experienced No cirrhosis or compensated cirrhosis	LDV/SOF for 12 weeks (n=109) LDV/SOF+RBV for 12 weeks (n=111) (note - 12 weeks RBV not licensed) LDV/SOF for 24 weeks (n=109) LDV/SOF+RBV for 24 weeks (n=111) (n=441 randomised, 1 of these not treated – allocated group unclear from patient flow chart)	SVR12 Discontinuation due to AEs

Trial identifiers	Study design	Population	Intervention(s) Sample size / N randomised or allocated	Primary outcome(s)[18]
ELECTRON[26] **P7977-0523** **NCT01260350**	Phase II Conducted in several parts Some randomised and some non-randomised arms	GT1 Treatment-naïve (no cirrhosis) Treatment-experienced (no cirrhosis) Treatment-experienced (compensated cirrhosis) Treatment-naïve or treatment-experienced with inherited blood disorders	LDV/SOF for 12 weeks (n=10 GT1 treatment-experienced with cirrhosis) LDV/SOF+RBV for 12 weeks (n=9 GT1 treatment-experienced with cirrhosis; n=14 inherited blood disorders) (12 weeks RBV not licensed) LDV+SOF (as single agents) +RBV for 12 weeks (n=25 GT1 treatment-naïve; n=9 GT1 treatment-experienced) Other arms not included in CS that did not include SOF and LDV together for GT1, or was unlicensed duration LDV/SOF+RBV for 6 weeks.	AEs occurring from baseline (day 1 for all groups) to 30 days following the last dose of study drug SVR12 included as a secondary outcome measure
ELECTRON-2[47;23;24] **GS-US-337-0122** **NCT01826981**	Phase II Randomised for GT3 treatment-naïve Non-randomised (case series) for other patients Ongoing at time of submission	Treatment-naïve, GT1, decompensated cirrhosis Treatment-naïve, GT3, no cirrhosis or compensated cirrhosis Treatment-experienced (prior SOF from ELECTRON trial), GT1, no cirrhosis Population not included in CS as data not available at time of submission: Treatment-experienced, GT3, no cirrhosis or compensated cirrhosis, n=50. Population not included in CS as GT6 not included: Treatment-naïve and treatment-experienced, HCV GT6, n=25.	LDV/SOF for 12 weeks (n=20 GT1 decompensated cirrhosis; n=25 GT3 treatment-naive) (12 weeks not licensed for GT3) LDV/SOF+RBV for 12 weeks (n=19 GT1 treatment-experienced; n=26 GT3 treatment-naïve)	SVR12 Discontinuation due to AEs
LONESTAR[27] **GS-US-337-0118** **NCT01726517**	Phase II	GT 1 Treatment-naïve non-cirrhotic Treatment-experienced (55% cirrhotic) (PI failures) [27]	LDV/SOF for 8 weeks n=20 GT1 treatment-naïve; LDV/SOF+RBV for 8 weeks n=21 GT1 treatment-naïve; LDV/SOF for 12 weeks n=19 GT1 treatment-naïve, n=19 GT1 treatment-experienced; LDV/SOF+RBV for 12 weeks n=21 GT1 treatment-experienced.[27]	SVR12 Discontinuation due to AEs

Trial identifiers	Study design	Population	Intervention(s) Sample size / N randomised or allocated	Primary outcome(s)[18]
SYNERGY[29;48] **CO-US-337-0117** **130066, 13-I-0066** **NCT01805882**	Phase II Non-randomised Ongoing at time of submission	GT1 Treatment experienced (prior SOF/RBV) from NIAID SPARE study No cirrhosis or compensated cirrhosis GT1 treatment-naïve,[redacted] Other group data not available at time of submission - GT4 treatment-naïve.	LDV/SOF for 12 weeks Other arms not included in CS that had unlicensed anti-viral agents [redacted]	SVR12 Incidence and severity of AEs during and following treatment
SIRIUS[28] **GS-US-337-0121** **2013-002296-17** **NCT01965535**	Phase II Randomised study Ongoing at time of submission	GT1 Treatment experienced (at least one PEG-IFN+RBV regimen followed by at least one PI+PEG-IFN+RBV regimen) Compensated cirrhosis	LDV/SOF (and placebo for RBV) for 24 weeks (n=77) PBO 12 weeks then LDV/SOF +RBV for 12 weeks (n=78)	SVR12
ERADICATE[30] **CO-US-337-0116** **NCT01878799**	Phase II Non-randomised Phase IIb Ongoing at time of submission	GT1 Treatment naïve No cirrhosis or compensated cirrhosis HCV/HIV co-infection (antiretroviral (ARV) untreated, or ARV treated)	LDV/SOF for 12 weeks (n=13 ARV untreated, n=37 ARV treated)	SVR12
SOLAR-1[25;49] **GS-US-337-0123** **NCT01938430**	Phase II Randomised study Ongoing at time of submission	GT1 or GT4 Decompensated liver cirrhosis, or post-liver transplant Treatment-naïve or treatment-experienced[25]	LDV/SOF+RBV for 12 weeks[redacted] No SVR12 data available at time of CS LDV/SOF+RBV for 24weeks [redacted]	SVR12 Discontinuation due to AEs

GT – genotype; HCV – hepatitis C virus; HIV – human immunodeficiency virus; SVR – sustained virologic response; AE – adverse event;
Note - SVR12 defined as HCV RNA<LLOQ, 12 weeks after the end of treatment, for all studies; lower limit of quantitation (LLOQ) was 25 IU/mL

Superseded — see erratum

The population in most of the included studies had GT1 disease. Some patients with GT3 disease were included in ELECTRON-2, and some GT4 patients were included in SYNERGY.

Two of the Phase III trials recruited treatment-naïve populations (ION-1 and ION-3). ION-2 recruited a treatment-experienced population, with prior virologic failure after treatment with an NS3/4A PI plus PEG-IFN and RBV, or a PEG-IFN/RBV regimen. Patients were classified as either non-responders (did not achieve undetectable HCV RNA≥LLOQ whilst on treatment), or relapse/breakthrough (achieved HCV RNA<LLOQ during treatment or within 4 weeks post-treatment but did not achieve SVR). Patients were ineligible for ION-2 if they had previously discontinued treatment due to an AE.

Of the Phase II trials providing supporting data to the Phase III trials (ELECTRON, ELECTRON-2, LONESTAR, SYNERGY, SIRIUS), all recruited treatment-experienced patients, and four additionally included treatment-naïve patients (ELECTRON, ELECTRON-2, LONESTAR and SYNERGY). For the Phase II trials with specific populations, ERADICATE recruited treatment-naïve patients, whereas SOLAR-1 patients had advanced liver disease, and prior HCV treatment naïve/experienced was not part of the eligibility criteria.

For the three Phase III trials, the eligibility criteria specified were: age ≥18 years; BMI≥18 kg/m^2; HCV RNA≥10^4 IU/mL at screening; confirmation of chronic HCV infection by positive anti-HCV, positive HCV RNA or positive HCV genotyping ≥6 months prior to baseline, or liver biopsy with evidence of CHC; ECG at screening without clinically significant abnormalities; general good health as determined by the investigator. The following laboratory parameters were also required at screening: ALT≤10 x ULN; AST≤10 x ULN; Direct bilirubin ≤1.5 x ULN; Platelets >50,000 (>90,000 for ION-3); HbA1c ≤8.5%; CLcr ≥60 mL/min; Haemoglobin ≥11 g/dL for female patients, ≥12 g/dL for male patients; Albumin ≥3 g/dL; INR≤1.5 x ULN or stable anticoagulant regimen.

Patients were excluded if they had: co-infection with HBV or HIV; decompensated liver disease; other chronic liver disease; major organ transplant; clinically relevant drug abuse; alcohol misuse; pregnancy or nursing, or men with pregnant partners; gastrointestinal disorder or post-operative condition that could interfere with absorption of the study drug; malignancy or psychiatric hospitalisation within five years; chronic use of systemically administered immunosuppressive agents.

Tables 9, 10 and 11 present the baseline characteristics of the Phase III trials included in the CS.[1] Baseline characteristics of the Phase II trials are shown in Tables 12-15.

Table 9: Baseline characteristics of ION-1 (GT1 treatment-naïve, taken from CS[1] Table 13)

Baseline characteristics ION-1	**12 weeks**		**24 weeks**	
	LDV/SOF (n=214)	**LDV/SOF+RBV (n=217)**	**LDV/SOF (n=217)**	**LDV/SOF+RBV (n=217)**
Mean age (range), years	52 (18–75)	52 (18–78)	53 (22–80)	53 (24–77)
Male, n (%)	127 (59)	128 (59)	139 (64)	119 (55)
Mean BMI (range), kg/m^2	27 (18–41)	27 (18–42)	27 (18–48)	26 (18–48)
Race, n (%)[‡]				
White	187 (87)	188 (87)	177 (82)	183 (84)
Black	24 (11)	26 (12)	32 (15)	26 (12)
Asian	1 (<1)	0	5 (2)	5 (2)
Other	2 (1)	3 (1)	3 (1)	3 (1)
Ethnic group, n (%)				
Hispanic	26 (12)	20 (9)	29 (13)	26 (12)
Non-Hispanic	187 (87)	197 (91)	188 (87)	190 (88)
Not disclosed	1 (<1)	0	0	1 (<1)
Region, n (%)				
US	125 (58)	118 (54)	132 (61)	137 (63)
Europe	89 (42)	99 (46)	85 (39)	80 (37)
HCV genotype, n (%)				
1a	144 (67)	148 (68)	146 (67)	143 (66)
1b	66 (31)	68 (31)	68 (31)	71 (33)
Other	4 (2)	1 (<1)	3 (1)	3 (1)
Mean HCV RNA±SD, $\log_{10}$ IU/mL	6.4±0.69	6.4±0.64	6.3±0.68	6.3±0.65
HCV RNA≥800,000 IU/mL, n (%)	169 (79)	173 (80)	168 (77)	173 (80)
IL28B genotype, n (%)				
CC	55 (26)	76 (35)	52 (24)	73 (34)
CT	113 (53)	107 (49)	119 (55)	112 (52)
TT	46 (21)	34 (16)	46 (21)	32 (15)
Cirrhosis, n (%)	34 (16)	33 (15)	33 (15)	36 (17)
ALT>1.5 x ULN, n (%)	120 (56)	119 (55)	109 (50)	112 (52)
IFN eligibility status, n (%)				
Eligible	200 (93)	197 (91)	198 (91)	203 (94)
Ineligible	14 (7)	20 (9)	19 (9)	14 (6)

BMI – body mass index; IFN – interferon; ALT - Alanine aminotransferase; ULN - Upper limit of the normal range

Table 10: Baseline characteristics of ION-3 (GT1 treatment-naïve, adapted from CS[1] Table 14)

Baseline characteristics ION-3	**8 week regimen**		**12 week regimen**
	LDV/SOF (n=215)	**LDV/SOF+RBV (n=216)**	**LDV/SOF (n=216)**
Mean age (range), years	53 (22–75)	51 (21–71)	53 (20–71)
Male, n (%)	130 (60)	117 (54)	128 (59)
Mean BMI (range), kg/m^2	28 (18–43)	28 (18–56)	28 (19–45)
Race, n (%)			
White	164 (76)	176 (81)	167 (77)
Black	45 (21)	36 (17)	42 (19)
Other	6 (3)	4 (2)	7 (3)
Ethnic group, n (%)			
Hispanic	13 (6)	12 (6)	14 (6)
Non-Hispanic	200 (93)	204 (94)	202 (94)
Not disclosed	2 (1)	0	0
HCV genotype, n (%)			
1a	171 (80)	172 (80)	172 (80)
1b	43 (20)	44 (20)	44 (20)
1 without confirmed subtype	1 (<1)	0	0
Mean HCV RNA±SD, $\log_{10}$ IU/mL	6.5±0.8	6.4±0.7	6.4±0.8
HCV RNA≥800,000 IU/mL, n (%)	181 (84)	171 (79)	172 (80)
IL28B genotype, n (%)			
CC	56 (26)	60 (28)	56 (26)
CT	120 (56)	128 (59)	124 (57)
TT	39 (18)	28 (13)	36 (17)
ALT>1.5 x ULN, n (%)	87 (40)	95 (44)	99 (46)
Fibrosis score from liver biopsy, n (%)[14]			
F0–F2	127 (59)	108 (50)	127 (59)
F3	29 (13)	28 (13)	29 (13)
FibroTest-Determined Metavir score[6]			
F0-F1	72 (33)	81 (38)	72 (33)
F2	65 (30)	61 (28)	65 (30)
F3-F4	77 (36)	71 (33)	79 (37)
Not interpretable	1 (<1)	3 (1)	0 (0)
IFN eligibility status, n (%)			
Eligible	202 (94)	203 (94)	203 (94)
Ineligible	13 (6)	13 (6)	15 (7)

BMI – body mass index; IFN – interferon; ALT - Alanine aminotransferase; ULN - Upper limit of the normal range

Table 11: Baseline characteristics of ION-2 (GT1 treatment-experienced, taken from CS[1] Table 15)

Baseline characteristics ION-2	**12 week regimen**		**24 week regimen**	
	LDV/SOF (n=109)	**LDV/SOF+RBV (n=111)**	**LDV/SOF (n=109)**	**LDV/SOF+RBV (n=111)**
Mean age (range), years	56 (24–67)	57 (27–75)	56 (25–68)	55 (28–70)
Male, n (%)	74 (68)	71 (64)	74 (68)	68 (61)
Mean BMI (range), kg/m^2	29 (19–47)	28 (19–45)	28 (19–41)	28 (19–50)
Race, n (%)				
White	84 (77)	94 (85)	91 (83)	89 (80)
Black	24 (22)	16 (14)	17 (16)	20 (18)
Asian	1 (1)	0	0	0
Hawaiian or Pacific Islander	0	1 (1)	0	1 (1)
Other	0	0	1 (1)	1 (1)
Ethnic group, n (%)				
Hispanic	7 (6)	12 (11)	11 (10)	11 (10)
Non-Hispanic	100 (92)	99 (89)	98 (90)	99 (89)
Not disclosed	2 (2)	0	0	1 (1)
HCV genotype, n (%)				
1a	86 (79)	88 (79)	85 (78)	88 (79)
1b	23 (21)	23 (21)	24 (22)	23 (21)
Mean HCV RNA±SD, $\log_{10}$ IU/mL	6.5±0.44	6.4±0.54	6.4±0.57	6.5±0.60
HCV RNA≥6 $\log_{10}$ IU/mL, n (%)	96 (88)	94 (85)	86 (79)	91 (82)
IL28B genotype, n (%)				
CC	10 (9)	11 (10)	16 (15)	18 (16)
CT	70 (64)	77 (69)	68 (62)	68 (61)
TT	29 (27)	23 (21)	25 (23)	25 (23)
Cirrhosis, n (%)	22 (20)	22 (20)	22 (20)	22 (20)
ALT>1.5 x ULN, n (%)	53 (49)	51 (46)	60 (55)	49 (44)
Prior treatment				
PEG-IFN or IFN, + RBV, n (%)	43 (39)	47 (42)	59 (54)	60 (54)
PI regimen, n (%)	66 (61)	64 (58)	50 (46)	51 (46)
Prior response to treatment, n (%)				
Relapse or virologic breakthrough	60 (55)	65 (59)	60 (55)	60 (54)
No response	49 (45)	46 (41)	49 (45)	51 (46)

BMI – body mass index; IFN – interferon; ALT - Alanine aminotransferase; ULN - Upper limit of the normal range; PI – protease inhibitor

Table 12: Baseline characteristics of GT1 treatment-naïve Phase II trials (adapted from CS[1] Table 31 Section 6.5.7 CS, and Gane 2014,[26] Lawitz 2013 [27] and Kohli 2014[48])

Characteristic	**ELECTRON**[26]	**ELECTRON-2 GT1, CPT class B**	**LONESTAR**[27]	**LONESTAR**[27]	**LONESTAR**[27]	**SYNERGY**[48]
	LDV+SOF+RBV 12 weeks N=25	**LDV/SOF N=20**	**LDV/SOF 8 weeks N=20**	**LDV+SOF+RBV 8 weeks N=21**	**LDV/SOF 12 weeks N=19**	**LDV/SOF 12 weeks** [redacted]
Mean age (range), years	45 (SD=9.2) (range NR)	56 (47–72)	48 (SD=10.7)	50 (SD=11.1)	46 (SD=11.6)	[redacted]
Male, n (%)	8 (32)	17 (85)	14 (70)	12 (57)	11 (58)	[redacted]
White, n (%)	23 (92)	17 (85)	Non-black 16 (80)	Non-black 21 (100)	Non-black 18 (95)	[redacted]
Mean BMI (range), kg/m^2	25.2 (SD=4.3) (range NR)	31 (20–50)	28.7 (SD6.9)	29.8 (5.5)	28.1 (5.8)	[redacted]
Cirrhosis	0%	20 (100)	20 (100)	21 (100)	19 (100)	[redacted]
IL28B CC, n (%)	9 (36)	7 (35)	4 (20)	7 (33)	1 (5)	[redacted]
GT 1a, n (%)	20 (80)	18 (90)	17 (85)	19 (90)	17 (89)	[redacted]
GT 1b, n (%)	5 (20)	2 (10)	3 (15)	2 (10)	2 (11)	[redacted]
Mean HCV RNA (range), log10 IU/mL	5.9 (SD=0.9) (range NR)	6.0 (4.9–6.7)	6.1 (SD=0.8)	6.0 (SD=0.8)	6.1 (SD=0.8)	[redacted]

BMI – body mass index; HCV – hepatitis C virus; GT – genotype; RNA – ribonucleic acid; HAI – Histologic Activity Index; SD – standard deviation; NR – not reported

Table 13: Baseline characteristics of GT1 treatment-experienced Phase II trials (adapted from CS[1] Table 31 and Section 6.5.7, Gane 2014,[26] Lawitz 2013[27]

Characteristic	**ELECTRON** LDV+SOF+RBV 12 weeks N=9 without cirrhosis [26]	**ELECTRON** LDV+SOF 12 weeks N=10 with cirrhosis[26]	**ELECTRON** LDV+SOF+RBV 12 weeks N=9 with cirrhosis[26]	ELECTRON-2 **GT1, prior SOF LDV/SOF+RBV n=19**	**LONESTAR[27] LDV/SOF 12 weeks N=19**	**LONESTAR[27]** LDV/SOF+RBV 12weeks N=21	**SYNERGY GT1 prior SOF/RBV[redacted] LDV/SOF 12 weeks N=14**	**SIRIUS LDV/SOF+PBO 24 weeks [redacted] and PBO 12 weeks followed by LDV/SOF+RBV 12 weeks [redacted]**
Mean age (range), years	50 (SD=13.0)	61 (SD=4.9)	57 (SD=5.2)	55 (39–65)	54 (SD=6.6)	52 (SD=9.8)	59.5[redacted]	[redacted]
Male, n (%)	7 (78)	10 (100)	8 (89)	13 (68)	15 (79)	14 (67)	13 (93)	[redacted]
White, n (%)	9 (100)	8 (80)	9 (100)	18 (95)	Non-black 17 (89)	Non-black 19 (90)	African – American (93)	[redacted]
Mean BMI (range), kg/m^2	25.6 (SD=2.3)	31.0 (6.8)	27.3 (SD=5.0)	27 (19–38)	31.4 (SD=4.7)	31.5 (7.3)	Median 28.5 [redacted]	[redacted]
Cirrhosis	0%	100%	100%	0%	11 (58)	11 (52)	(Cirrhosis NR; 50% had HAI stage 3-4 fibrosis. Fibrosis staging prior to enrollment in NIAID SPARE study)	[redacted]
IL28B CC, n (%)	0 (0%)	4 (40)	2 (22)	4 (21)	2 (11)	1 (5)	IL28B CT/TT 12 (86)	[redacted]
GT 1a, n (%)	8 (89)	8 (80)	7 (78)	17 (89)	18 (95)	16 (76)	8 (57)	[redacted]
GT 1b, n (%)	1 (11)	2 (20)	2 (22)	2 (11)	1 (5)	5 (24)		
Mean HCV RNA (range), log10 IU/mL	6.9 (SD=0.2)	6.5 (SD=0.6)	6.3 (SD=0.8)	6.3 (4.8–7.0)	6.3 (0.5)	6.2 (0.4)	[redacted]	[redacted]

BMI – body mass index; HCV – hepatitis C virus; GT – genotype; RNA – ribonucleic acid; SD – standard deviation; HAI – Histologic Activity Index; NR – not reported;

Table 14: Baseline characteristics of the GT1 HIV co-infection Phase II trial (taken from CS[1] Table 34)

Characteristic	**ERADICATE ARV untreated n=13**	**ERADICATE ARV treated n=37**
Median age (IQR), years	59 [redacted]	58 [redacted]
Male, n (%)	7 (54)	30 (81)
Median BMI (IQR), kg/m^2	26 [redacted]	26 [redacted]
BMI ≥30, n (%)	[redacted]	[redacted]
Race or ethnicity, n (%)		
White	3 (13)	4 (11)
Black	10 (77)	32 (86)
Hispanic	0	1 (3)
Knodell HAI Fibrosis, n (%)		
0–2	8 (62)	29 (78)
3–4	5 (38)	8 (22)
HCV GT1 subtype, n (%)		
1a	9 (75)	30 (81)
1b	3 (25)	7 (19)
IL28B genotype, n (%)		
CC	[redacted]	[redacted]
CT	[redacted]	[redacted]
TT	[redacted]	[redacted]
Median baseline HCV RNA (IQR), $\log_{10}$ IU/mL	6.1 [redacted]	6.0 [redacted]
HCV RNA >800,000 IU/mL, n (%)	[redacted]	[redacted]
Median Baseline CD4 (IQR)	[redacted]	[redacted]
Antiretroviral use	0	37 (100)
Tenofovir/emtricitabine plus:		
Efavirenz	N/A	15 (41)
Raltegravir	N/A	10 (27)
Rilpivirine	N/A	8 (21)
Raltegravir/rilpivirine	N/A	3 (8)
Raltegravir/efavirenz	N/A	1 (3)

IQR – interquartile range; BMI – body mass index; HAI - Histologic Activity Index; HCV – hepatitis C virus; RNA – ribonucleic acid; ARV – antiretroviral; N/a - not applicable

Table 15: Baseline characteristics of the GT3 Phase II trial (taken from CS[1] Table 31)

Characteristic	ELECTRON-2 GT3 treatment-naïve	
	LDV/SOF n=25	LDV/SOF+RBV n=26
Mean age (range), years	43 (22–63)	48 (28–64)
Male, n (%)	13 (52)	11 (42)
White, n (%)	22 (88)	23 (88)
Mean BMI (range), kg/m^2	27 (19–37)	28 (18–42)
Cirrhosis	3 (12)	5 (19)
IL28B CC, n (%)	9 (36)	15 (58)
GT 3a, n (%)	25 (100)	26 (100)
Mean HCV RNA (range), log10 IU/mL	6.3 (4.0–7.3)	6.3 (4.3–7.6)

BMI – body mass index; RNA – ribonucleic acid; HCV – hepatitis C virus

For patients with GT1 and GT4 decompensated liver cirrhosis or post-liver transplant, the SOLAR-1 study is described in Section 6.5.7 of the CS.[1]

[redacted] Published abstracts for SOLAR-1 have different numbers of patients than in the CS, so baseline characteristics would not apply.

4.2.2 Clinical effectiveness - LDV/SOF trials sustained virological response

The CS presents virologic response data at timepoints during treatment and post-treatment (see CS[1] Section 6.5). Based on clinical expert advice received by the ERG, on-treatment responses do not seem to be predictive of SVR post-treatment. The absence of viraemia at four weeks post therapy is a good marker of SVR but there is a relapse rate between four and twelve weeks, hence it is not a suitable surrogate for cure. The ERG report concentrates on SVR at twelve weeks after completion of treatment (SVR12) as this is the virologic outcome of main clinical interest.[12] Historically, SVR24 has been used to measure patient response to therapy. However, research has indicated that SVR12 is highly predictive of SVR24[50,51] Within the three Phase III trials, all patients achieving SVR12 also achieved SVR24 (see CS[1] - ION-1 page 80 CS, ION-3 page 86 CS, ION-2 page 94).

SVR12 data are shown separately for GT1 treatment-naïve patients (Table 16), and GT1 treatment-experienced patients (Table 17). There were also some data for GT3 and GT4 patients, presented below.

GT1 treatment-naïve SVR12

SVR12 data for GT1 treatment-naive patients were available from two Phase III trials (ION-1 and ION-3). Data were also available from five Phase II trials (ELECTRON, ELECTRON-2, ERADICATE, LONESTAR and SYNERGY).

As can be seen from Table 16, for the overall populations of ION-1 and ION-3, SVR12 rates ranged from 93% to 99% across all treatment arms for GT1 treatment-naïve patients. The SYNERGY trial, with any HAI fibrosis score patients, had a reported SVR rate of 100%.

Table 16: SVR12 in GT1 treatment-naïve patients

Population	Study	LDV/SOF 8wks		LDV/SOF +RBV 8wks (not licensed)		LDV/SOF 12wks		LDV/SOF +RBV 12wks (not licensed)		LDV/SOF 24wks		LDV/SOF +RBV 24wks	
		n/N	% 95%CI	n/N	% 95%CI	n/N	% 95%CI	n/N	% 95%CI	n/N	% 95%CI	n/N	% 95%CI
GT1 Non-cirrhotic and compensated cirrhosis (overall trial population)	ION-1[17]					211/214	98.6 [redacted]	211/217	97.2 [redacted]	213/217	98.2 [redacted]	215/217	99.1 [redacted]
GT1 Non-cirrhotic*	ION-1					179/180	99.4 96.9–100	178/184	96.7 93.0–98.8	181/184	98.4 95.3–99.7	179/181	98.9 96.1–99.9
GT1 compensated cirrhosis*	ION-1					32/34	94.1 80.3–99.3	33/33	100 89.4–100	32/33	97.0 84.2–99.9	36/36	100 90.3–100
GT1a Non-cirrhotic and compensated cirrhosis	ION-1[13]					141/142	99.3 96.1	143/143	100 97.5-100	143/143	100 97.5-100	141/141	100 97.4-100
GT1b Non-cirrhotic and compensated cirrhosis	ION-1[13]					66/66	100 94.6-100	67/67	100 94.6-100	66/68	97.1 89.8-99.6	71/71	100 94.9-100
GT1a Cirrhotic	ION1[17]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GT1a non-cirrhotic	ION1[17]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GT1b Cirrhotic	ION1[17]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GT1b non-cirrhotic	ION1[17]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GT1 Non-cirrhotic (overall trial population)	ION-3	202/215	94.0 89.9–96.7	201/216	93.1 88.8-96.1	208/216	96.3 92.8-98.4						

Superseded – see erratum

Population	Study	LDV/SOF 8wks		LDV/SOF +RBV 8wks (not licensed)		LDV/SOF 12wks		LDV/SOF +RBV 12wks (not licensed)		LDV/SOF 24wks		LDV/SOF +RBV 24wks	
		n/N	**% 95%CI**	**n/N**	**% 95%CI**	**n/N**	**% 95%CI**	**n/N**	**% 95%CI**	**n/N**	**% 95%CI**	**n/N**	**% 95%CI**
GT1a Non-cirrhotic*	ION-3[14]	159/171	93.0 88.1-96.3	159/172	92.4 87.4-95.9	163/172	163/172 91.8-98.3						
GT1b Non-cirrhotic*	ION-3[14]	42/43	97.7 87.7-99.9	42/44	95.5 84.5-99.4	43/44	97.7 88.0-99.9						
GT1 decompensated cirrhosis (CPT class B)	ELECTRON-2					13/20	65 [redacted]						
GT1 co-infection HIV, non-cirrhotic	ERADICATE interim analysis[6]					39/40	98						
GT1 co-infection HIV, non-cirrhotic	ERADICATE					49/50	98 NR						
GT1non-cirrhotic	ELECTRON[26]							25/25	100 86-100				
GT1 no cirrhosis	LONESTAR[27]	19/20	95 75-100	21/21	100 84-100	18/19	95 74-100						
GT1 (any HAI fibrosis score)	SYNERGY[48]					20/20	100						

GT – genotype; HIV – human immunodeficiency virus; HAI – Histologic Activity Index; CI – confidence interval
**stratified subgroup*

Superseded – see erratum

In ION-1, 15 patients in the FAS did not achieve SVR12: two patients relapsed following completion of therapy (one cirrhotic patient receiving 12 weeks LDV/SOF and one cirrhotic patient receiving 24 weeks LDV/SOF); one patient experienced virologic failure on treatment 24 weeks LDV/SOF (suspected non-compliance based on plasma concentrations of the intervention drug, see CS[1] page 81); three patients withdrew consent and nine patients were lost to follow-up. In ION-3, 36 patients in the FAS did not achieve SVR12: 23 patients had a virologic relapse after the end of treatment, 11 patients were lost to follow up and 2 patients withdrew consent.

Comparisons with historical controls SVR12 rates for GT1 treatment-naïve patients (see Section 4.1.3.1 of this report and Table 17 of the CS[1]) were statistically significant for the ION-1 (see CS[1] page 79) and ION-3 (see CS[1] page 84) trials. In ION-1, LDV/SOF SVR12 rates in all four treatment arms ranged from 97–99% and were higher than the designated historical rate of 60% ($p<0.001$ for all four arms). In ION-3, the LDV/SOF SVR12 rates in all three treatment arms ranged from 93–96% and were higher than the designated historical rate of 60% ($p<0.001$ for all three arms).

For ION-1, randomisation was stratified by genotype and presence or absence of cirrhosis. In the ION-3 trial, randomisation was stratified by genotype. Outcomes for stratified subgroups are presented in Table 16.

For GT1a treatment-naïve patients, SVR12 rates ranged from 92.4% to 100% in the ION trials [redacted]

For GT1b treatment-naïve patients, SVR12 rates ranged from 95.5% to 100% in the ION trials [redacted]

For GT1 treatment-naïve non-cirrhotic patients, SVR12 rates ranged from 93.1% to 99.4% in the ION trials, and 95% to 100% in the LONESTAR trial.

For GT1 treatment-naïve patients with compensated cirrhosis, SVR12 rates ranged from 94.1% to 100% in the ION-1 trial.

For GT1 treatment-naïve patients with decompensated cirrhosis, the SVR12 rate was 65% (reported within the ELECTRON-2 trial).

In GT1 patients co-infected with HIV, 13/13 (100%) of patients without antiretroviral (ARV) treatment achieved SVR12, and 36/37 (97%) ARV treated patients achieved SVR12, in the ERADICATE trials (see CS[1] page 105).

Superseded – see erratum

There was some investigation of subgroups that were not stratified at randomisation. This means subgroups may not be well-balanced and thus introduces the possibility of bias. Across the four treatment arms of ION-1, SVR12 rates ranged from 97% to 99% among patients with a non-CC IL28B allele, and from 91% to 100% among black patients (see CS[1] page 79). Across the three treatment arms of ION-3 (see CS[1] page 84), patients with characteristics associated with poor response to IFN-based treatment had SVR12 rates similar to patients without these characteristics. The SVR12 rates in patients who received 8 weeks of LDV/SOF ranged from 89% to 100% in all subgroups (see CS[1] page 84).

In ION-3, the baseline viral load was predictive of relapse if given 8 weeks treatment (see CS[1] page 87).

[redacted]

GT1 treatment-experienced patients SVR12

The SVR rates for GT1 treatment-experienced patients in the ION-2 trial ranged from 93.6% to 99.1% (see Table 17). For prior treated patients with non-cirrhotic and compensated cirrhosis, LONESTAR reported 95% to 100% SVR12, and SYNERGY with HAI fibrosis stages 0-4 reported an SVR12 rate of 100%.

In ION-2, 11 patients in the FAS in the 12 week treatment groups (see CS[1] page 94) had a virologic relapse after the end of treatment; 10 patients had a relapse by post-treatment week 4 and one patient had a relapse between post-treatment weeks 4 and 12. Two patients in the 24 week treatment groups did not achieve SVR12: one patient had virologic rebound during treatment (investigators suspected non-compliance to the study regimen); one patient withdrew consent.

Comparison with historical controls for the GT1 treatment-experienced ION-2 trial (see CS[1] page 91) found all four treatment arms had significantly higher SVR12 outcomes than the designated historical control rate of 25% ($p<0.001$ for all comparisons).

In the ION-2 trial (see CS[1] page 91, and EPAR[6]) the addition of RBV (in the LDV/SOF+RBV 8 weeks arm) did not significantly enhance the observed SVR12 rates (*p*-values not reported) compared with either LDV/SOF 8 weeks treatment (treatment difference 0.9%; 95% confidence interval: -3.9% to 5.7%), or LDV/SOF 12 weeks treatment (treatment difference -2.3%; 97.5% confidence interval: -7.2% to 3.6%).[6]

Superseded – see erratum

In the ION-2 trial, randomisation was stratified by genotype, presence or absence of cirrhosis and response to prior HCV therapy (relapse or virologic breakthrough versus no response). Outcomes for these subgroups are shown in Table 17.

For patients who previously relapsed or had virologic breakthrough, SVR12 ranged from 95.0 to 100% in the ION-2 trial.

For patients with no response to prior therapy, SVR12 ranged from 91.8% to 100% in the ION-2 trial.

For GT1a treatment-experienced patients, SVR12 rates ranged from 95.3% to 98.8% in ION-2.

For GT1b treatment-experienced patients, SVR12 rates ranged from 87.0% to 100% in ION-2.

For GT1 treatment-experienced non-cirrhotic patients, SVR12 rates ranged from 95.4% to 100% in ION-2, and the SVR12 rate was 100% in the ELECTRON and ELECTRON-2 trials.

For GT1 treatment-experienced patients with compensated cirrhosis, SVR12 rates ranged from 81.8% to 100% in ION-2, and 70% to 100% in the ELECTRON trial, and from 96% to 97% in the SIRIUS trial.

In patients with cirrhosis there was a significant difference (p=0.007) in SVR12 rates between the 12-week (82-86% SVR12) and 24-week (100% SVR12) treatment regimen groups (see CS[1] page 91). However, this observation is preliminary, since the study was not powered for intergroup comparisons. Based on multivariate exact logistic-regression analysis, the absence of cirrhosis was the only baseline factor associated with a significant increase in SVR12 rates (see CS[1] page 91).

Superseded – see erratum

Table 17: SVR12 in GT1 treatment-experienced patients

Population	Study	LDV/SOF 12wks		LDV/SOF +RBV 12wks (not licensed)		LDV/SOF 24wks		LDV/SOF+RBV 24wks	
		n/N	% 95%CI	n/N	% 95%CI	n/N	% 95%CI	n/N	% 95%CI
GT1 Non-cirrhotic and compensated cirrhosis	ION-2	102/109	93.6 87.2-97.4	107/111	96.4 91.0-99.0	108/109	99.1 95.0-100	110/111	99.1 95.1-100
GT1 Non-cirrhotic*	ION-2	83/87	95.4 88.6–98.7	89/89	100 95.9–100	86/87	98.9 93.8–100	88/89	98.9 93.9–100
GT1 compensated cirrhosis*	ION-2	19/22	86.4 65.1–97.1	18/22	81.8 59.7–94.8	22/22	100 84.6–100	22/22	100 84.6–100
GT1a* Non-cirrhotic and compensated cirrhosis	ION-2[15]	82/86	95.3 88.5-98.7	84/88	95.5 88.8-98.7	84/85	98.8 93.6-100	87/88	98.8 93.8-100
GT1b* Non-cirrhotic and compensated cirrhosis	ION-2[15]	20/23	87.0 66.4-97.2	23/23	100 85.2-100	24/24	100 85.8-100	23/23	100 85.2-100
GT1 prior therapy relapse or virologic breakthrough*	ION-2[15]	57/60	95.0 86.1-99.0	63/65	96.9 89.3-99.6	60/60	100 94.0-100	59/60	98.3 91.1-100
GT1 no response to prior therapy*	ION-2[15]	45/49	91.8 80.4-97.7	44/46	95.7 85.2-99.5	48/49	98.0 89.1-99.9	51/51	100 93.0-100
GT1, prior SOF treatment, non-cirrhotic	ELECTRON-2			19/19	100 [redacted]				
GT1 no cirrhosis	ELECTRON[26]			9/9	100 66-100				
GT1 cirrhosis	ELECTRON[26]	7/10	70 35-93	9/9	100 66-100				
GT1 Non-cirrhotic and compensated cirrhosis	LONESTAR[27]	18/19	95 74-100	21/21	100 84-100				
GT1 compensated cirrhosis	SIRIUS	PBO 12wks followed by LDV/SOF+RBV 12 weeks 74/77	96 NR	NR		LDV/SOF + matched RBV PBO 75/77	97 NR		
GT1 (prior SOF/RBV treatment in NIAID SPARE study) (HAI fibrosis stages 0-4)	SYNERGY[29]	14/14	100						

GT – genotype; HAI – Histologic Activity Index; CI – confidence interval
**stratified subgroup*

Superseded — see erratum

There was some investigation of subgroups that were not stratified at randomisation, meaning subgroups may not be well-balanced; this introduces the possibility of bias. SVR12 rates across the treatment arms of ION-2 (see CS[1] page 91) were similar among patients who had been previously treated with PEG-IFN+RBV (93.0–100%) and those who had previously been treated with PI+PEG-IFN+RBV (93.9–100%). For patients with cirrhosis who were treated with 12 weeks LDV/SOF, the SVR12 rate was 85.7% for previous PI+PEG-IFN+RBV failures and 87.5% for previous PEG-IFN+RBV failures. For both these groups, 100% SVR12 was achieved for those treated with 24 weeks LDV/SOF.

The ELECTRON trial investigated GT1 patients who were either treatment-naïve or treatment-experienced and had an inherited blood disorder. For these 14 patients, 100% achieved SVR12.

GT3 or GT4 patients

Data were available from 51 GT3 treatment-naïve patients with or without cirrhosis, from the ELECTRON-2 trial. For patients treated with LDV/SOF for 12 weeks, the SVR12 rate was 64% (16/25 patients), whereas for patients treated with LDV/SOF+RBV for 12 weeks, all 26 patients (100%) achieved SVR12 (see CS[1] Table 33). Note that LDV/SOF is recommended for GT3 patients with cirrhosis and/or prior treatment failure, for 24 weeks with RBV.[6]

Data from GT3 treatment-experienced patients from ELECTRON-2 were not included in the CS[1] as data were not available at time of submission. The company's response to clarification[2] (question B5) provides data from ELECTRON-2 treatment-experienced GT3 patients (n=50), with either no cirrhosis or with compensated cirrhosis. The SVR12 rate was 41/50 (82%). The SVR4 rate from these GT3 treatment-experienced patients was reported in the CS[1] page 12 as 25/28 (89%) in non-cirrhotic patients, and 17/22 (77%) in cirrhotic patients, thus giving an overall SVR4 rate of 42/50 (84%).[47]

The CS[1] (page 98) states that *"two patients with GT4 HCV infection were enrolled into the ION-1 study. One patient received LDV/SOF for 12 weeks; another patient received LDV/SOF+RBV for 24 weeks. Both achieved SVR12."*

An interim analysis of SYNERGY (see CS[1] page 98), found that 14/14 (100%) GT4 patients treated with LDV/SOF for 12 weeks achieved SVR12.

[redacted]

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[redacted]

4.2.3 Clinical effectiveness trials - development of resistance to LDV/SOF

Cell culture studies found reduced susceptibility to LDV was associated with the primary NS5A substitution Y93H in both genotype 1a and 1b, and a Q30E substitution developed in genotype 1a replicons.[6] Reduced susceptibility to SOF was associated with the primary NS5B substitution S282T.[6]

All three Phase III ION trials assessed the development of resistance, as described in Table 10 of the CS.[1] Deep sequencing of the NS5A and NS5B regions of the HCV RNA was performed in all patients at baseline and at the time of virologic failure in those that had virologic failure. The resulting sequences were compared to detect resistance-associated variants that emerged during treatment. Only variants present in >1% of sequence reads were reported.

At baseline, variants associated with resistance to NS5A inhibitors were detected in 140 of 861 (16%) patients in the ION-1 trial (see CS[1] page 81), 116 (18%) of the 647 patients in the ION-3 trial (see CS[1] page 86), and 62 of 439 (14%) patients in the ION-2 trial (see CS[1] page 94). The majority of these patients achieved SVR12: 97% ION-1; 90% ION-3; 89% ION-2 (see CS[1] pages 81, 86 and 94).

Across the three ION trials, 37 patients (29 with genotype 1a and 8 with genotype 1b) qualified for resistance analysis due to virologic failure or early study drug discontinuation and having HCV RNA > 1,000 IU/mL.[6] NS5A resistance-associated variants (RAVs) were observed in post-baseline isolates from 29/37 patients (22/29 genotype 1a and 7/8 genotype 1b) not achieving sustained virologic response.[6]

None of the three ION trials detected patients with the NS5B S282T variant, which is associated with reduced susceptibility to SOF, in any patient at baseline or at the time of virologic failure (see CS[1] pages 81, 86 and 94). One patient with the NS5B S282T variant was detected at failure in the LONESTAR study.[6] This patient achieved SVR following retreatment with 24 weeks LDV/SOF+RBV.[6]

Based on clinical expert advice received by the ERG, the term resistance may be misleading in this context, as “resistant associated variants” at baseline do not predict treatment failure. If treatment does fail, these populations may still respond on rechallenge with the same drugs given for longer. In addition, the clinical advisors to the ERG were unaware of any development of double-resistant variants on treatment with LDV/SOF.

4.2.4 Mortality and adverse effects of treatment LDV/SOF

The CS[1] provides details of AEs from the three Phase III trials. The CS additionally provides AE data from one of the Phase II trials (SIRIUS) which had 12 weeks of data allowing comparison of placebo with LDV/SOF. Tables 18-20 presented outcome data on AEs from the Phase III trials. Table 21 presents AEs from the first 12 weeks of the SIRIUS study.

Mortality

No deaths were reported in any of the Phase III ION trials.

There were no deaths reported from treatment arms included in the CS for the Phase II trials ELECTRON-2, ERADICATE, ELECTRON, LONESTAR, or SYNERGY.

[redacted]

Treatment discontinuation due to AE

In ION-1, no patients on the 12 week regimens discontinued treatment due to AEs. Ten patients on the 24 week regimens discontinued treatment due to AEs, four (2%) in the LDV/SOF group and six (3%) in the LDV/SOF+RBV group (see CS[1] page 126).

In ION-3, three patients discontinued the study treatment due to AEs; one receiving LDV/SOF+RBV 8 weeks (owing to a road accident) and two receiving LDV/SOF 12 weeks (one owing to arthralgia and one to lung cancer, see CS[1] page 127).

In ION-2, there were no treatment discontinuations due to AEs (see CS[1] page 129).

In the SIRIUS trial, no patients from the LDV/SOF treatment arm, and one patient (1.3%) from the placebo arm, discontinued treatment due to AEs.

Treatment discontinuation due to AEs in other Phase II trials included in the CS (see clarification response[2] question B5) were as follows:

ELECTRON-2: 1/25 GT3 treatment-naïve patients in the treatment arm LDV/SOF 12 weeks (also one GT3 treatment-experienced, although this group was not included in the CS as data were not

published at time of submission). No treatment discontinuations were reported in other arms included in the CS.[1]

ERADICATE: No treatment discontinuations due to AEs.

ELECTRON: 1/25 GT1 treatment-naïve patients in the SOF+LDV+RBV treatment arm. No treatment discontinuations were reported in other arms included in the CS.[1]

LONESTAR: No treatment discontinuations due to AEs.

[redacted]

SYNERGY: No treatment discontinuations due to AEs.

AEs and SAEs

The LDV/SOF SmPC reports two adverse drug reactions as being very common (that is, occurring in one in ten patients or more): headache and fatigue.

From the Phase III trials, the most common AEs were fatigue, headache, insomnia, and nausea (see CS[1] Section 6.9). Across the treatment arms of the Phase III trials, 67–93% of patients experienced at least one AE. Of these, the majority of AEs were mild to moderate in severity. Patients in the groups that received LDV/SOF+RBV had higher rates of AEs known to be associated with RBV treatment (fatigue, insomnia, headache, nausea, asthenia, rash, cough, pruritus, and anaemia).

In ION-1, 33 patients out of 845 patients (3.8%) experienced a serious adverse event (SAE). The most common SAEs were cellulitis, chest pain, gastroenteritis, hand fracture, non-cardiac chest pain, and pneumonia.

In the ION-3 trial, ten patients experienced an SAE. In the LDV/SOF+RBV group, one patient had a pituitary tumour. SAEs in the LDV/SOF groups occurred in 9 patients out of 647 patients (1.4%), and were anaphylactic reaction, colitis, diabetes mellitus inadequate control, hypertension, lower gastrointestinal haemorrhage, abdominal pain, bile duct stone, haemothorax, hypoglycaemia, intestinal perforation, jaundice, mental status changes, respiratory failure, rhabdomyolysis, road traffic accident, skeletal injury, and squamous cell carcinoma of the lung.

For the treatment-experienced patients, in the ION-2 trial, patients on 12 weeks treatment had no SAEs, and 9 patients out of 220 patients (4.1%) on 24 weeks treatment experienced SAEs. These included angina unstable, convulsion, hepatic encephalopathy, intervertebral disc protrusion, non-

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cardiac chest pain, spondylolisthesis, upper gastrointestinal haemorrhage, cholecystitis, vaginal prolapse, and wound infection.

Table 18: AEs reported within ION-1 (taken from CS[1] Table 43)

Adverse events ION-1	**12 week**		**24 week**	
	LDV/SOF (N=214)	**LDV/SOF+RBV (N=217)**	**LDV/SOF (N=217)**	**LDV/SOF+RBV (N=217)**
Duration of treatment in weeks, mean (SD)	12.1 (0.8)	12.0 (0.7)	23.6 (2.6)	23.7 (1.9)
≥1 AE, n (%)	173 (81)	187 (86)	178 (82)	202 (93)
Grade 3 or 4 AE	4 (1.9)	14 (6.5)	21 (9.7)	12 (5.5)
≥1 SAE, n (%)	1 (<1)	7 (3)	18 (8)	7 (3)
Discontinuation of LDV/SOF due to AEs, n (%)	0	0	4 (2)	6 (3)
Common AEs, n (%)				
Fatigue	46 (22)	79 (36)	53 (24)	84 (39)
Headache	53 (25)	50 (23)	54 (25)	65 (30)
Insomnia	17 (8)	45 (21)	26 (12)	46 (21)
Nausea	24 (11)	37 (17)	29 (13)	32 (15)
Asthenia	14 (7)	23 (11)	20 (9)	26 (12)
Diarrhoea	24 (11)	18 (8)	24 (11)	14 (6)
Rash	16 (7)	21 (10)	16 (7)	26 (12)
Irritability	11 (5)	17 (8)	17 (8)	24 (11)
Cough	6 (3)	22 (10)	16 (7)	25 (12)
Pruritus	11 (5)	22 (10)	8 (4)	20 (9)
Anaemia	0	25 (12)	0	22 (10)
Haematologic abnormality, n (%)				
Decreased haemoglobin level				
<10 g/dL	0	20 (9)	0	16 (7)
<8.5 g/dL	0	1 (<1)	0	0
Lymphocyte count <350/mm^3	0	1 (<1)	0	0
Neutrophil count 500 to <750/mm^3	1 (<1)	0	3 (1)	0
Platelet count 25,000 to <50,000/mm^3	1 (<1)	0	1 (<1)	0

AE – adverse event; SAE – serious adverse event; SD – standard deviation

Table 19: AEs reported within ION-3 (taken from CS[1] Table 44)

Adverse events ION-3	**8 week**		**12 week**
	LDV/SOF (N=215)	**LDV/SOF+RBV (N=216)**	**LDV/SOF (N=216)**
Duration of treatment in weeks, mean (SD)	8.1 (0.2)	8.0 (0.9)	12.0 (0.9)
≥1 AE, n (%)	147 (68)	166 (77)	150 (69)
Grade 3 or 4 AE	2 (0.9)	8 (3.7)	7 (3.2)
≥1 SAE, n (%)	4 (2)	1 (<1)	5 (2)
Discontinuation of LDV/SOF due to AEs, n (%)	0	1 (<1)	2 (1)
Common AEs, n (%)[†]			
Fatigue	45 (21)	75 (35)	49 (23)
Headache	30 (14)	54 (25)	33 (15)
Nausea	15 (7)	38 (18)	24 (11)
Insomnia	11 (5)	26 (12)	15 (7)
Irritability	3 (1)	29 (13)	10 (5)
Diarrhoea	15 (7)	13 (6)	9 (4)
Arthralgia	9 (4)	12 (6)	16 (7)
Constipation	9 (4)	12 (6)	8 (4)
Dizziness	6 (3)	13 (6)	9 (4)
Rash	3 (1)	20 (9)	5 (2)
Pruritus	2 (1)	16 (7)	5 (2)
Cough	3 (1)	12 (6)	7 (3)
Anaemia	2 (1)	17 (8)	2 (1)
Muscle spasms	3 (1)	12 (6)	6 (3)
Dyspnoea	0	11 (5)	1 (<1)
Haematologic abnormality, n (%)			
Haemoglobin level <10 g/dL	0	11 (5)	1 (<1)
Lymphocyte count 350 to <500/mm^3	0	1 (<1)	0
Neutrophil count 500 to <750mm^3	0	1 (<1)	1 (<1)

AE – adverse event; SAE – serious adverse event; SD – standard deviation

Table 20: AEs reported within ION-2 (taken from CS[1] Table 45)

Adverse events ION-2	**12 week**		**24 week**	
	LDV/SOF (N=109)	**LDV/SOF+RBV (N=111)**	**LDV/SOF (N=109)**	**LDV/SOF+RBV (N=111)**
Duration of treatment in weeks, mean (SD)	12.2 (0.2)	12.1 (0.2)	23.9 (1.6)	24.0 (1.7)
≥1 AE, n (%)	73 (67)	96 (86)	88 (81)	100 (90)
Grade 3 or 4 AE	2 (1.8)	3 (2.7)	10 (9.2)	8 (7.2)
≥1 SAE, n (%)	0	0	6 (6)	3 (3)
Treatment discontinuation due to AEs, n (%)	0	0	0	0
Common AEs, n (%)[†]				
Fatigue	23 (21)	45 (41)	26 (24)	50 (45)
Headache	28 (26)	26 (23)	25 (23)	35 (32)
Nausea	13 (12)	20 (18)	7 (6)	25 (23)
Insomnia	10 (9)	18 (16)	4 (4)	19 (17)
Arthralgia	7 (6)	13 (12)	7 (6)	17 (15)
Cough	5 (5)	16 (14)	5 (5)	16 (14)
Diarrhoea	7 (6)	5 (5)	9 (8)	17 (15)
Rash	2 (2)	11 (10)	6 (6)	16 (14)
Irritability	2 (2)	13 (12)	4 (4)	12 (11)
Dizziness	3 (3)	8 (7)	7 (6)	12 (11)
Upper respiratory tract infection	4 (4)	6 (5)	7 (6)	11 (10)
Dyspnoea	0	16 (14)	3 (3)	9 (8)
Muscle spasm	1 (1)	8 (7)	2 (2)	12 (11)
Anaemia	0	9 (8)	1 (1)	12 (11)
Dry skin	0	3 (3)	3 (3)	11 (10)
Haematologic abnormality, n (%)				
Decreased haemoglobin level				
<10 g/dL	0	2 (2)	0	9 (8)
< 8.5 g/dL	0	0	0	2 (2)
Decreased lymphocyte count				
350 to <500/mm^3	1 (1)	1 (1)	1 (1)	3 (3)
< 350/mm^3	0	1 (1)	0	1 (1)
Platelet count 25,000 to <50,000/mm^3	1 (1)	0	2 (2)	0

AE – adverse event; SAE – serious adverse event; SD – standard deviation

One of the Phase II trials, SIRIUS, had 12 weeks of data allowing comparison of placebo with LDV/SOF.

Table 21 and shows safety data for 12 weeks on treatment (taken from Table 46 of the CS[1]).

Table 21: Adverse events from the first 12 weeks of the SIRIUS study (taken from CS[1] Table 46)

Adverse event	LDV/SOF 12 Weeks (N=77)	Placebo 12 Weeks (n=78)
≥1 AE, n (%)	65 (84.4)	65 (83.3)
Grade 3 or 4 AE, n (%)	2 (2.6)	1 (1.3)
≥1 SAE, n (%)	3 (3.9)	1 (1.3)
Treatment discontinuation due to AEs, n (%)	0	1 (1.3)
Common AEs, n (%)[†]		
Asthenia	28 (36.4)	25 (32.1)
Headache	27 (35.1)	16 (20.5)
Insomnia	11 (14.3)	10 (12.8)
Pruritus	4 (5.2)	14 (17.9)
Fatigue	13 (16.9)	3 (3.8)
Nausea	7 (9.1)	8 (10.3)
Diarrhoea	7 (9.1)	4 (5.1)
Hypertension	7 (9.1)	4 (5.1)
Sleep disorder	7 (9.1)	4 (5.1)
Arthralgia	5 (6.5)	5 (6.4)
Dry skin	4 (5.2)	6 (7.7)
Irritability	8 (10.4)	2 (2.6)
Abdominal pain upper	4 (5.2)	5 (6.4)
Decreased appetite	5 (6.5)	4 (5.1)
Back pain	6 (7.8)	2 (2.6)
Cough	5 (6.5)	2 (2.6)
Influenza like illness	4 (5.2)	3 (3.8)
Myalgia	5 (6.5)	2 (2.6)
Constipation	4 (5.2)	2 (2.6)
Bronchitis	4 (5.2)	1 (1.3)
Rhinitis	1 (1.3)	4 (5.1)

AE – adverse event; SAE – serious adverse event; SD – standard deviation

4.2.5 Clinical effectiveness trials - health-related quality of life

HRQoL data were unpublished at time of submission, however the CS included details of HRQoL outcomes for the three Phase III trials. As the trials were open-label, HRQoL outcomes are subject to bias.

All three ION trials employed four HRQoL questionnaires: SF-36; CLDQ-HCV; FACIT-F; and WPAI: Hep C.[1]

In GT1 treatment-naïve patients, for ION-1 (see CS[1] page 81), patients were unaware of whether they had achieved SVR at the time of post-treatment questionnaire completion. The CS[1] states that *"overall results from the HRQL questionnaires indicated that the LDV/SOF groups did not experience a statistically significant worsening in HRQL between baseline and end of treatment for most responses for the SF-36, FACIT-F and WPAI:Hep C questionnaires. In contrast, a statistically significant (p<0.05) worsening in HRQL was observed with the LDV/SOF+RBV groups while on*

treatment. The mean scores for all scales improved from end of treatment to 12 and 24 weeks post-treatment."

In the ION-3 trial (see CS[1] page 86) four HRQoL questionnaires were used in ION-3: SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C. The CS states that *"Overall results indicated that the LDV/SOF groups did not experience a statistically significant worsening in HRQL for most responses for the SF-36, FACIT F and WPAI: Hep C questionnaires between baseline and end of treatment. In contrast, a statistically significant (p<0.05) worsening in HRQL was observed with the LDV/SOF+RBV groups while on-treatment. The mean scores for most scales improved from end of treatment to 12 and 24 weeks post-treatment."* The CS also states that *"In addition, persistent statistically significant between-treatment differences in mean changes from baseline for the SF-36 mental component score were observed between the LDV/SOF 8 week and LDV/SOF+RBV 8 week treatment groups at post-treatment week 4 and 12, although this was not maintained to week 24. These results should be interpreted with caution as multiple endpoints were tested and the study was not powered to test these exploratory endpoints."*

In GT1 treatment-experienced patients, the ION-2 study (see CS[1] page 95), included the use of four HRQL questionnaires: SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C. The CS states that "*Overall results from the HRQL questionnaires indicated that the LDV/SOF groups did not experience a statistically significant worsening in HRQL (SF-36 domains of physical functioning, role physical, vitality, social functioning (24 Week group only), role emotional, and mental component (24 week group only) and the FACIT-F trial outcome index (24 week group only)) between baseline and end of treatment. In contrast, a statistically significant (p<0.05) worsening in HRQL was observed with the LDV/SOF+RBV groups while on-treatment. The mean scores for most scales improved from end of treatment to 24 weeks post-treatment.*"

4.3 Trials providing clinical effectiveness data in comparator drug regimens

No head-to head trials of LDV/SOF versus any of the comparators were identified. A formal network meta-analysis was not conducted by the company (see CS[1] Section 6.7, page 114). Comparator regimens included in the CS[1] (page 35) were as follows:

For GT1:

- PEG-IFN+RBV
- TVR+PEG-IFN+RBV
- BOC+PEG-IFN+RBV
- SOF+RBV±PEG-IFN
- SMV+PEG-IFN+RBV
- SMV+SOF (patients ineligible for IFN)

For GT3:

- PEG-IFN+RBV
- SOF+RBV±PEG-IFN

For GT4:

- PEG-IFN+RBV
- SOF+RBV±PEG-IFN
- SMV+PEG-IFN+RBV
- SMV+SOF (patients ineligible for IFN)

Best supportive care (no treatment) was considered as a comparator for all genotypes, GT1, GT3 and GT4, in the company's health economic analyses except for the GT3 cirrhotic subgroup (see Section 5.2.1).

Although the three ION trials had used historical controls, different data were used to inform SVR rates for comparators within the company's health economic analyses. This allowed separate consideration of TVR and BOC, additional trials for TVR, and additional comparator drug regimens to be considered. The historical controls used in the ION trials are not considered further here.

Eighteen trials provided SVR data for comparator drug regimens. Study quality of these trials is discussed in Section 4.1.3.3.

For the drug regimen comparators, Table 22 presents the study characteristics of trials selected for inclusion by the CS.

Table 22: Trials used for comparator regimens (adapted from CS[1] Table 38)

Population	Comparator regimen	Source	Design	HCV diagnosis	Treatment experience	Liver histology	SVR definition
GT1 treatment-naïve (non-cirrhotic and cirrhotic)	SOF+PEG-IFN+/RBV 12w	NEUTRINO[32,33]	Phase III, single arm, open-label	HCV GT1/4/5/6, plasma HCV RNA >10^4 IU/mL at screening	Naïve	Cirrhosis allowed in ~20% of patients but decompensated cirrhosis excluded	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ = 25 IU/mL
GT1 treatment-naïve (non-cirrhotic and cirrhotic)	SMV+PEG-IFN+RBV 24w	QUEST (C208)[34,35]	Phase III, randomised, multicentre, placebo-controlled, double-blind	HCV GT1 HCV RNA≥10^4 IU/mL at screening	Naïve	Cirrhosis allowed if ultrasound ≤6 months showed no signs of HCC. Decompensated cirrhosis excluded	HCV RNA concentration of <25 IU/mL undetectable at EOT and <25 IU/mL detectable or undetectable 12 weeks after the planned EOT
GT1 treatment-naïve (non-cirrhotic and cirrhotic)	SMV+PEG-IFN+RBV 24w	QUEST 2 (C216)[34;36]	Phase III, randomised, multicentre, placebo-controlled, double-blind	HCV GT1 HCV RNA≥10^4 IU/mL at screening	Naïve	Cirrhosis allowed if ultrasound ≤6 months showed no signs of HCC. Decompensated cirrhosis excluded	HCV RNA concentration of <25 IU/mL undetectable at EOT and <25 IU/mL detectable or undetectable 12 weeks after the planned EOT
GT1 treatment-naïve (non-cirrhotic and cirrhotic)	SMV+SOF 12w	COSMOS[34;38]	Phase II, randomised, multicentre, open-label	HCV GT1 HCV RNA≥10^4 IU/mL at screening	Cohort 1: Previous non-responders to PEG-IFN+RBV Cohort 2: Tx naïve or previous non-responders to PEG-IFN+RBV	Cohort 1: METAVIR F0-F2 Cohort 2: METAVIR F3-F4	SVR12 (HCV RNA titres <25 IU/mL)

Population	Comparator regimen	Source	Design	HCV diagnosis	Treatment experience	Liver histology	SVR definition
GT1 treatment-naïve (non-cirrhotic and cirrhotic)	TVR+PEG-IFN+RBV	ADVANCE[19;21]	Phase III, randomised, placebo-controlled, double-blinded	Documented CHC GT1 infection	Naïve	Compensated cirrhosis allowed. Decompensated cirrhosis excluded	Undetectable HCV RNA 24 weeks after EOT LLOD = 10 IU/mL, LLOQ = 25 IU/mL
GT1 treatment-naïve (non-cirrhotic and cirrhotic)	TVR+PEG-IFN+RBV	ILLUMINATE[21]	Phase III, randomised, open-label	Compensated liver disease, detectable HCV RNA and liver histopathology consistent with CHC. GT1 infection	Naïve	Compensated cirrhosis allowed	Undetectable HCV RNA as measured at the Week 72 visit LLOQ = 25 IU/mL
GT1 treatment-naïve (non-cirrhotic and cirrhotic)	TVR+PEG-IFN+RBV	Study C211[21]	Phase III, randomised, open-label	GT infection	Naïve	Compensated cirrhosis allowed	Undetectable HCV RNA 12 weeks after EOT LLOQ = 25 IU/mL
GT1 treatment-naïve (non-cirrhotic and cirrhotic)	BOC+PEG-IFN+RBV	SPRINT-2 Poordad *et al*, 2013[20]	Phase III, randomised, open-label	Chronic HCV GT1, HCV RNA $\geq 10^4$ IU/mL	Naïve	Decompensated liver disease excluded	Undetectable HCV RNA 24 weeks after EOT LLOD = 9.3 IU/mL, LLOQ = 25 IU/mL
GT1 treatment-naïve (non-cirrhotic and cirrhotic)	PEG-IFN+RBV 48w	IDEAL[37]	Phase NR, randomised, multicentre, double-blinded	Detectable plasma HCV RNA level and chronic HCV GT1 infection	Naive	Compensated liver disease	Undetectable HCV RNA 24 weeks after EOT LLOD: 27 IU/ml

Population	Comparator regimen	Source	Design	HCV diagnosis	Treatment experience	Liver histology	SVR definition
GT1 treatment-experienced (non-cirrhotic and cirrhotic)	SMV+PEG-IFN+RBV 48w	PROMISE (HPC3007)[34;39]	Phase III, randomised, multicentre, placebo-controlled, double-blind	HCV GT1 HCV RNA≥10^4 IU/mL at screening	Relapsed following ≥24 weeks IFN-based therapy	Bridging fibrosis (F3) or cirrhosis (F4) allowed if ultrasound performed ≤6months before screening with no findings suspicious for HCC. Decompensated cirrhosis excluded.	HCV RNA <25 IU/mL undetectable at actual EOT and HCV RNA<25 IU/mL
GT1 treatment-experienced (non-cirrhotic and cirrhotic)	SMV+PEG-IFN+RBV 48w	ASPIRE (C206)[34]	Phase II, randomised, placebo-controlled, double-blind	HCV GT1	Failed prior therapy with PEG-IFN+RBV (including prior relapsers, partial responders or null responders)	Cirrhosis was permitted	NR
GT1 treatment-experienced (non-cirrhotic and cirrhotic)	SMV+SOF 12w	COSMOS[34;38]	Phase II, randomised, multicentre, open-label	HCV GT1 HCV RNA≥10^4 IU/mL at screening	Cohort 1: Previous non-responders to PEG-IFN+RBV Cohort 2: Tx naïve or previous non-responders to PEG-IFN+RBV	Cohort 1: METAVIR F0-F2 Cohort 2: METAVIR F3-F4	SVR12 (HCV RNA titres <25 IU/mL)
GT1 treatment-experienced (non-cirrhotic and cirrhotic)	TVR+PEG-IFN+RBV	REALIZE[21]	Phase III, randomised, placebo-controlled, double-blind	Compensated liver disease, detectable HCV RNA and liver histopathology consistent with CHC. GT1 infection	Prior relapsers and prior non-responders on PEG-IFN+RBV	Compensated cirrhosis allowed.	Undetectable HCV RNA as measured at the Week 72 visit LLOQ = 25 IU/mL

Population	Comparator regimen	Source	Design	HCV diagnosis	Treatment experience	Liver histology	SVR definition
GT1 treatment-experienced (non-cirrhotic and cirrhotic)	BOC+PEG-IFN+RBV	RESPOND-2[22]	Phase III, randomised, open-label	Chronic HCV GT1 infection	Prior relapsers and prior non-responders on IFN	Compensated cirrhosis allowed. Decompensated cirrhosis excluded	Undetectable HCV RNA at Week 24 of follow up
GT1 treatment-experienced (non-cirrhotic and cirrhotic)	PEG-IFN+RBV 48w	REALIZE[21]	Phase III, randomised, placebo-controlled, double-blind	Compensated liver disease, detectable HCV RNA and liver histopathology consistent with CHC. GT1 infection	Prior relapsers and prior non-responders on PEG-IFN+RBV	Compensated cirrhosis allowed.	Undetectable HCV RNA as measured at the Week 72 visit LLOQ = 25 IU/mL
GT3 treatment-naïve (non-cirrhotic and cirrhotic)	SOF+PEG-IFN+RBV 12 w	ELECTRON[32;41]	Phase II, randomised, multicentre, open-label	HCV GT2/3, plasma HCV RNA >50,000 IU/mL at screening	Naïve	Cirrhosis excluded	Undetectable HCV RNA 12 weeks after EOT LLOD = 15 IU/mL
GT3 treatment-naïve (non-cirrhotic and cirrhotic)	SOF+PEG-IFN+RBV 12w	PROTON [31;32]	Phase II, single cohort, open-label (also has randomised, multicentre, placebo-controlled part of study, but only cohort of GT2/3 n=25 used as comparator)	HCV GT2/3, plasma HCV RNA >50,000 IU/mL at screening	Naïve	Cirrhosis excluded	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOD = 15 IU/mL
GT3 treatment-naïve (non-cirrhotic and cirrhotic)	SOF+PEG-IFN+RBV 12w	LONESTAR-2[32;46]	Phase II, single-arm, open-label	HCV GT2/3, plasma HCV RNA >10^4 IU/mL at screening	Experienced: Virologic failure with prior IFN-based treatment (provides data in cirrhotic patients in absence of cirrhotic treatment naïve)	Cirrhosis in ~50% of patients but decompensated cirrhosis excluded	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ = 25 IU/mL

Population	Comparator regimen	Source	Design	HCV diagnosis	Treatment experience	Liver histology	SVR definition
GT3 treatment-naïve (non-cirrhotic and cirrhotic)	SOF+RBV 24w	VALENCE[32;40]	Phase III, randomised, multicentre placebo-controlled, double-blind	HCV GT2/3, plasma HCV RNA >10^4 IU/mL at screening	Naïve and experienced (either IFN intolerant or a treatment failure)	Cirrhosis in ~20% of patients but decompensated cirrhosis excluded	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ = 25 IU/mL
GT3 treatment-naïve (non-cirrhotic and cirrhotic)	PEG-IFN+RBV 24w	FISSION[32;33]	Phase III, randomised, multicentre, open-label	HCV GT2/3, plasma HCV RNA >10^4 IU/mL at screening	Naive	Cirrhosis in ~20% of patients but decompensated cirrhosis excluded	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ = 25 IU/mL
GT3 treatment-experienced (non-cirrhotic and cirrhotic)	SOF+RBV 24w	VALENCE[32;40]	Phase III, randomised, multicentre placebo-controlled, double-blind	HCV GT2/3, plasma HCV RNA >10^4 IU/mL at screening	Naïve and experienced (either IFN intolerant or a treatment failure)	Cirrhosis in ~20% of patients but decompensated cirrhosis excluded	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ = 25 IU/mL

GT – genotype; HCV – hepatitis C virus; RNA – ribonucleic acid; LLOQ – lower limit of quantification; IFN – interferon; EOT – end of treatment; HCC – hepatocellular carcinoma; CHC – chronic hepatitis C

Eighteen trials provided SVR data for comparator drug regimens. SVR data are reported in Section 5.2.3.2.

Nine trials provided SVR data for comparator drug regimens in GT1 treatment-naïve patients. NEUTRINO (SPC[32] and Lawitz *et al* 2013[33]) provided data on SOF+PEG-IFN+/RBV. Two studies provided data on SMV+PEG-IFN+RBV: QUEST (C208) (SPC[34] and Jacobsen 2014[35]); and QUEST 2 (C216) (SPC[34] and Manns *et al* 2014[36]). Poordad *et al*, 2013[20] provided data on BOC+PEG-IFN+RBV. Three studies provided data on TVR+PEG-IFN+RBV: ADVANCE (Study 108; Jacobson *et al*, 2011[19] and SPC[21]); ILLUMINATE (Study 111) (SPC[21]); and Study C211 (SPC[21]). IDEAL[37] provided data on PEG-IFN+RBV. COSMOS (SPC[34] and Lawitz *et al*, 2014[38]) provided data on SMV+SOF in GT1 treatment-naïve patients and also in GT1 treatment-experienced patients.

Five trials (including COSMOS as mentioned above) provided SVR data for comparator drug regimens in GT1 treatment-experienced patients. RESPOND-2[22] provided data on BOC+PEG-IFN+RBV. Two trials provided data on SMV+PEG-IFN+RBV: PROMISE (HPC3007) (SPC[34] and Forns *et al* 2014[39]); and ASPIRE (C206) (SPC[34]). REALIZE (Study C216, SPC[21]) provided data on two treatment regimens, PEG-IFN+RBV and also TVR+PEG-IFN+RBV.

Five trials provided SVR data for comparator drug regimens in GT3 treatment-naïve patients. FISSION (SPC[32] and Lawitz *et al*, 2013[33]) provided data on PEG-IFN+RBV. VALENCE (SPC[32] and Zeuzem *et al*, 2014[40]) provided data on SOF+RBV in GT3 treatment-naïve patients and also in GT3 treatment-experienced patients. Both ELECTRON (SPC[32] and Gane 2013[41]) and PROTON (SPC,[32] Lawitz *et al*, 2013[31] and CSR[42]) provided data on SOF+PEG-IFN+RBV. The CS also used the treatment arm SOF+PEG-IFN+RBV from LONESTAR-2 for data on cirrhotic patients in the GT3 treatment-naïve analysis even though the study was conducted in GT3 treatment-experienced patients, with the CS explaining this as otherwise no data would be available for cirrhotic patients in this treatment regimen (see CS[1] page 118).

VALENCE[32,40] (as mentioned above) was the only study that provided data for GT3 treatment-experienced patients.

The ELECTRON study was the same study as included for LDV/SOF trials, but a different part of this study was used for the comparator.

Patient baseline characteristics from these eighteen trials, and the three ION trials, are shown in Tables 23-26 (these are taken from the CS[1] Tables 39-42).

The CS[1] (page 114) suggests that the baseline characteristics of the trial populations used for GT1 patient populations were similar except that there was a higher proportion of patients with cirrhosis and GT1a in the LDV/SOF trials. Based on clinical advice received by the ERG, GT1a, along with baseline viral load and IL28B CC genotype, have less impact on LDV/SOF treatment than other treatments. No statistical analysis comparing baseline characteristics of the comparator trials and the LDV/SOF trials was undertaken within the CS. Based on clinical advice received by the ERG, there were not considered to be meaningful differences in baseline characteristics that would impact significantly on outcomes.

Table 23: Baseline patient characteristics in GT1 treatment-naïve comparator studies (taken from CS[1] Table 39)

		ION-1		ION-3		NEUTRINO	QUEST	QUEST2	COSMOS		ADVANCE (Study 108)	ILLUMINATE (Study 111)	Study C211	Poordad 2013	IDEAL
		LDV/ SOF 12wks	LDV/ SOF 24wks	LDV/ SOF 8wks	LDV/ SOF 12wks	SOF+ PR12	SMV+ PR24	SMV+ PR24	SMV+ SOF12 Cohort1†	SMV+ SOF12 Cohort2†	TVR+PR	TVR+ PR	TVR+ PR	BOC+ PR	PR48
N		214	217	215	216	327	264	257	14	14	363	540	371[§]	500[‡]	1,035
Age	**Mean**	52	53	53	53	52	48	46	56 (median)	58 (median)	49 (median)	51 (median)	51 (median)	50	48
Race	**White %**	87%	82%	76%	77%	79%	86%	92%	79%	86%	90%	NR	NR	77%	71%
	Black %	11%	15%	21%	19%	17%	10%	6%	21%	14%	7%	14%	5%	18%	19%
Viral load (RNA IU/mL)	**>400,000**	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	91%	NR
	>600,000	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NA	82%
	>800,000	79%	77%	84%	80%	82%	83%	77%	NR	NR	77%	82%	85%	NA	NR
Advanced liver disease	**F3/4**	47%	49%	13% (F3)	13% (F3)	NR	29%	22%	0%	50% (F3)	NR	NR	NR	14%	11%
	Cirrhosis	16%	15%	0%	0%	17%	12% (F4)	7% (F4)	0%	50% (F4)	6%	11%	14%	10%	NR
Genotype	**% GT1**	98%	99%	100%	100%	89%	100%	99%	100%	100%	100%	NR	100%	100%	100%
	% GT1a	67%	67%	80%	80%	69%	56%	41%	71%	79%	59%	72%	57%	67%	61%
	% GT1b	31%	31%	20%	20%	20%	44%	58%	29%	21%	41%	27%	43%	29%	36%
BMI	**Median [Range] or (SD)**	27 (mean) [18–41]	27 (mean) [18–48]	28 (mean) [18–43]	28 (mean) [19–45]	29 (mean) [18–56]	26.6 [16.5–45.2]	25.8 [17.5–53.5]	28.3 [21.7–36.6]	31.6 [22.5–40.6]	26.2 [17-46]	NR	NR	28.1 (5.8)	NR
Weight	**Mean (SD)**	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	82.8 (16.6)
IL28B	**CC**	26%	24%	26%	26%	29%	29%	29%	100%	71%	NR	NR	29%	31%	NR
	CT	53%	55%	56%	57%	55%	57%	55%	0%	NR	NR	NR	56%	51%	NR
	TT	21%	21%	18%	17%	16%	14%	16%	0%	NR	NR	NR	15%	17%	NR

BMI - body mass index; BOC - boceprevir; GT - genotype; LDV - ledipasvir; NR - not reported; PR - pegylated interferon+ribavirin; RNA - ribonucleic acid; SD - standard deviation; SMV - simeprevir; SOF - sofosbuvir; TVR – telaprevir

† Cohort 1 did not comprise any treatment naïve patients, however is used to provide additional non-cirrhotic patients to the analysis. Cohort 2 comprised treatment naïve (n=7) and prior non-responders to PEG-IFN+RBV (n=7). Patient characteristics are shown for each full cohort. ‡ Poordad reports patient characteristics for a sub-group of 500 of 687 patients enrolled. These 500 patients were those that became anaemic during the study. § N number for arm treated with TVR 750 mg three times daily. Patient characteristics only available for whole study cohort treated with either TVR 750 mg three times daily or 1,125 mg twice daily.

Table 24: Baseline patient characteristics in GT1 treatment-experienced comparator studies (taken from CS[1] Table 40)

		ION-2		PROMISE	ASPIRE	COSMOS		REALIZE	RESPOND-2	REALIZE
		LDV/ SOF12	**LDV/ SOF24**	**SMV+PR48**	**SMV+PR48** ‡	**SMV+SOF12 Cohort1**†	**SMV+SOF12 Cohort2**†	**TVR+PR**	**BOC+PR**	**PR 48**
N		109	109	260	120	14	14	266‡‡	162	132‡‡
Age	**Mean**	56	56	52 (median)	50	56 (median)	58 (median)	51 (median)	52.9	51 (median)
Race	**White %**	77%	83%	93.5%	93%	79%	86%	NR	88%	NR
	Black %	22%	16%	2.7%	5%	21%	14%	5%	11%	5%
Viral load (RNA IU/mL)	**> 400,000**	NR	NR	NR	NR	NR	NR	NR	NR	NR
	> 600,000	NR	NR	NR	NR	NR	NR	NR	NR	NR
	> 800,000	88% (≥6 $\log_{10}$)	79% (≥6 $\log_{10}$)	NR	86%	NR	NR	89%	91%	89%
Advanced liver disease	**F3/4**	58%	58%	17.6% (F3)	19% (F3)	0%	50% (F3)	NR	20%	NR
	Cirrhosis	20%	20%	15.6% (F4)	18% (F4)	0%	50% (F4)	26%	10%	26%
Genotype	**% GT1**	100%	100%	100%	NR	100%	100%	100%	99%	100%
	% GT1a	79%	78%	42%	41%	71%	79%	54%	58%	54%
	% GT1b	21%	22%	58%	58%	29%	21%	46%	41%	46%
BMI	**Median [Range] or (SD)**	29 (mean [19–47]	28 (mean [19–41]	27.2 [14.3–47.7]	NR	28.3 [21.7–36.6]	31.6 [22.5–40.6]	NR	28.8 (mean)	NR
Weight	**Mean (SD)**	NR	NR	NR	NR	NR	NR	NR	NR	NR
IL28B	**CC**	9%	15%	24%	18%	100%	71%	NR	NR	NR
	CT	64%	62%	64%	65%	0%	NR	NR	NR	NR
	TT	27%	23%	12%	18%	0%	NR	NR	NR	NR
Previous therapy	**PR**	39%	54%	95%	100%§	100%¶	100% TE pts¶	100%††	100%	100% TE pts††
	PI	61%	46%	NR	NR	NR	NR	NR	NR	NR
	Other	NR	NR	5%	NR	NR	NR	NR	NR	NR

BMI - body mass index; BOC - boceprevir; GT - genotype; LDV - ledipasvir; NR - not reported; PI - protease inhibitor; PR - pegylated interferon+ribavirin; RNA - ribonucleic acid; SD - standard deviation; SMV - simeprevir; SOF - sofosbuvir; TE - treatment experienced; TVR - telaprevir.

† Cohort 1 comprised of prior non-responders to PEG-IFN+RBV. Cohort 2 comprised treatment naïve (n=7) and prior non-responders to PEG-IFN+RBV (n=7). Patient characteristics are shown for each full cohort.

‡ N shown for pooled 150 mg SMV for 12, 24 or 48 weeks with PEG-IFN+RBV for 48 weeks; patient characteristics shown for overall trial population.

§ Based on inclusion criteria of study (patients who had failed prior therapy with PEG-IFN+RBV).

¶ Based on inclusion criteria of study (non-responders to previous PEG-IFN+RBV).

†† Based on inclusion criteria of study (did not achieve SVR with prior treatment with PEG-IFN+RBV).

‡‡ N number for treatment arm, patient characteristics for overall study population.

Table 25: Baseline patient characteristics in GT3 treatment-naïve comparator studies (taken from CS Table 41)

		ELECTRON-2	ELECTRON	PROTON	LONESTAR-2	VALENCE	FISSION
		LDV/SOF+ RBV12	SOF+PR12	SOF+PR12	SOF+PR12‡	SOF+R24†	PR24
N		26	11	25	47	250	243
Age	**Mean**	48	46	47	56	48	48
Race	**White %**	88%	82%	80%	96%	94%	87%
	Black %	0%	NR	16%	NR	0%	2%
Viral load (RNA IU/mL)	**> 400,000**	NR	NR	NA	NR	NR	NR
	> 600,000	NR	NR	NA	NR	NR	NR
	> 800,000	77%	NR	52%	NR	NR	65%
Advanced liver disease	**Cirrhosis**	19%	0%	0%	55%	23%	21%
Genotype	**% GT3**	100%	64%	40%	51%	100%	72%
BMI	**Median [Range] or (SD)**	28 (mean) [18–42]	24 (mean) [21-28]	29 (4.8)	31 [21-53]	25 [17-41]	28 [19-52]
IL28B	**CC**	58%	36%	28%	36%	34%	44%
	CT	23%	45%	68%	NR	52%	40%
	TT	19%	18%	4%	NR	13%	16%

BMI - body mass index; GT - genotype; LDV - ledipasvir; NR - not reported; PI - protease inhibitor; PR - pegylated interferon+ribavirin; R - ribavirin; RNA - ribonucleic acid; SD - standard deviation; SMV - simeprevir; SOF - sofosbuvir.

† SOF/R24 arm in VALENCE comprised 42% HCV treatment naïve, 58% treatment experienced. Patient characteristics are presented for the entire arm of the trial.

‡ LONESTAR-2 enrolled treatment experienced patients only. This study is used to provide data on cirrhotic patients in the GT3 treatment naïve population in the absence of this data in a treatment naïve population.

Table 26: Baseline patient characteristics in GT3 treatment-experienced comparator studies (taken from CS[1] Table 42)

		VALENCE
		SOF+R24†
N		250
Age	**Mean**	48
Race	**White %**	94%
	Black %	0%
Viral load (RNA IU/mL)	**> 400,000**	NR
	> 600,000	NR
	> 800,000	NR
Advanced liver disease	**Cirrhosis**	23%
Genotype	**% GT2**	0%
	% GT3	100%
BMI	**Mean [Range] or (SD)**	25 [17-41]
IL28B	**CC**	34%
	CT	52%
	TT	13%
Previous therapy	**PR**	NR§
	PI	NR
	Other	NR

BMI - body mass index; GT - genotype; LDV - ledipasvir; NR - not reported; PI - protease inhibitor; PR - pegylated interferon+ribavirin; R - ribavirin; RNA - ribonucleic acid; SD - standard deviation; SMV - simeprevir; SOF - sofosbuvir.
† SOF/R24 arm in VALENCE comprised 42% HCV treatment naïve, 58% treatment experienced. Patient characteristics are presented for the entire arm of the trial.
§ Based on inclusion criteria of study, all treatment experienced patients were defined as IFN intolerant or a treatment failure on previous IFN-based therapy (IFN or PEG-IFN).

4.4 Critique of the indirect comparison and/or multiple treatment comparison

Estimates of treatment effects relative to standard therapies (i.e. comparators) using concurrent controls are not available in the Phase III trials because they did not include a control intervention. Including a control intervention is generally required not only to allow an assessment of whether the experimental treatment was effective but also whether the study worked (i.e. assay sensitivity). However, in the clinical programme the experimental treatments were assumed to be associated with high response rates and the trial designs were approved by the US Food and Drugs Administration (FDA) and the EMA without concurrent controls. The trials were designed to test the hypothesis that the primary efficacy outcome for LDV/SOF treated patients would be superior to a historical control based on previously reported data for the protease inhibitors TVR and BOC, in a trial population of cirrhotic and non-cirrhotic GT1 infected patients.

The CS[1] (page 120) asserts that no network meta-analysis (NMA) was possible for LDV/SOF and made reference to the SOF submission in support of this assertion; in particular, because the Phase III trials evaluated LDV/SOF regimes with and without RBV for different treatment durations without including a comparator treatment, it was not possible to perform a coherent synthesis and comparison of the evidence across all comparators and interventions. Nevertheless, ION-1 (ignoring patients with compensated cirrhosis) and ION-3 constitute a network of evidence, albeit disconnected from all of the comparator treatments. The ERG considers that it may have been useful for the company to attempt to analyse the six active interventions in a coherent model and generate the joint posterior distribution of treatment effect for these (which would be a (log) odds ratio for LDV/SOF); indeed, it is reasonable to assume that effectiveness depends on duration of treatment. Similarly, the ERG believes that a coherent synthesis of the evidence associated with the comparator treatments may have been useful.

An important feature of a NMA is transitivity so that treatment effects are unbiased. In general, this means that there must be a balance in known and unknown treatment effect modifiers in trials comparing different pairs of treatments. It does not appear that the efficacy of the new intervention(s) depends on the patient characteristics that were pre-specified in the analysis plan. However, given that various treatment effect modifiers were pre-specified, it seems reasonable to assume that these may affect the efficacy of some of the comparator treatments. The impact of patient characteristics on comparator treatment SVR rates mean that responses are likely to vary much more than any estimate provided by a single study. Interestingly, the company claims that the patient populations in the LDV/SOF trials include patients that are harder to treat (see CS[1] page 114), although they also state that the patient populations are similar (see CS[1] Tables 39-42).

The ERG also notes that in general, Phase II evidence should not be treated as if it were comparable to Phase III evidence. Phase II clinical trials are conducted in more restricted patient populations and treatment effects tend to be exaggerated relative to those estimated in Phase III trials. However, in this case it is difficult to criticise the use of Phase II evidence from NEUTRINO in the assessment.

The purpose of a NMA is primarily to estimate relative efficacy. However, it is also used to quantify uncertainty associated with absolute response rates as required for subsequent health economic analysis. Given the high SVR rates associated with the experimental treatments, it probably makes little difference to point estimates that a deterministic analysis is being performed. However, there is still uncertainty in the intervention and comparator response rates that the approach used does not fully capture. The use of fixed, naïve estimates of response rates (formed by summing the number of responses in each arm of each study and dividing these by the total number of patients in each arm of each study) breaks randomisation and ignores uncertainty in response rate (see Section 5). This does not appear to affect SOF response rates which appear to be independent of patient characteristics. However, response rate does vary according to patient characteristics in comparator-treated patients and this should be acknowledged when setting parameter estimates.

4.5 Conclusions of the clinical effectiveness section

The approach to searching the evidence base for comparator terms and AEs was not systematic, especially given the use of targeted searches and the absence of a full systematic review. Whilst it is unlikely that there are any major omissions in the studies retrieved, there is potential for evidence to have been missed and the overall reporting of the searches is such that the ERG could not make a fully informed critique of this element of the CS.

No head-to head trials of LDV/SOF versus any of the comparators specified in the final NICE scope[5] were identified. It is unlikely that any such trials were missed.

Clinical evidence regarding LDV/SOF in the CS mainly concentrates on three Phase III trials (ION-1, ION-2 and ION-3). These trials had been completed and published at the time of the company submission. These trials are randomised comparisons of different durations of LDV/SOF treatment, eight, twelve or twenty-four weeks, with or without RBV. None of the trials include a placebo comparator and none of the comparator drug regimens relate to those specified in the final NICE scope.[5]

The generation of randomisation sequences and allocation concealment, were adequate for all three Phase III LDV/SOF trials. The trials were well balanced between groups in terms of baseline

characteristics. Each of the three included Phase III trials provided data from a FAS, which is a modified ITT analysis, including only randomised patients who received at least one dose of the study drug. These factors suggest a low risk of bias in the comparison between groups within each study. All three of the Phase III trials were open-label. Outcome assessment for post-treatment HCV RNA results were blinded to the investigator for the three ION trials. Other outcome data were not blinded, leading to risk of bias, particularly for subjective HRQoL outcomes.

Seven Phase II studies of LDV/SOF were included. Five of the Phase II studies were considered to provide supporting data for the Phase III studies (ELECTRON, ELECTRON-2, LONESTAR, SYNERGY, SIRIUS). Two of the Phase II studies were conducted in specific populations not represented in the Phase III studies: in ERADICATE, the population was co-infected with HIV; in SOLAR-1, the population had decompensated liver cirrhosis or had undergone liver transplant. Two of the Phase II studies (ELECTRON and LONESTAR) had been completed at the time of company submission, whereas the remaining five Phase II studies were ongoing (ELECTRON-2, SYNERGY, SIRIUS, ERADICATE, SOLAR-1).

Data from the trials are mostly from populations with GT1 HCV (with some limited data for patients GT3 and GT4 disease). No clinical data were provided for patients with GT2, GT5 or GT6 HCV. However, as recommended treatment (by the EMA) is for GT1, GT3 and GT4, this was considered appropriate. For GT1 patients, both treatment-naïve and treatment-experienced patients were represented.

The three Phase III trials were multicentre studies. ION-1 had some trial centres in Europe, as well as sites in the US. ION-3 and ION-2 had sites only in the US. Whilst trial populations are likely to be similar to the UK population, expert advice received by the ERG suggests that it is possible that there are fewer black and ethnic minority patients in UK practice than in US trial centres, but otherwise demographics are similar. The ERG's clinical experts suggest that disease diagnostic criteria and SVR outcomes[12] used in trials are representative of current UK practice.

For LDV/SOF clinical effectiveness and AE data, the main evidence is drawn from the three Phase III trials. Data from the Phase II trials were consistent with data from the Phase III trials.

For LDV/SOF treated patients, reported SVR12 rates ranged from 93% to 99% across all treatment arms for GT1 treatment-naïve patients in the ION-1 and ION-3 trials.

For subgroups of GT1 treatment-naïve patients, SVR12 rates ranged from 92.4% to 100% for GT1a patients; and from 95.5% to 100% for GT1b patients. For GT1 treatment-naïve non-cirrhotic patients, SVR12 rates ranged from 93.1% to 99.4%. SVR rates for patients with compensated cirrhosis were reported to range from 94.1% to 100%.

For LDV/SOF-treated patients, the SVR12 rates for GT1 treatment-experienced patients in the ION-2 trial ranged from 93.6% to 99.1%.

For subgroups of GT1 treatment-experienced patients, GT1a patients, SVR12 rates ranged from 95.3% to 98.8%, and for GT1b patients, SVR12 rates ranged from 87.0% to 100%. For GT1 treatment-experienced non-cirrhotic patients, SVR12 rates ranged from 95.4% to 100%. For patients with compensated cirrhosis, SVR rates ranged from 81.8% to 100% in ION-2.

The most common AEs for LDV/SOF treated patients were fatigue, headache, insomnia, and nausea. Across the treatment arms of the Phase III trials, 67% to 93% of patients had at least one AE. Of these, the majority of AEs were mild to moderate in severity.

Within the three Phase III trials, historical controls were used to compare LDV/SOF treatment with TVR or BOC treatment. They combined TVR and BOC into the same control group, and were different to the data used within the company's health economic analysis.[1] Eighteen clinical trials were selected to provide data for comparator drug regimens in the CS.[1] Comparator data were provided by single arms of RCTs, or non-RCTs. The selection process was not transparent in the CS[1] or in the company's response to clarification from the ERG.[2] Data were mostly for GT1, with some data from GT3 and GT4.

The CS does not include the use of NMA to synthesise the available evidence base. The ERG consider that it may have been useful for the company to attempt to analyse the six active interventions from ION-1 and ION-3 in a coherent model and generate the joint posterior distribution of treatment effect for these. Similarly, the ERG believes that a coherent synthesis of the evidence associated with the comparator treatments may have been useful. Furthermore, no data for SVR rates for the comparators were detailed within the clinical effectiveness section of the CS.

Superseded – see erratum

5. COST-EFFECTIVENESS

This chapter presents a summary and critical appraisal of the methods and results of the company's review of published economic evaluations and the *de novo* health economic analyses presented within the CS.[1] The summary and critique of the company's review of existing cost-effectiveness studies is presented in Section 5.1. A description of the company's analysis is detailed in Section 5.2. The results presented by the company are presented in Section 5.3. A critical appraisal of the company's health economic analysis is presented in Section 5.4. Additional exploratory analyses undertaken by the ERG are also presented in Section 5.5. The ERG's conclusions are presented in Section 5.6.

5.1 Description of company's review of published cost-effectiveness studies

The CS presents a systematic review of existing studies of the cost-effectiveness of treatments for HCV. The CS states that the review was undertaken *"to identify all published studies that had assessed the cost-effectiveness of treatments currently used for chronic HCV"* (see CS,[1] page 144). The review itself is substantial; the main body of the CS (Section 7.1, pages 144-153) includes a summary of the findings of the review; 108 pages of additional information are reported in Appendices 10 and 11 of the CS.[1]

5.1.1 Search strategy

The company's review included an initial search undertaken on the 4th September 2012, followed by a first update undertaken on the 10th October 2013 and a second update undertaken on the 5th August 2014. Searches were undertaken across four electronic databases:

- PubMed;
- EMBASE (Ovid);
- Medline (Ovid), and;
- CRD databases – i.e. Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), and the NHS-Economic Evaluation Database (NHS-EED).

The searches were limited to studies published in the last 10 years (from 2002 onwards). Study searches were not limited by language. The CS states that all searches were designed to build on previous searches performed in systematic literature reviews by NICE and the Cochrane Collaboration.[1] The CS also states that alongside the electronic searches, the reference lists of included systematic reviews published from 2010 onwards were also handsearched to ensure that no relevant publications missed by the searches.

5.1.2 Inclusion/exclusion criteria

Table 27 presents the inclusion and exclusion criteria employed within the company's review of cost-effectiveness evidence.

Table 27: Inclusion and exclusion criteria employed within the company's review of cost-effectiveness evidence (reproduced from CS,[1] Table 49, page 145)

Category	Inclusion criteria	Exclusion criteria
Disease and population	• Infection with Hepatitis C virus (HCV), genotypes 1, 3, 4 • Adults (> 18 years) • Treatment-naïve patients • Treatment-experienced patients: relapsers, non- partial- and null-responders • HIV co-infected patients	• Studies in children • Economic studies on following disease and population: • Not focussed on adults (> 18 years) • Studies of smaller populations (<10) • Acute HCV • Recurrent HCV • HCV/HBV co-infected • Renal dysfunction • Depression • Studies focussing on homeless populations and intravenous drug users (IDU)
Interventions	• HCV screening programmes* • HCV treatments (e.g., PEG-IFN, RBV, LDV, SOF, telaprevir, boceprevir, daclatasvir, asunaprevir, simeprevir, faldaprevir) • Watchful waiting	Studies not reporting impact on economic outcomes
Outcomes	• Costs • Resource use • QALYs • LYG • Productivity losses	• Non-economic outcomes • Efficacy • Safety • QoL • HCV sequence
Study type	Economic evaluations • Health technology assessments • Systematic reviews	Studies not reporting impact on economic outcomes
Language	Studies in English, French, German, Spanish Italian	All other languages besides English, French, German, Spanish Italian

HBV - hepatitis B virus; HCV - hepatitis C virus; HIV - human immunodeficiency virus; IDU - intravenous drug users; LDV - ledipasvir; LYG- life years gained; QALY - quality-adjusted life year; QoL - quality of life; RBV - ribavirin; SOF - sofosbuvir; TE - treatment-experienced; TN - treatment-naïve.
**Note: In the original review HCV screening programmes were considered a relevant comparator to provide data on another outcome (assess burden of illness) but were not included in the most recent update*

5.1.3 Methods for review and appraisal

All potentially eligible references were imported into Reference Manager software and duplicates were removed. The titles and abstracts of the remaining references were reviewed by two independent reviewers based on the inclusion and exclusion criteria (see Table 27). In the instance of discrepancies between the two decisions, arbitration was undertaken by third independent reviewer. The full publication of any articles that were deemed relevant for full-text review was obtained. Two independent researchers reviewed each full-text article and, in the instance of any disagreement, a third reviewer was consulted.[1]

Studies selected for inclusion in the systematic review were critically appraised using the Drummond and Jefferson checklist for economic evaluations.[52]

5.1.4 Results of the company's review of cost-effectiveness evidence

An overview of included economic analyses presented in Appendix 10 of the CS[1] (see CS Table 156). A summary critical appraisal of all included studies based on Drummond and Jefferson presented in Appendix 11 of the CS[1] (see CS[1], Tables 157 to 176).

One hundred and eighty two citations were deemed to meet the inclusion criteria for the review (53 from original search, 59 studies from update 1 and 70 studies from update 2). Of these, 98 unique citations reporting economic evaluation studies were included in the company's final review.

The main body of the CS summarises the economic comparisons made for the intervention and comparators defined in the final NICE scope including a list of studies in which the intervention was found to be dominant or cost-effective (acceptability criterion unspecified, see CS,[1] Table 50). Sixteen studies reported on the cost-effectiveness of alternative treatment options from the perspective of the UK NHS (economic outcomes valued in pounds sterling (£)), although several of these are available only in abstract form. Only one of the identified studies assessed the cost-effectiveness of the LDV/SOF fixed dose combination (McGinnis *et al*[53]); this study was published only in abstract form and cost-effectiveness estimates are presented in US dollars ($).

The CS also includes a brief summary of the model type, perspective, HRQoL health states and disease progression health states employed in the included studies. It appears from later sections of the CS that this information was used to inform the *de novo* economic model.

5.1.5 ERG comments on the company's review of cost-effectiveness studies

ERG comments on the company's search methods

The CS[1] states that: *"All searches were designed to build on previous searches performed in systematic literature reviews by NICE and the Cochrane Collaboration"* However, no further details are provided; it is therefore unclear how the searches were derived. Specifically, there are no references for the economic search filters employed within the search strategies. Clarification on how the economic filters were derived was sought from the company (see clarification response,[2] question A2). The company's response states that they were based on two published HTA submissions (items 1 and 2 of the reference list provided as part of the company's clarification response). The company goes on to describe the methods by which the search filters were adapted for the purposes of the current appraisal. The ERG does not believe that amending filters is good practice, even where search

terms result in no additional studies, as it is important to demonstrate that the searches are both thorough and rigorous.

The strategy for all economic studies (see CS[1] Appendix 10.10) yields a smaller number of results than would be expected for PubMed. The ERG applied the Scottish Intercollegiate Guidelines Network (SIGN) economics filter (http://www.sign.ac.uk/methodology/filters.html#econ) to PubMed to cross-check the number of results; the SIGN filter was far more sensitive (732,428 citations). This calls into question the suitability of the economics filters used by the company.

It is also noteworthy that the population terms are different for the main searches and the subsequent update searches. Specifically, in the original searches, certain disease terms were excluded using the 'NOT' Boolean operator. This could have resulted in potentially relevant studies being excluded from the review, especially where articles have been indexed with both the included and excluded subject headings. For example, a study indexed with "HIV" may also have made reference to "Hepatitis C." This issue is demonstrated by the number of results for the disease terms in the original searches compared with the two updates). Initially, this issue was noted by the ERG for the quality of life searches only, and so clarification on why the 'NOT' operator was used was only sought for the quality of life searches (see clarification response[2] question A1). The response from the company states that *"The use of the 'NOT' Boolean operator with the disease terms could have resulted in the exclusion of important articles that were indexed with these terms but contained information relevant to the appraisal. In order to account for this, systematic reviews and economic studies identified by the search were reviewed to identify any relevant articles cited within them that may have been excluded by the Boolean operator 'NOT'"* The ERG does not consider this to be good practice, as the main searches are not rigorous and there is an over-reliance on reference tracking of systematic reviews and economic studies to capture any relevant evidence excluded by the use of the Boolean operator 'NOT'.

The ERG also notes that there are some reporting errors for Update 1 (PubMed), although this is not likely to reflect errors in how the searches were conducted.

The ERG also sought clarification on why two search updates were required for the cost-effectiveness and quality of life searches (see clarification response[2] question A3). The company's clarification response states that both the initial searches and Update 1 were performed in support of the NICE appraisal for Sofosbuvir,[12] explaining the need for a second update to cover the intervening period between October 2013 and August 2014.

ERG comments on the company's review

The ERG considers that whilst the methods of the review are broadly appropriate, its purpose is largely unclear – whilst the company states that their intention was to identify all previously published economic analyses of treatments for HCV, it is not clear what they would then do with these. Specifically, it is unclear whether it was the intention of the company to explore current knowledge concerning the cost-effectiveness of LDV/SOF for hepatitis C, to explore current knowledge regarding the cost-effectiveness of all antiviral treatments for hepatitis C, or to examine existing models to inform the *de novo* economic analysis (or indeed, some combination of these).

Given the scale of the company's review, it is surprising that there is no discussion of the results of the individual studies of relevant interventions and comparators specified in the final NICE scope[5] and that there is very little interpretation of the broader economic evidence available in terms of what this means for the cost-effectiveness of LDV/SOF and its comparators. Furthermore, it is particularly surprising that there is no discussion of McGinnis *et al*[53] given that this is the only study which has previously assessed the cost-effectiveness of LDV/SOF for the treatment of chronic hepatitis C.

The ERG considers that questions regarding current knowledge about the cost-effectiveness of LDV/SOF for hepatitis C are best addressed through consideration of the analysis reported by McGinnis *et al*.[53] Questions regarding current knowledge about the cost-effectiveness of LDV/SOF and other comparators, within the context of this appraisal, are however probably best addressed by focussing on the UK-relevant studies included in the company's review. Examining the evidence base as a whole may be helpful in the design of the company's model. To these ends, the ERG presents a brief summary of McGinnis *et al*[53] and a summarised extraction of the UK economic studies included within the company's review.

Summary of McGinnis et al[53]

McGinnis *et al* present a cost-effectiveness analysis of alternative treatment options for patients with chronic hepatitis C. The analysis uses a Markov model to simulate the natural disease progression of hepatitis C infection and the impact of treatment for a cohort of 1,000 hypothetical treatment-naïve patients with genotype 1 disease over a 20-year time horizon. The model compares four options: (1) no treatment; (2) boceprevir+pegylated interferon+ribavirin (BOC+PEG-IFN+RBV); (3) telaprevir+ pegylated interferon+ribavirin (TVR+PEG-IFN+RBV), and; (4) sofosbuvir+ledipasvir+ribavirin (LDV/SOF+RBV). Cost-effectiveness is evaluated in terms of the incremental cost per QALY gained. The perspective of the analysis adopted within the study is not reported. The results suggested that BOC+PEG-IFN+RBV and TVR+PEG-IFN+RBV were weakly dominated, whilst LDV/SOF+RBV

was the most cost-effective therapy; the ICER for LDV/SOF+RBV versus no treatment was estimated to be $61,291 per QALY gained ($US).

The ERG notes that the study reported by McGinnis *et al.*[53] is of limited relevance to this appraisal for four reasons:

1. It is a US study; treatment patterns, care pathways, unit costs and health preferences may not reflect those associated with usual clinical practice in England and Wales.
2. The selection of comparators included in the study is narrower than those included in the final NICE scope.[5]
3. Consideration is given only to those patients with genotype 1 hepatitis C; the marketing authorisation of LDV/SOF also includes patients with genotype 3 and genotype 4 disease.
4. The study is published in abstract form only, hence a detailed critical appraisal of the quality of the economic evaluation and the underlying model upon which the analysis is based is not possible.

Summarised extraction of UK-relevant published economic evaluations of treatments for hepatitis C included in the company's review

Table 28 presents a brief summary of the UK-based full economic evaluations studies included in the company's systematic review (note that the summary is restricted only to *de novo* analyses which are reported as full publications - abstracts and review papers are excluded from the table).

Table 28: UK studies included in the company's review (full publications)

Study	Type of economic evaluation	Model type	Perspective	GT	Interventions & comparators	Headline cost-effectiveness results
Jones *et al*, 2011[54]	CUA	Markov	NHS & PSS	1	(1) TVR+PEG-IFN-2a+RBV; (2) PEG-IFN-2a+RBV	Treatment-naïve: ICER for TVR+PEG-IFN-2a+RBV vs. PEG-IFN-2a+RBV=£13,553 per QALY gained. Treatment-experienced: ICER for TVR+PEG-IFN-2a+RBV vs. PEG-IFN-2a+RBV=£8,688 per QALY gained.
Hartwell *et al*, 2011/2012[55, 56]	CUA	Markov	NHS & PSS	1/4; 2/3	People who have been previously treated with PEG-IFN+RBV/ those with HCV/HIV co-infection: (1) PEG-IFN+RBV; (2) BSC. People who meet criteria for receiving shortened courses of PEG-IFN+RBV: (1) Shortened duration PEG-IFN+RBV; (2) standard duration PEGIFN+RBV.	ICERs for shortened treatment with PEG-IFNα-2a ranged from £35,000/QALY to £65,000/QALY for patients with GT1. In patients with GT2/3, shortened treatment dominated standard treatment. For patients with GT1 with LVL/RVR, shortened treatment with PEG-IFNα-2b dominated standard treatment. In patients with GT1 and those with GT non-1 who were retreated with PEG-IFNα-2a, ICERs were £9,169/QALY and £2,294/QALY, respectively. In patients with GT1/4, who were retreated with PEG-IFNα-2b, the ICER was £7,681/QALY, whereas retreatment dominated BSC for patients with GT2/3. In patients co-infected with HCV/HIV, who were receiving PEG-IGNα-2a, the ICER was £7,941/QALY in patients with GT1/4, whereas in patients with GT2/3 PEG-IFNα-2a dominated BSC. In co-infected patients receiving PEG-IFNα-2b, the ICER was £11,806/QALY in GT1/4 and £2,161/QALY in GT2/3.
Grishchenko *et al*, 2009[57]	CUA	Markov	NHS	1; non-1	(1) PEG-IFN-2a+/-RBV (2) No antiviral treatment	ICER for PEG-IFNa-2a +/-RBV vs no antiviral treatment ranges from dominating to £8,017/QALY gained across all subgroups.
Shepherd *et al*, 2007[58]	CUA	Markov	NHS&PSS	1; non-1	(1) PEG-IFN+RBV; (2) PEG-IFN monotherapy (for those who cannot tolerate RBV); (3) Dual therapy with IFN+RBV; (4) BSC	ICERs for GT1: - Watchful waiting with IFN+RBV versus BSC = £3,097–£6,585 per QALY gained - Early treatment with IFN+RBV versus watchful waiting with IFN + RBV = £5,043–£8,092 per QALY gained

Study	Type of economic evaluation	Model type	Perspective	GT	Interventions & comparators	Headline cost-effectiveness results
						- Watchful waiting with PEG-IFN2a+RBV versus best supportive care = £3,052 per QALY gained - Early treatment with PEG-IFN2a+RBV versus watchful waiting with PEG 2a + RBV = £5,900 per QALY gained - Watchful waiting with PEG-IFN2b+RBV versus BSC = £2,534 per QALY gained - Early treatment with PEG-IFN 2b+RBV versus watchful waiting with PEG 2b + RBV = £5,774 per QALY gained
Mendes *et al*, 2011[59]	CUA	Markov	NHS&PSS	1	(1) BOC+PEG-IFN+RBV; (2) PEG-IFN+RBV	Base case ICER for treatment-naïve=£11,601/QALY gained. Base case ICER for treatment-experienced=£2,744/QALY gained.
Cure *et al*, 2013[60]	CUA	Markov	NHS	1	(1) TVR+ PEG-IFN+RBV; (2) IFN+RBV	ICER for TVR+IFN+RBV vs IFN+RBV (treatment experienced)=£6,079/QALY gained.
McEwan *et al*, 2013[61]	CUA	Markov	Healthcare payer	1	(1) RGT; (2) SDT PEG-IFN2a+RBV; (3) No treatment	Overall, RGT was a dominant scenario being associated with a lower risk of complications, increased QALYs (0.08) and cost saving (£101).
Miners *et al*, 2014[62]	CUA	Markov	NHS	1; 2/3	(1) HCV case-finding; (2) No intervention	ICER for intervention vs comparator=£23,200/QALY gained

CUA – cost-utility analysis; ICER – incremental cost-effectiveness ratio; RGT - response-guided therapy; SDT - standard duration therapy; HCV – hepatitis C virus

The published economic analyses suggest that ICER for PEG-IFN versus other antiviral options ranges from dominating to below £10,000/QALY gained.[57,58] TVR+PEG-IFN-2a+RBV vs. PEG-IFN-2a+RBV in patients with genotype 1 hepatitis C is associated with an ICER of less than £14,000 per QALY gained.[54,60] The ICER for BOC+PEG-IFN+RBV versus PEG-IFN+RBV is estimated to be below £12,000 per QALY gained. Response-guided therapy dominates standard duration therapy and no treatment.[61] Shortened duration therapy may result in in cost-savings, but in some scenarios also resulted in poorer outcomes, compared with standard duration therapy.[55,56] The ICER for hepatitis case finding versus no intervention was estimated to be around £23,200 per QALY gained.[62]

5.2 Description of company's *de novo* health economic model

5.2.1 Model scope

The CS presents details of the methods and results of a *de novo* model developed to simulate the experience of patients with chronic hepatitis C over a lifetime horizon from the perspective of the NHS and PSS. The company also submitted the executable health economic model from which the analysis contained within the CS was drawn. Within the company's health economic analysis, cost-effectiveness is expressed in terms of the incremental cost per QALY gained. The evaluation considers patients with genotype 1, genotype 3 and genotype 4 disease; consideration is given to patients who are treatment-naïve/treatment-experienced, patients who have compensated cirrhosis and those who are ineligible for treatment using IFN. Within all analyses presented by the company, the intervention is defined as a fixed dose combination of LDV/SOF (90mg LDV plus 400mg SOF) with or without RBV. The comparators considered in the company's economic analysis differ according to the characteristics of the population and the licensed indications for each drug/combination; these include: (i) PEG-IFN2a+RBV; (ii) SMV+PR; (iii) TVR+PEG-IFN2a+RBV; (iv) BOC+PEG-IFN2b+RBV; (v) SOF+ PEG-IFN2a+RBV; (vi) SOF+SMV; (vii) SOF+RBV, and; (viii) no treatment. The interventions and comparators included in the company's economic analysis are summarised in Table 29 (based on Table 54 of the CS[1]). All costs and outcomes are discounted at an annual rate of 3.5%.[63]

Table 29: Interventions and comparators included in the company's health economic analysis (adapted from CS[1] Table 54)

Population	Intervention	Comparators considered within subgroup
Genotype 1, treatment-naïve	LDV/SOF (90mg/400mg OD) for 8, 12 or 24wks	SOF (400 mg OD) + PEG-IFN2a (180 µg/wk) + weight-based RBV (1,000-1,200 mg OD) for 12wks
		SMV (150 mg OD) + PEG-IFN2a (180 µg/wk)+ weight-based RBV (1,000-1,200 mg OD) for 24wks
		TVR (750 mg q8h) + PEGIFN2a (180µg/wk) + weight-based RBV (15mg/kg OD) for 24 or 48wks based in stopping rules and eRVR status
		BOC (800 mg TID) + PEGIFN2b (1.5µg/kg/wk)+ weight-based RBV (15mg/kg OD) for 28 or 48wks based on futility rules
		PEG-IFN2a (180µg/wk) + weight-based RBV (15mg/kg OD) for 48wks
		SMV (150 mg OD)+SOF (400 mg OD) for 12wks
		No treatment
Genotype 1, treatment-experienced	LDV/SOF (90mg/400mg OD) for 12 or 24wks	SOF (400 mg OD) + PEG-IFN2a (180 µg/wk) +weight-based RBV (1,000-1,200 mg OD) for 12wks
		SMV (150 mg OD) + PEG-IFN2a (180 µg/wk)+weight-based RBV (1,000-1,200 mg OD) for 48wks
		TVR (750 mg q8h) + PEGIFN2a (180µg/wk) +weight-based RBV (15mg/kg OD) for 24 or 48wks based in stopping rules and eRVR status
		BOC (800 mg TID) + PEGIFN2b (1.5µg/kg/wk)+ weight-based RBV (15mg/kg OD) for 28 or 48wks based on futility rules
		PEG-IFN2a (180µg/wk) + weight-based RBV (15mg/kg OD) for 48wks
		SMV (150 mg OD) + SOF (400 mg OD) for 12wks
		No treatment (PI failures)
Genotype 4, treatment-naïve	LDV/SOF (90mg/400mg OD) for 12 or 24wks	PEG-IFN2a (180µg/wk) + weight-based RBV (15mg/kg OD) for 48wks
		SOF (400 mg OD) + PEG-IFN2a (180 µg/wk) +weight-based RBV (1,000-1,200 mg OD) for 12wks
		SMV (150 mg OD) + PEG-IFN2a (180 µg/wk)+weight-based RBV (1,000-1,200 mg OD) for 24wks
		SMV (150 mg OD) + SOF (400 mg OD) for 12wks
		No treatment
Genotype 4, treatment-experienced	LDV/SOF (90mg/400mg OD) for 12 or 24wks	PEG-IFN2a (180µg/wk) + weight-based RBV (15mg/kg OD) for 48wks
		SOF (400 mg OD) + PEG-IFN2a (180 µg/wk) +weight-based RBV (1,000-1,200 mg OD) for 12wks
		SMV (150 mg OD) + PEG-IFN2a (180 µg/wk)+weight-based RBV (1,000-1,200 mg OD) for 48wks
		SMV (150 mg OD) + SOF (400 mg OD) for 12wks
		No treatment (PI failures)
Genotype 3 treatment-naïve	LDV/SOF (90mg/400 mg OD) + weight-based RBV (1,000-1,200 mg OD) for 12 or 24wks	SOF (400 mg OD) + PEG-IFN2a (180 µg/wk) +weight-based RBV (1,000-1,200 mg OD) for 12wks
		SOF (400 mg OD) + weight-based RBV (1,000-1,200 mg OD) for 24wks
		PEG-IFN2a (180 µg/wk) + weight-based RBV (800 mg OD) for 24wks
		No treatment
Genotype 3 treatment-experienced (IFN ineligible only)	LDV/SOF (90mg/400 mg OD) + weight-based RBV (1,000-1,200 mg OD) for 24wks	SOF (400 mg OD) + weight-based RBV (1,000-1,200 mg OD) for 24wks
		No treatment

It should be noted that the option of no treatment is not considered within the company's analysis of the subgroup of patients with GT3 disease with compensated cirrhosis who are treatment-naïve or within the subgroup of patients with GT3 disease with compensated cirrhosis who are treatment-experienced and IFN-ineligible. Clinical advisors to the ERG suggest this to be appropriate due to disease severity. It should also be noted that the company's analysis of treatment-experienced patients with GT1/4 includes both BOC and TVR; neither product is licensed for use in patients with GT4 disease (this is mentioned in the footnotes to the results tables within the CS but is not discussed further). Table 30 summarises the comparisons presented within the base case analysis section of the CS.[1] Within the treatment-experienced GT3 subgroup, IFN-based treatments are not included as comparators.

Table 30: Comparisons considered within the CS

Treatment option	**Subgroup**						
	GT1 TN	**GT4 TN**	**GT1/4 TE**	**GT3 TN**	**GT3 TN with compensated cirrhosis**	**GT3 TE IFN-ineligible**	**GT3 TE IFN-ineligible with compensated cirrhosis**
LDV/SOF	✓	✓	✓	×	×	×	×
LDV/SOF+RBV	×	×	×	✓	✓	✓	✓
PEG-IFN2a+RBV	✓	✓	✓	✓	×	×	×
SMV+ PEG-IFN2a+RBV	✓	✓	✓	×	×	×	×
TVR+PEG-IFN2a+RBV	✓	×	✓	×	×	×	×
BOC+PEG-IFN2b+RBV	✓	×	✓	×	×	×	×
SOF+ PEG-IFN2a+RBV	✓	✓	✓	×	✓	×	×
SOF+SMV	✓	✓	✓	×	×	×	×
SOF+RBV	×	×	×	×	✓	×	✓
No treatment	✓	✓	✓	✓	×	✓	×

GT –genotype; TN – treatment-naïve; TE – treatment-experienced; IFN - interferon

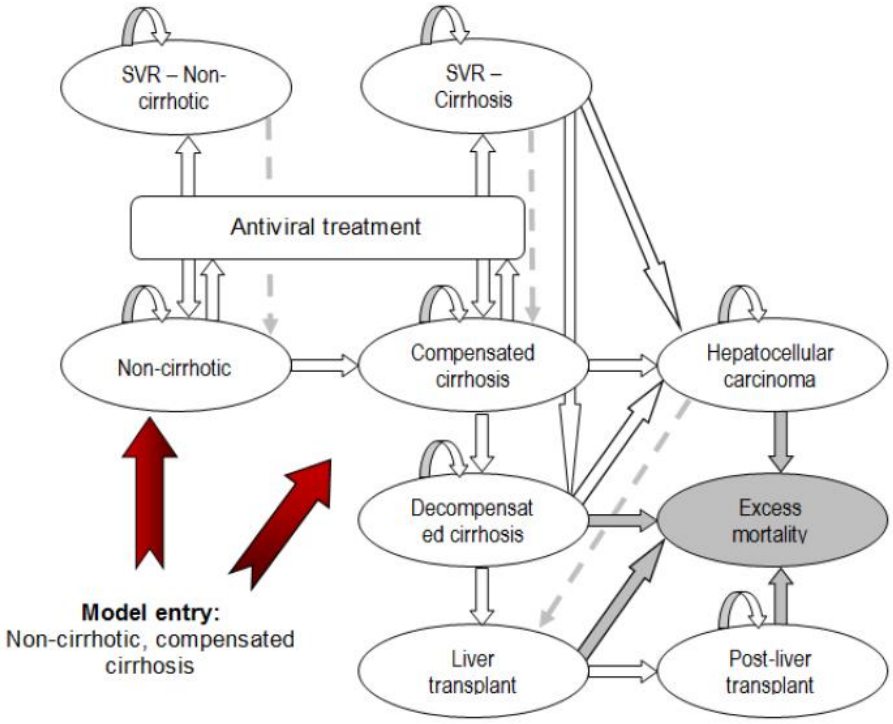
5.2.2 Model structure

The company's model takes the form of a state transition model (see Figure 1). The model includes a total of twelve health states, including two death states. These states are: (1) non-cirrhotic on treatment; (2) cirrhotic on treatment; (3) non-cirrhotic post-treatment; (4) compensated cirrhosis post-treatment; (5) non-cirrhotic post-treatment [post-treatment, with SVR]; (6) compensated cirrhosis [post-treatment, with SVR]; (7) decompensated cirrhosis; (8) hepatocellular carcinoma [HCC]; (9) liver transplant; (10) post-liver transplant; (11) death due to background mortality, and; (12) death due to HCV. Over the course of the time horizon, the model uses three different cycle durations: a monthly cycle length is used for the first eighteen cycles (up to 18 months post-model entry); a 3-monthly cycle length is used for the subsequent two cycles (up to 24 months post-model entry) and an annual cycle length is used thereafter. A half-cycle correction is applied to health state occupancy within the model from month 36 onwards; prior to this point, costs and health outcomes are not half-cycle corrected. Whilst the model includes states reflecting cirrhotic status, costs and health outcomes

Superseded — see erratum

are evaluated separately for those patients who are cirrhotic and those patients who are non-cirrhotic at model entry in subgroups of treatment-naïve patients with genotype 1/4 disease; the model does not evaluate both patient groups simultaneously for these subgroups. For analyses of GT1/4 treatment-naïve subgroups in which a proportion of patients are cirrhotic and a proportion are non-cirrhotic, the model evaluates health state trajectories, events and costs separately for each group and produces a weighted mean of these accordingly.

Figure 1: Company's model structure[1]



Abbreviations: SVR, sustained virologic response.
Notes: Patients can die in each health state.
The grey health state "excess mortality" represents the disease-specific mortality associated with having decompensated cirrhosis, liver transplant or hepatocellular carcinoma.
Dashed arrows represent health state transitions only investigated in sensitivity analysis.

The model logic operates as follows. Patients enter the model in either the cirrhotic or non-cirrhotic on treatment states. They remain in this state for up to 10 cycles whilst receiving treatment (this is dependent on mean treatment time for the treatment option under consideration). All patients then transit to the non-cirrhotic/compensated cirrhosis states for a further three 1-month cycles. Following this point, a proportion of patients transit to the non-cirrhotic/compensated cirrhosis SVR states according to the SVR rate for the intervention under consideration. Non-cirrhotic patients who achieve SVR are assumed to remain in the non-cirrhotic post-treatment SVR state until they die of other causes (i.e. they are assumed to be cured indefinitely). Non-cirrhotic patients who do not achieve SVR are assumed to have an ongoing risk of developing compensated cirrhosis and are

subsequently at risk of subsequently developing decompensated cirrhosis and HCC. Cirrhotic patients who achieve SVR are assumed to have an ongoing risk of developing decompensated cirrhosis and HCC, however these risks are lower than in those who do not achieve SVR. Liver transplant and post-liver transplant states are included for patients with decompensated cirrhosis. The model assumes that the adverse consequences of developing hepatitis C, that is, cirrhosis and HCC and associated impacts on HRQoL and survival, are possible only after 9 model cycles; prior to this point, patients cannot develop sequelae nor can they die as a result of any cause.

Health-related quality of life (HRQoL) is captured within the model by assigning different health utilities to each health state. In addition, the utilities associated with on treatment health states differ for each treatment option; this is intended to reflect the disutility impacts of treatment-specific AEs.

The model includes costs associated with drug treatment, the management of treatment-related AEs, monitoring and health state costs (e.g. post-treatment monitoring, liver transplantation and post-transplantation follow-up).

The use of different therapies changes the trajectory of patients through the health states in the model thereby producing different profiles of costs and QALY gains for each treatment option.

The company's model employs the following key assumptions:

- Patients cannot suffer sequelae of hepatitis C or die as a consequence of any cause until 9 months following model entry.
- Patients who enter the model in the non-cirrhotic state and who subsequently achieve SVR are assumed to never become re-infected with hepatitis C. Patients who enter the model in the compensated cirrhosis state and who subsequently achieve SVR are assumed to have an ongoing risk of reinfection with hepatitis C.
- The non-cirrhotic state combines fibrosis states F0 to F3 (these have been modelled separately in previous economic models of antiviral treatments)
- Non-cirrhotic patients with SVR are followed up clinically only until the end of year two (and subsequently incur no further costs but continue to gain QALYs).
- The rate of patients spontaneously achieving SVR is assumed to be zero.
- All patients in the decompensated cirrhosis health state are assumed to be candidates for liver transplantation.
- Patients with HCC are assumed not to be candidates for liver transplantation (base case analysis only).

- Transition probabilities from the non-cirrhotic state to the cirrhotic state are based on age at treatment.
- During treatment, patients may experience a decrement in HRQoL resulting from treatment-related AEs. This impact differs by treatment regimen.
- Treatment disutilities are applied to the entire treatment cycle rather than the specific time spent receiving the drug.
- Patients who achieve SVR experience an improvement over their baseline HRQoL.
- Data for the treatment of CHC GT1 patients with LDV/SOF are assumed to be generalisable for the treatment of GT4 patients.
- Patients with HCV/HIV co-infection have the same response profile as those with HCV mono-infection and therefore are not modelled separately.
- SVR rates are directly comparable across different clinical trials.

5.2.3 Evidence used to inform the company's model parameters

Table 31 summarises the evidence sources used to inform the parameters of the company's model. The derivation of the model parameter values using these sources is described in further detail in the following sections.

Table 31: Summary of evidence sources used to inform the model parameters

Parameter type	Parameter	Sources
Patient characteristics	Proportion of cirrhotic patients from HCV	HCV UK Research Database[64]
	Mean age at treatment, and mean weight from	Hartwell *et al*[55]
SVR - genotype 1/4 (treatment-naïve)	SVR - LDV/SOF (8, 12 or 24 wks)	ION-1[17] and *post hoc* analysis of ION-3[11]
	SOF+PEG-IFN2a+ RBV (12 wks)	NEUTRINO[32,33]
	SMV+PEG-IFN2a+RBV (24 wks)	Pooled data from studies QUEST[35] and QUEST 2,[36] taken from Simeprevir SPC 2014[34]
	TVR+PEG-IFN2a+RBV[†] (24 or 48 wks)	ADVANCE[65], ILLUMINATE[21] and Grishchenko *et al*, 2009[57]
	BOC+PEG-IFN2b+RBV[†] (28 or 48 wks)	SPRINT-2[20]
	PEG-IFN2a+RBV (48 wks)	IDEAL[37]
	SMV+SOF (12 wks)	COSMOS[34,38]
	No treatment	Assumption
SVR - genotype 1/4 (treatment-experienced)	LDV/SOF (12 or 24 wks)	ION-2 [15]
	SOF+PEG-IFN2a+ RBV (12 wks)	Pol *et al*, 2014[66]
	SMV+PEG-IFN2a+RBV (48 wks)	Pooled data from studies PROMISE [39] and ASPIRE, taken from Simeprevir SPC 2014[34]
	TVR+PEG-IFN2a+RBV (24 or 48 wks)	REALIZE, taken from Telaprevir SmPC 2014[21]

Parameter type	Parameter	Sources
	BOC+PEG-IFN2b+RBV (48 wks)	Bacon BR *et al*, 2011[22]
	PEG-IFN2a+RBV (48 wks)	REALIZE, taken from Telaprevir SmPC 2014[21]
	SMV+SOF (12 wks)	COSMOS[34,38]
	No treatment	Assumption
SVR - genotype 3 (treatment-naive)	LDV/SOF + RBV (12 or 24 wks)	ELECTRON-2[24]
	SOF+PEG-IFN2a+ RBV (12 wks)	ELECTRON[32 41] and PROTON[42]
	SOF+RBV (24 wks)	VALENCE [40 32]
	PEG-IFN2a+RBV (24 wks)	FISSION [32;33]
	No treatment	Assumption
SVR - genotype 3 (treatment-naive)	LDV/SOF + RBV (24 wks)	ELECTRON-2[24]
	SOF+RBV (24 wks)	VALENCE [40 32]
	No treatment	Assumption
Transition probabilities (TPs)	Non-cirrhotic state to compensated cirrhosis	Thomson *et al*, 2008[67]
	Recurrence and re-infection from SVR states	Expert opinion
	Compensated cirrhosis to decompensated cirrhosis and HCC	Cardoso *et al*[68]
	From decompensated cirrhosis to liver transplant	Siebert *et al*[69]
	From decompensated cirrhosis and HCC to death	Fattovich *et al*[70]
	From liver transplant to death	Shepherd *et al*[58]
Health-related quality of life	Health state utilities	Wright *et al*,[71] Vera-Llonch *et al*, 2013[65]
Treatment-related utility decrements (GT1 and GT4 TN, GT1 and GT4 TE)	LDV/SOF (8, 12 or 24 wks)	ION-1[17], ION-2[15]and ION-3[11]
	SOF+PEG-IFN2a+ RBV (12 wks)	NEUTRINO[32,33]
	SMV+PEG-IFN2a+RBV (24 wks)	SMV NICE submission[72]
	TVR+PEG-IFN2a+RBV†	ADVANCE[19], taken from Telaprevir SmPC[21]
	BOC+PEG-IFN2b+RBV†	Boceprevir NICE TA253[44,73]
	PEG-IFN2a+RBV (48 wks)	Shepherd *et al*[58]
	SMV+SOF	Assumed equal to LDV/SOF
Treatment-related utility decrements (GT3 TN)	LDV/SOF+ RBV (12 or 24 wks)	FUSION , FISSION and POSITRON[74]
	SOF+PEG-IFN2a+ RBV (12 wks)	NEUTRINO[32,33]
	SOF+RBV (24 wks)	FUSION , FISSION and POSITRON[74]
	PEG-IFN2a+RBV (24 wks)	Shepherd *et al*[58]
Treatment-related utility decrements (GT3 TE)	LDV/SOF+ RBV (24 wks)	FUSION, FISSION and POSITRON[74]
	SOF+RBV	FUSION , FISSION and POSITRON[74]
Costs	Drug acquisition costs	Price of LDV/SOF sourced from company. Costs of comparators taken from British National Formulary (BNF) 2014[75]
	Monitoring costs	Unit cost estimates taken from NHS Reference costs[76] Shepherd *et al*,[58] Wright *et al*,[71] Stevenson *et al*[77]and expert opinion. Sources used for resource use associated with monitoring unclear

Parameter type	Parameter	Sources
	Health state costs	Cost estimates taken from Wright *et al* 2006,[71] Grishchenko *et al*, 2009[57]and Longworth *et al*, 2014.[78]
	AE costs	Unit costs of drugs to treat treatment-related AEs and treatment duration taken from BNF 2014,[75] Telaprevir company's submission to NICE (TA252)[45] and Gao *et al*, 2012.[79]
	Outpatient, hospital registrar and specialist costs	Expert opinion
Treatment duration (GT1/4)	LDV/SOF	ION-1[17]and *post hoc* analysis of ION-3[11]
	SOF+PEG-IFN2a+ RBV	NEUTRINO[32,33]
	SMV+PEG-IFN2a+RBV	Pooled data from studies QUEST[35] and QUEST 2[36] taken from Simeprevir SPC 2014[34]
	TVR+PEG-IFN2a+RBV	ADVANCE[65], ILLUMINATE[21] and Grishchenko *et al*, 2009[57]
	BOC+PEG-IFN2b+RBV	SPRINT-2[20]
	PEG-IFN2a+RBV	IDEAL[37]
	SMV+SOF	COSMOS[34,38]
Treatment duration (GT3)	LDV/SOF+RBV	ELECTRON-2[24]
	SOF+PEG-IFN2a+RBV	ELECTRON[32;41] and PROTON[42]
	SOF+RBV	VALENCE [40 32]
	PEG-IFN2a+RBV	FISSION [32;33]

SVR – sustained virologic response; TN – treatment-naïve; TE – treatment-experienced; SmPC – summary of product characteristics; HCV – hepatitis C virus
†not applicable for GT4 TN patients

5.2.3.1Patient characteristics

The mean age at treatment and the proportion of cirrhotic patients used in the model for the different genotype subgroups are as shown in Table 32. These groups are further divided according to treatment history (treatment-naive or treatment-experienced). The proportion of patients with cirrhosis was obtained from querying 5,000 anonymised patient records in the UK the HCV UK Research Database.[64] It is unclear whether these are representative of the UK HCV population. The mean age (either 40 or 45 years) and mean weight (79kg) of patients were taken from Hartwell *et al*.[55]

Table 32: Patient characteristics assumed within the company's model

Population	% cirrhotic patients†	Mean age at treatment (yrs)‡	Mean weight (kg)‡
Genotype 1 and 4			
GT1/4 treatment-naïve	21%	40	79
GT1/4 treatment-experienced	21%	45	79
Genotype 3			
GT3 treatment-naïve	25%	40	79
GT3 treatment-experienced	25%	45	79

GT - genotype; yrs - years.
Source: † HCV UK Research Database Query[64],
‡ Hartwell et al, 2011[55]

The CS states that the co-infected population is not modelled separately in the base case analysis as the HCV/HIV co-infected populations are treated with the same regimens and will respond to treatment in a similar manner as HCV mono-infected populations (see CS[1] page 165). The CS states that this is a conservative assumption as HCV/HIV co-infected patients, if left untreated, are likely to transit faster to the more advanced disease states, and therefore LDV/SOF would be more cost-effective in HCV/HIV co-infected population compared to the mono-infected population (see CS[1] page 256). The accuracy of this assertion is not examined further within the CS.

5.2.3.2 Clinical effectiveness parameters

The key clinical effectiveness parameters used in the model relate to SVR rates. SVR rates are estimated at 12 weeks after treatment cessation (SVR12) or at 24 weeks after treatment cessation (SVR24). The CS suggests that SVR12 and SVR24 are closely correlated. The ERG notes that the company's economic model assumes that SVR12 is equivalent to SVR24.

SVR is used in the model as a baseline probability of response within the relevant treatment period. Different SVR rates are used for patients with cirrhosis and those without cirrhosis at the start of treatment. SVR estimates for LDV/SOF and the comparators for each combination of HCV genotype, treatment experience and IFN eligibility (for GT3 TE patients) considered in the company's base case analysis are summarised in Table 33.

Table 33: Summary of genotype-specific SVR rates (%) used in the economic model (adapted from CS[1] Tables 58, 61, 63, 66, 69)

Treatment	SVR(%) non-cirrhotic patients	SVR(5) for cirrhotic patients	Source
HCV genotype 1, treatment-naive			
LDV/SOF	97.0%	94.3%	ION-1[17] and *post hoc* analysis of ION-3[11]
SOF+PEG-IFN2a+ RBV	91.7%	80.8%	NEUTRINO[32,33]
SMV+PEG-IFN2a+RBV	82.0%	60.4%	Pooled data from studies QUEST[35] and QUEST 2[36], taken from Simeprevir SPC 2014[34]
TVR+PEG-IFN2a+RBV	77.3%	53.4%	ADVANCE,[65] ILLUMINATE[21] and Grishchenko *et al*, 2009[57]
BOC+PEG-IFN2b+RBV	64.1%	55.0%	SPRINT-2[20]
PEG-IFN2a+RBV	43.6%	23.6%	IDEAL[37]
SMV+SOF	92.9%	92.9%	COSMOS[34,38]
HCV genotype 4, treatment-naive			
LDV/SOF	97.7%	94.3%	ION-1[17] and *post hoc* analysis of ION-3[11]
SOF+PEG-IFN2a+ RBV	91.7%	80.8%	NEUTRINO[32,33]
SMV+PEG-IFN2a+RBV	82.0%	60.4%	Pooled data from studies QUEST[35] and QUEST 2[36], taken from Simeprevir SPC 2014[34]
PEG-IFN2a+RBV	43.6%	23.6%	IDEAL[37]
SMV+SOF	92.9%	92.9%	COSMOS[34,38]
HCV genotype 1 and genotype 4, treatment-experienced			
LDV/SOF	95.6%	89.8%	ION-2[15]
SOF+PEG-IFN2a+ RBV	74.0%	74.0%	Pol *et al*, 2014[66]
SMV+PEG-IFN2a+RBV	76.5%	66.7%	Pooled data from studies PROMISE [39] and ASPIRE, taken from Simeprevir SPC 2014[34]
TVR+PEG-IFN2a+RBV	72.2%	47.2%	REALIZE, taken from Telaprevir SmPC 2014[21]
BOC+PEG-IFN2b+RBV	64.4%	35.3%	Bacon BR *et al*, 2011[22]
PEG-IFN2a+RBV	17.6%	10.0%	REALIZE, taken from Telaprevir SmPC, 2014[21]
SMV+SOF	92.9%	92.9%	COSMOS[34,38]
HCV genotype 3, treatment-naive			
LDV/SOF	100.0%	100.0%	ELECTRON-2[24]
SOF+PEG-IFN2a+ RBV	97.4%	83.3%	ELECTRON[32 41] and PROTON [32; 31]
SOF+RBV (24 wks)	92.3%	-	VALENCE [40;32]
PEG-IFN2a+RBV (24 wks)	71.2%	29.7%	FISSION [32;33]
HCV genotype 3, treatment-experienced			
LDV/SOF	89.3%	77.3%	ELECTRON-2[24]
SOF+RBV (24 wks)	87.0%	60.0%	VALENCE [40;32]

SVR – sustained virologic response

Superseded – see erratum

SVR rates for LDV/SOF

For LDV/SOF, the company's model uses the clinical effectiveness data from the LDV/SOF trials to estimate SVR rates. It should be noted that the SVR rates for LDV/SOF and LDV/SOF+RBV are based on "blended comparisons", which involve taking a weighted average of SVR rates and treatment durations for different options given over different treatment durations based on the expected proportion of patients who would receive each. For, patients with genotype 1/4 HCV, as reported in Table 33, the SVR rates are estimated from more than one trial using a weighted average (blended comparison) of SVR12 rates for different treatment durations. For patients with genotype 3 HCV, the estimates were SVR4 rates taken from ELECTRON-2,[24] a Phase II study.

Genotype 1 treatment-naïve population

The SVR rate for LDV/SOF within the genotype 1 treatment-naïve non-cirrhotic population was estimated by the company as 97.0%, using a weighted average of the efficacy of 8-week and 12-week treatment regimens of LDV/SOF. This is based on the assumption that 8 weeks LDV/SOF will be used for genotype 1 treatment-naïve patients without cirrhosis who have a baseline viral load of <6million IU/mL, and 12 weeks LDV/SOF in patients with a baseline viral load ≥6million IU/mL. The company used a 79% to 21% split of 8-week and 12-week treatment regimens of LDV/SOF, stating that patient-level data from the HCV Research UK database showed that 79% of genotype 1 non-cirrhotic patients (n=408) in the UK had a pre-treatment viral load <6million IU/mL. It should be noted that the cut-off of 6 million IU/ml is based on a *post hoc* analysis of the ION-3 study (see CS[1] Section 6.5.5 page 89) and is not consistent with the treatment indication mentioned in the EPAR.[6]

The efficacy for LDV/SOF within the genotype 1 treatment-naïve cirrhotic population was estimated by the company as 94.3%, using a weighted average of the efficacy of 12-week and 24-week treatment regimens of LDV/SOF, assuming a 95% to 5% split, respectively. Table 48 of CS[1] states that, according to the data from ION-1 study, there is no benefit of extending treatment duration from 12 to 24 weeks. It was assumed by the company that all patients who are treatment-naïve prior to LDV/SOF exposure and do not achieve an SVR are potential candidates for subsequent re-treatment with an IFN-free PI-based regimen. The company state that, based upon this rationale, a conservative estimate of 5% has been used in the economic analysis for treatment-naïve cirrhotic patients who will be given 24 weeks treatment (see Table 48 of CS[1]).

Genotype 4 treatment-naïve population

The SVR rate for LDV/SOF within the genotype 4 treatment-naïve non-cirrhotic population was assumed to be equal to the SVR rate observed in the 12 weeks LDV/SOF treatment regimen for GT1 treatment-naïve non-cirrhotic patients in the ION-1 and ION-3 studies. The rationale given by the

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company is that all GT4 patients should receive 12 weeks of treatment. The SVR rate used in the GT4 treatment-naïve non-cirrhotic population is 97.7%.

The SVR rate for LDV/SOF within the genotype 4 treatment-naïve cirrhotic population was assumed to be the same as the LDV/SOF SVR rate in the GT1 treatment-naïve cirrhotic population, estimated from ION-1 study. The SVR rate used in the GT4 treatment-naive cirrhotic population is 94.3%.

Genotype 1/4 treatment-experienced population

The efficacy for LDV/SOF within the genotype 1 and genotype 4 treatment-experienced non-cirrhotic population was estimated using a weighted average of the efficacy of 12-week and 24-week treatment regimens of LDV/SOF from the ION-2[15] study, assuming a 95% to 5% split, respectively. Table 48 of CS[1]states that patients that are PI+PEG-IFN+RBV-experienced have the potential re-treatment option of SOF+PEG-IFN+RBV (or SOF+RBV if intolerant to IFN), should they not achieve SVR with 12 weeks LDV/SOF. As it is expected that there would be very few patients in England and Wales who would be considered as not having a re-treatment option following LDV/SOF, a conservative estimate of 5% has been incorporated into the model for the population that will receive 24 weeks of treatment. The SVR rate used in the GT1/4 treatment-experienced non-cirrhotic population is 95.6%.

The efficacy for LDV/SOF within the genotype 1 treatment-experienced cirrhotic population was estimated from ION-2[15] and SIRIUS[28] studies using a weighted average of the efficacy of 12-week and 24-week treatment regimens of LDV/SOF, assuming a 75% to 25% split, respectively. Table 48 of CS[1] states that the data from ION-2 study[15] suggests a potential benefit of extending treatment duration from 12 to 24 weeks. As it is expected that a small number of patients in England and Wales would not have a subsequent re-treatment option should they not achieve SVR with LDV/SOF, the assumption has been made by the company that 25% of treatment-experienced cirrhotic patients may be at risk of clinical progression. The SVR rate used in the GT1/4 treatment-experienced cirrhotic population is 89.8%.

Genotype 3 treatment-naïve population

The SVR rate for LDV/SOF+RBV within the genotype 3 treatment-naïve non-cirrhotic population was estimated from the 12 weeks LDV/SOF+RBV treatment regimen in ELECTRON-2,[24] an ongoing, open-label Phase II study in New Zealand. It should be noted that this SVR rate is based on data from only 21 patients. The SVR rate used in the GT3 treatment-naïve non-cirrhotic population is 100%.

The SVR rate for LDV/SOF+RBV within the genotype 3 treatment-naïve cirrhotic population was estimated from the 24 weeks LDV/SOF+RBV treatment regimen in ELECTRON-2.[24] It should be noted that this SVR rate is based on data from only 5 patients. The SVR rate used in the GT3 treatment-naïve cirrhotic population is 100%.

Genotype 3 treatment-experienced IFN –ineligible population

The SVR rate for LDV/SOF+RBV within the genotype 3 treatment-experienced IFN-ineligible population was based on preliminary SVR4 data from ELECTRON-2.[24] The CS states that given the recommended 24-week LDV/SOF+RBV treatment duration for all patients in the GT3 treatment-experienced population, this regimen would not be cost-effective when compared against the 12-week IFN-containing regimen of SOF+PEG-IFN2a+RBV due to the longer treatment duration and therefore higher treatment cost. Consequently, the company modelled only the IFN-ineligible sub-population compared against the IFN-free regimen of SOF+RBV and against no treatment.

The SVR rate for LDV/SOF+RBV within the genotype 3 treatment-experienced non-cirrhotic population was estimated from the 24 weeks LDV/SOF+RBV treatment regimen in ELECTRON-2.[24] The SVR rate for LDV/SOF+RBV used in GT3 treatment-experienced cirrhotic population is 89.3%. The ERG notes that this is based on SVR4 data from only 28 patients.

The SVR rate for LDV/SOF+RBV within the genotype 3 treatment-experienced cirrhotic population was estimated from the 24 weeks LDV/SOF+RBV treatment regimen in ELECTRON-2.[24] The SVR rate for LDV/SOF+RBV used in GT3 treatment-experienced cirrhotic population is 77.3%. The ERG notes that this is based on SVR4 data from only 22 patients.

SVR rates for comparators

SVR rates for all comparators in each subgroup used in the company's model are presented in Table 33. These SVR rates were estimated from individual (or sometimes, pooled) studies selected by the company, rather than from a meta-analysis of all relevant studies. It should be noted that clear selection criteria for choosing the studies used to inform the SVR rates in the company's model were not presented within the CS,[1] nor were they provided following a request for clarification (see clarification response,[2] question B6).

For GT1/4 patients, the SVR rates of the comparators, except TVR+PEG-IFN2a+RBV and BOC+PEG-IFN2b+RBV, were based on estimates based on a single treatment duration i.e. blended estimates were not used. However, for TVR+PEG-IFN2a+RBV and BOC+PEG-IFN2b+RBV in

GT1/4 patients, the SVR rates are based on blended estimates from different treatment durations (see CS[1] Tables 59 and 64). For GT3 patients, the SVR rates of the comparators are all based on estimates assuming a single treatment duration.

The CS does not provide any indication of the range of SVR estimates possible for the comparators. As such, it is not clear whether the studies chosen represent conservative estimates or whether they reflect a more optimistic case for LDV/SOF. It should be noted that, given the studies selected by the company for SVR rates of comparators, LDV/SOF is always more effective than each individual comparator in each subgroup.

5.2.3.3 Transition probabilities

Disease progression within the company's model is represented using transition probabilities between different health states. The model assumes the same probabilities for all HCV genotypes with the exception of the probability of transition from the non-cirrhotic state to the compensated cirrhosis state, which is different between genotype 1 and other genotypes.

Non-cirrhotic state to compensated cirrhosis

The company's model structure uses only non-cirrhotic and compensated cirrhosis states rather than using mild, moderate and cirrhotic stages. Transition probabilities for the non-cirrhotic state to the compensated cirrhosis state were estimated by the company using probabilities for transition between mild, moderate and cirrhotic stages of disease obtained from Thomson *et al*,[67] a study reporting outcomes of combination therapy in a cohort of HCV-infected individuals (n= 347) in the UK. The description of the methods used to estimate these transition probabilities is presented below. However, it should be noted that there is insufficient detail for the ERG to comment on the robustness of the approach. During the clarification stage, the ERG requested details of the calculations used to derive these transition probabilities; these were not however provided by the company.

The company ran a three-state Markov model assuming that 78% of patients started in the mild state and 22% of patients started the model in the moderate state. The model was run for 10, 15 and 20 years where patients moved from mild to moderate and then from moderate to the cirrhotic stage, using transition probabilities obtained from Thomson *et al.*[67] The company developed another Markov model which considered only the non-cirrhotic and cirrhotic states (two-state model) and used the Microsoft Excel Solver add-in to obtain the transition probability for the non-cirrhotic to cirrhotic transition such that the number of patients occupying the cirrhotic stage at the end of follow up was equal between the two- and three-state models.

Superseded – see erratum

The CS states that transition probabilities were obtained for follow-up periods of 10, 15 and 20 years and the two-state Markov model was then re-run using the different transition probabilities for these follow-up periods. The root mean square deviation for the difference between the numbers of patients in the cirrhotic state in the two- and three-state Markov model was then estimated. The CS[1] states that probabilities for the transition between non-cirrhotic and cirrhotic states selected for use in the model for each treatment initiation age were those which resulted in the lowest root mean square deviation.
The probabilities estimated for the non-cirrhotic state to the compensated cirrhosis state were different depending on the genotype and starting age at treatment (see Table 34). However, the starting age in the economic model base cases is either 40 or 45 (see CS[1] Table 56). Only the probability at age 40 years is used in the company's model.

Table 34: Transition probabilities from non-cirrhotic state to compensated cirrhosis

	Genotype 1/4	**Genotype 3**
Annual transition probability from non-cirrhotic state to compensated cirrhosis state	30 years: 0.006 40 years: 0.009 50 years: 0.016	30 years: 0.008 40 years: 0.013 50 years: 0.024

Transition probabilities used in the model

The remaining transition probabilities used in the company's model are assumed to be common across all patient populations and comparators. The values for the probabilities used in the model and their sources are presented in Table 35.

The annual probabilities of transiting from the non-cirrhotic SVR state and the cirrhotic SVR state to the non-cirrhotic state and the cirrhotic state, respectively either due to recurrence and re-infection, were assumed to be zero based on external expert opinion. Similarly, the probability of obtaining a liver transplant whilst in the HCC state was also based on external expert opinion.

The probabilities of transiting from compensated cirrhosis and compensated cirrhosis with SVR to decompensated cirrhosis were estimated from data in Cardoso *et al.*[68] The probabilities of transiting from compensated cirrhosis or decompensated cirrhosis to HCC were assumed to be the same (0.0631); this value was obtained from Cardoso *et al.*[68] The probability of transiting from compensated cirrhosis with SVR to HCC was estimated as 0.0128 from data also reported by Cardoso *et al.*[68] The probability of transiting from decompensated cirrhosis to liver transplant was taken from Siebert *et al*.[69] The probability of transiting to death from the decompensated cirrhosis and HCC states were obtained from Fattovich *et al*,[70] which the CS states were also used by Wright *et al*[71] and the

previous HTA assessments of Hartwell *et al*[55] and Shepherd *et al*.[58] The probability of death from liver transplant or post-liver transplant was drawn from Shepherd *et al*.[58]

Table 35: Annual transition probabilities

From state	To state	Transition probability	Source
Non-cirrhotic, SVR	Non-cirrhotic (recurrence)	For both health states: Base case: 0 Min: 0 Max: 0.01†	Expert opinion
	Non-cirrhotic (re-infection)		
Compensated cirrhosis	Decompensated cirrhosis	0.0438	Cardoso *et al*[68]
	HCC	0.0631	
Compensated cirrhosis with SVR	Compensated cirrhosis (recurrence)	For both health states: Base case: 0 Min: 0 Max: 0.01†	Expert opinion
	Compensated cirrhosis (re-infection)		
	Decompensated cirrhosis	0.0064	Cardoso *et al*[68]
	HCC	0.0128	
Decompensated cirrhosis	HCC	0.0631	Cardoso *et al*[68]
	Liver transplant	0.022	Siebert *et al*[69]
	Death	0.13	Fattovich *et al*[70]
HCC	Liver transplant	Base case: 0 Min: 0 Max: 0.01	Expert opinion
	Death	0.43	Fattovich *et al*[70]
Liver transplant	Death (year 1)	0.21	Shepherd *et al*[58]
Post-liver transplant	Death (year 2+)	0.057	

HCC, hepatocellular carcinoma; SVR - sustained virologic response
†sensitivity analysis only

Mortality

The risk of death for patients with decompensated cirrhosis, HCC, liver transplant, and post-liver transplantation states was modelled by applying age-specific general population mortality rates to each health state in the model, obtained from ONS.[80] Other-cause mortality estimates were not adjusted to remove deaths associated with the consequences of HCV (see clarification response,[2] question C9).

5.2.3.4 Adverse events

The CS states that the rates of Grade 3/4 AEs for LDV/SOF and comparators were obtained from relevant trials or SmPCs. AEs included within the model were nausea, vomiting, diarrhoea, pruritis, rash, anaemia, blood transfusion for anaemia, thrombocytopenia, neutropenia and depression. These are modelled as rates per patient and are used to estimate the AE costs (see CS[1] Section 7.5.7). It should be noted that there is no explicit link between the treatment specific utility decrements presented in Table 36 and the AE rates for different treatments.

Superseded – see erratum

5.2.3.5 Health related quality of life

The company's model includes health utilities associated with the each of the different model health states as well as HRQoL decrements associated with adverse impacts of treatment. The latter is applied only in states in which the patient in receiving antiviral treatment. The company performed a systematic search for HRQoL evidence (see CS[1] Appendix 12). A total of 77 studies examining different aspects of HRQL in hepatitis C patients were included in the company's final review. However, the CS does not include any narrative synthesis of the findings of the review.

The utilities chosen for the health states model were taken from two HTA reports on hepatitis C (Hartwell *et al*, 2011[55] and Shepherd *et al*, 2007[58]); these were predominantly based on data from the UK trial of mild HCV by reported Wright *et al*.[71] The CS does not include discussion regarding why this study was considered to be the most appropriate source for HRQoL estimates. Whilst the CS states that the utilities reported by Wright *et al*[71] are based on UK-representative Euroqol EQ-5D scores, no further detail is provided. The utility values and their sources for the health states are summarised in Table 36.

Patients achieving SVR are assumed to have an increase in utility of 0.04 based on data from Vera-Llonch *et al*, 2013[65] as the CS states that it is the most recent study and that the data are less uncertain than those presented by Wright *et al*, 2006[71] (which uses a value of 0.05). Vera-Llonch *et al*, 2013[65] performed a *post hoc* analysis of HRQoL in genotype 1 treatment-naïve chronic hepatitis C patients receiving TVR combination treatment and suggested that SVR at week 72 was associated with an improvement of 0.041 in the EQ-5D index (estimated from EQ-5D health states by assigning US-specific valuation weights to each of the levels in each dimension).

Table 36: Baseline health state utilities and sources

Health state	Utility value	Source
SVR (utility increment)	0.04	Vera-Llonch *et al*[65] (US EQ-5D tariff)
After treatment at non-cirrhotic stage	0.79	Calculation (baseline utility+SVR increment)
After treatment at cirrhotic stage	0.59	Calculation (baseline utility+SVR increment)
Baseline – non-cirrhotic	0.75	Wright *et al*[71] (UK mild HCV trial, UK EQ-5D tariff)
Baseline – compensated cirrhosis	0.55	
Decompensated cirrhosis	0.45	
HCC	0.45	
Liver transplant	0.45	
Post-liver transplant	0.67	

SVR – sustained virologic response; HCV – hepatitis C virus

Utilities for patients receiving treatment are estimated by applying treatment-related utility decrements to baseline utilities. The utility decrements differ according to the treatment received (see CS[1] Tables 73-76) and are assumed to apply to the entire duration of treatment. It should be noted that

the utility decrements are independent of the states (i.e. non-cirrhotic and compensated cirrhotic states). Health utilities do not change with increasing age within the model. The SMV+PEG-IFN2a+RBV decrement is valued in absolute terms; all other decrements are multiplicative.

For GT1/4 patients, the utility decrement for LDV/SOF was assumed to be zero based on the SF-36 data from ION studies (see CS[1] Section 7.4.3). The utility decrement for SOF+PEG-IFN2a+RBV was based on SF-6D values derived from mapping from SF-36 data of NEUTRINO.[32,33] For SMV+PEG-IFN2a+RBV, the utility decrement whilst on treatment was sourced from the Simeprevir NICE submission.[72] The utility decrements for TVR+PEG IFN2a+RBV and BOC+PEG-IFN2b+RBV were obtained from NICE technology appraisals of TVR[45] and BOC,[44] respectively. However, the CS does not provide any detail about the actual source of the data and the type of instrument used (e.g. EQ-5D). The CS states that utility decrement for PEG-IFN2a+RBV was obtained from Shepherd *et al.*[58] For SMV+SOF, the utility decrement whilst receiving treatment was assumed to be equal to that experienced by patients treated with LDV/SOF (zero).

For GT3 patients, utility decrements for LDV/SOF+RBV, SOF+PEG-IFN2a+RBV and SOF+RBV were based on SF-6D values derived from mapping from SF-36 data of the respective trials (see CS[1] Section 7.4.4). The utility decrement for PEG-IFN2a+RBV was assumed to be same as the utility decrement for PEG-IFN2a+RBV in GT1/4 patients (see Table 37).

Table 37: Treatment-specific HRQoL decrements

Regimen	**Treatment-naïve**	**Treatment-experienced**	**Source**
Genotype 1/4			
LDV/SOF	0.0%	0.0%	ION-1[17], ION-2[15] and ION-3[11]
SOF+PEG-IFN2a+RBV	-14.5%	-14.5%	NEUTRINO[32,33]
SMV+PEG-IFN2a+RBV	-0.081	-0.119	SMV NICE submission[72]
TVR+PEG-IFN2a+RBV	-14.3%	-14.6%	ADVANCE[65], taken from TVR SmPC[21]
BOC+PEG-IFN2b+RBV	-12.2%	-12.2%	Boceprevir NICE TA253[44]
PEG-IFN2a+RBV	-14.7%	-14.7%	Shepherd *et al.*[58]
SMV+SOF	0.0%	0.0%	Assumed equal to LDV/SOF
Genotype 3			
LDV/SOF+RBV	-4.98%	-4.98%	Calculated assuming a weighted average of disutility of FUSION, FISSION and POSITRON[74]
SOF+PEG-IFN2a+RBV	-14.5%	n/a	NEUTRINO[32,33] (SF-6D)
SOF+RBV	-4.98%	-4.98%	Calculated assuming a weighted average of disutility of FUSION, FISSION and POSITRON[74]
PEG-IFN2a+RBV	-14.7%	n/a	Shepherd *et al,*[58] assuming a split of 78:22% between mild and moderate from the ION trials

GT - genotype; HCV - hepatitis C virus; TN - treatment-naïve

5.2.3.6 Costs

The CS states that the costs used within the model reflect those relevant to an NHS and PSS perspective. Costs include those associated with antiviral treatment, the management of treatment-related AEs, treatment monitoring and health state costs. Unit costs of LDV/SOF were provided by the company (Gilead) as commercial-in-confidence information; the unit costs of comparator treatments were taken from the BNF August 2014.[75] AE costs include the costs of drugs and outpatient, hospital registrar and specialist resources used to treat AEs (see CS[1] Table 82). The unit costs of these were sourced from the BNF August 2014[75] and from NHS Reference Costs[76]whilst management strategies were taken from a previous telaprevir HTA report[45] and expert opinion. Monitoring costs, which include the initial evaluation/investigation costs and the monitoring costs on treatment, are presented in Tables 78-80 of the CS.[1] Costs for the different health states used in the model were based on results of the systematic review conducted to identify relevant resource data for the UK (see CS[1] Appendix 13). However, the CS does not provide any discussion about how choices were made with respect to the selection of identified studies for use in the model.

Drug acquisition costs

Unit costs for LDV/SOF were sourced from the company, whilst unit costs for comparator regimens were obtained from the BNF (August 2014).[75] These costs are summarised in Table 38. The cost per patient over the model time horizon was based on the number of weeks of treatment. It should be noted that the CS does not explicitly specify the treatment durations (i.e. the actual time receiving the treatment), estimated as a 'blended' treatment of the different LDV/SOF treatment regimens.

Table 38: Treatment unit costs and overall treatment costs

Drug	Cost per pack	Unit dose	Quantity per pack	Source
LDV/SOF	£12,993.33	400mg	28	Gilead[1]
SOF	£11,660.98	400mg	28	BNF, August 2014[75]
RBV	£246.65	400mg	56	
PEG-IFN2a	£124.40	180µg	1	
SMV	£1,866.50	150mg	7	
TVR	£1,866.50	375mg	42	
BOC	£2,800	200mg	336	

BNF - British National Formulary; OD - once daily;

Health state costs

The CS[1] states that the health state costs identified within the systematic review chosen for inclusion in the model were those used by the most recent HTAs except for incorporating updated liver transplant costs published in 2014. It should be noted that no references to these HTAs are provided by the company. The health state costs were derived from Wright *et al*[71] except for the costs for patients who reached SVR which were sourced from Grishchenko *et al.*[57] The CS states that the costs

for the non-cirrhotic health state were estimated using the costs of mild and moderate HCV states from Wright *et al*[71] assuming a 78:22 split between mild and moderate as reported in the ION trials, however no references are provided. The costs of liver transplant and post-liver transplant were based on data from Longworth *et al*.[78] All costs were updated to 2012/2013 prices using the Hospital and Community Health Services (HCHS) Pay and Prices Index. A summary of the health state costs included in the company's model are reproduced from CS in Table 39.

Table 39: Annual health state costs

Health state	Inflated-values cost year 2012-2013	Source
Non-cirrhotic, SVR†	£245	Grishchenko *et al*[57]
Compensated cirrhosis, SVR	£506	
Non-cirrhotic, NT†	£363	Wright *et al*[71]
Compensated cirrhosis, NT	£1,540	
Decompensated cirrhosis	£12,339	
HCC	£10,994	
Liver transplant	£83,505	Longworth *et al*[78]
Post-liver transplant follow-up phase (0-12 months)	£27,512	
Post-liver transplant follow-up phase (12-24 months)††	£4,111	

HCC - hepatocellular carcinoma; NT - no treatment; SVR - sustained virologic response.
†Weighted average of mild and moderate health state costs; 78% of patients in the sofosbuvir trials were calculated to be mild and 22% moderate. Non-cirrhotic health state cost calculated as 78%£187+22%*£988.*
††applied to all subsequent annual cycles

Monitoring costs

The costs of monitoring within the company's model include the initial evaluation/investigation costs and the monitoring costs on treatment. The costs of monitoring patients whilst receiving treatment with either LDV/SOF or comparator strategies include costs of outpatient appointments, inpatient day care, tests and investigations (virology, chemical pathology, haematology, immunology/chemistry, radiology, molecular pathology, other tests) and procedures (liver biopsy, Fibroscan, Fibrotest and endoscopy diagnosis). Unit costs of resource use for monitoring (see CS[1] Table 78) were sourced from NHS Reference Costs,[76] Shepherd *et al*,[58] Stevenson *et al*,[77] Wright *et al*[71] and expert opinion. The amount of resource use per patient for different evaluations, visits, checks and assessments during the course of treatment is presented in Appendix 15 of CS[1] however no detail was provided with respect to the sources used for the resource use estimates.

The total costs of the monitoring phases for non-cirrhotic and compensated cirrhotic patients according to the duration of treatment are presented in Table 40. The CS[1] (Table 80) also reports the total monitoring costs by indication. The CS assumes that there is no difference between the

monitoring requirements of IFN-containing and IFN-free regimens, stating that the costs of monitoring are conservative in favour of IFN-containing regimens.

Table 40: Monitoring costs

Item		**Non-cirrhotic**	**Cirrhotic**
Initial evaluation of a new patient with confirmed HCV		£630	£822
Further investigations for treatment group		£471	£471
Monitoring during active treatment	Treatment duration	**Non-cirrhotic**	**Cirrhotic**
LDV/SOF, LDV/SOF+RBV, SOF+PEG-IFN2a+RBV, SOF+RBV	4 weeks	£615	£615
	8 weeks (excl. final visit)	£736	£736
	8 weeks (incl. final visit)	£1,000	£1,002
	12 weeks of treatment	£1,122	£1,123
	24 weeks of treatment	£1,365	£1,367
SMV+PEG-IFN2a+RBV, TVR+PEG-IFN2a+RBV, BOC+PEG-IFN2b+RBV, SMV+SOF†	4 weeks	£722	£722
	8 weeks	£968	£968
	12 weeks	£1,381	£1,505
	24 weeks	£1,876	£2,374
SMV+PEG-IFN2a+RBV, TVR+PEG-IFN2a+RBV, BOC+PEG-IFN2b+RBV	28 weeks	£2,059	£2,557
	36 weeks	£2,323	£2,944
	48 weeks	£2,818	£3,962
PEG-IFN2a+RBV	4 weeks	£722	£722
	8 weeks	£968	£968
	12 weeks	£1,320	£1,444
	24 weeks	£1,755	£2,252
PEG-IFN2a+RBV	28 weeks	£1,877	£2,374
	36 weeks	£2,140	£2,761
	48 weeks	£2,575	£3,719

HCV – hepatitis C virus

Adverse event costs

The model includes the costs of drugs and outpatient, hospital registrar and specialist resource use associated with the treatment of AEs. AEs considered were nausea, vomiting, diarrhoea, pruritis, rash, anaemia, blood transfusion for anaemia, thrombocytopenia, neutropenia and depression.

The dosing and duration of drugs used to treat AEs were taken from a previous telaprevir HTA report[45] and the unit costs of the drugs were obtained from the BNF August 2014 (see CS[1] Tables 82 and 83). Unit costs relating to outpatient, hospital registrar and specialist resource use were sourced from NHS Reference Costs[76] and resource use was estimated using expert opinion (see CS[1] Tables 84-86). The model does not include the costs of any inpatient episodes as a result of AEs; this assumption was based on expert opinion.

5.2.3.7 Treatment duration

Treatment duration is an important parameter as the economic model uses the average treatment duration to estimate the drug acquisition costs and monitoring costs whilst on treatment. However, the treatment durations used in the model are not explicitly mentioned in the CS.[1]

Treatment duration differs by intervention and whether or not the patient has cirrhosis. The average treatment duration for LDV/SOF was estimated as the weighted average of the duration of the "blend" of treatments indicated for the population i.e. the proportion of patients in each treatment regimen was multiplied by the treatment duration for the corresponding regimen. The ERG notes that the proportions of patients in different regimens used by the company have no clinical justification.

For the comparators, treatment duration was calculated as the weighted average of the indicated treatment duration for each treatment multiplied by the proportion of patients achieving these durations, taking into account the average time to discontinuation of treatment. The treatment durations used in the model are used in the CS summarised in Table 41.

Table 41: Treatment duration (weeks)

Regimen	**Treatment-naïve**		**Treatment-experienced**	**Source**
	Non-cirrhotic	**Cirrhotic**	**Non-cirrhotic & cirrhotic**	
Genotype 1/4				
LDV/SOF	8.84	12.6	13.10	ION-1[17] and *post hoc* analysis of ION-3[11]
SOF+PEG-IFN2a+ RBV	11.84	11.84	11.84	NEUTRINO[32,33]
SMV+PEG-IFN2a+RBV	23.20	23.20	45.60	Pooled data from studies QUEST[35] and QUEST 2[36], taken from Simeprevir SPC 2014[34]
TVR+PEG-IFN2a+RBV	26.94	26.94	38.99	ADVANCE[19,21], ILLUMINATE[21] and Grishchenko *et al*, 2009[57]
BOC+PEG-IFN2b+RBV	34.17	42.98	42.52	SPRINT-2[20]
PEG-IFN2a+RBV	38.40	38.40	30.30	IDEAL[37]
SMV+SOF	12.00	12.00	12.00	COSMOS[34,38]
Genotype 3				
LDV/SOF+RBV		15.00	24.00	ELECTRON-2[24]
SOF+PEG-IFN2a+RBV		12.00	11.08	ELECTRON[32 41] and PROTON[32;31]
SOF+RBV		23.96	23.96	VALENCE [40;32]
PEG-IFN2a+RBV		21.00	39.16	FISSION[32,33]

5.2.4 Model validation undertaken by the company

The CS reports that three quality assessments of the model were made to assess its internal consistency (see CS[1] Section 7.8). The first was conducted by a senior modeller and a senior statistician with previous experience in HCV. The second check was made by a second modeller who was not familiar with the project. A third validation was undertaken by an independent modeller via a series of logical and consistency checks by testing a number of hypothetical scenarios and comparing the model results with the expected outcomes.

The CS also states that input from key opinion leaders was sought to validate the major assumptions employed within the LDV/SOF model (see CS[1] section 7.8). However, the submission states (see CS[1] Section 7.3.5) that it was the previous sofosbuvir model that was validated with two external clinical experts and that as the same assumptions have been consistently used in both the LDV/SOF and the sofosbuvir models, and that no further expert input was sourced for this submission.

5.2.5 Budget impact analysis

In their budget impact analysis, the company predicts a little over [redacted]) will be eligible for treatment each year. The clinical experts suggest that the current treatment rate in England is 3000-5000 per year. The clinical experts also believe that numbers of patients coming forward for treatment may be considerably greater than the company's estimate as patients will no longer be deterred by the side effect profile of PEG-IFN.

5.3 Cost-effectiveness results presented by the company

5.3.1 Central estimates of cost-effectiveness

Table 42 presents the central estimates of cost-effectiveness reported within the company's base case analysis.[1] These results have been reproduced by the ERG using the company's model and compared with the results reported within the CS (see CS[1] Tables 94-101, pages 205-213). It should be noted that the company's base case analysis is based on point estimates of parameters rather than the expectation of the mean. Table 43 summarises the cost-effectiveness acceptability curves (CEACs) reported by the company based on the probabilities of each intervention producing the greatest net benefit at willingness to pay thresholds of £20,000 per QALY gained and £30,000 per QALY gained. The probabilities presented in the table have been drawn from the text reported by the CS; where these are not reported, estimated probabilities have been derived by the ERG by reading points directly from the reported CEACs. These results are summarised below.

Superseded – see erratum

Table 42: Summary of central estimates of cost-effectiveness reported by the company

(i) Genotype 1 treatment-naïve					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF	15.66	£38,712.99	1.68	£13,404.95	**£7,985**
SMV+SOF	15.57	£65,630.27	-	-	dominated
SOF+PEG-IFN2a+RBV	15.40	£45,775.52	-	-	dominated
SMV+PEG-IFN2a+RBV	15.02	£38,730.64	-	-	dominated
TVR+PEG-IFN2a+RBV	14.85	£40,237.39	-	-	dominated
BOC+PEG-IFN2b+RBV	14.66	£41,298.70	-	-	dominated
PEG-IFN2a+RBV	13.98	£25,308.04	0.97	£6,351.67	£6,548
No treatment	13.01	£18,956.37	-	-	-
(ii) Genotype 4 treatment-naïve					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF	15.66	£46,898.06	1.68	£21,590.02	**£12,860**
SMV+SOF	15.57	£65,630.27	-	-	dominated
SOF+PEG-IFN2a+RBV	15.40	£45,775.52	-	-	dominated
SMV+PEG-IFN2a+RBV	15.02	£38,730.64	-	-	dominated
PEG-IFN2a+RBV	13.98	£25,308.04	0.97	£6,351.67	£6,548
No treatment	13.01	£18,956.37	-	-	-
(iii) Genotype 1/4 treatment-experienced					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF	14.72	£49,537.45	2.32	£31,394.60	**£13,527**
SMV+SOF	14.71	£64,720.05	-	-	dominated
SOF+PEG-IFN2a+RBV	14.21	£46,756.27	-	-	ext dom
SMV+PEG-IFN2a+RBV	14.13	£43,626.05	-	-	ext dom
TVR+PEG-IFN2a+RBV	13.90	£42,101.49	-	-	ext dom
BOC+PEG-IFN2b+RBV	13.69	£45,896.81	-	-	dominated
PEG-IFN2a+RBV	12.75	£24,960.10	-	-	ext dom
No treatment	12.40	£18,142.84	-	-	-
(iv) Genotype 3 treatment-naïve					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV	15.48	£57,909.34	1.47	£38,972.71	**£26,491**
PEG-IFN2a+RBV	14.01	£18,936.63	-	-	-
No treatment	12.24	£21,509.26	-	-	dominated
(v) Genotype 3 treatment-naïve with compensated cirrhosis					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV	10.23	£102,644.92	0.84	£39,226.39	**£46,491**
SOF+RBV	9.87	£95,947.03	-	-	ext dom
SOF+PEG-IFN2a+RBV	9.38	£63,418.53	-	-	-
(vi) Genotype 3 treatment-experienced, IFN-ineligible					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV	14.17	£89,521.70	2.46	£68,907.21	**£28,048**
No treatment	11.71	£20,614.48	-	-	-
(vii) Genotype 3 treatment-experienced IFN-ineligible with compensated cirrhosis					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV	8.76	£105,760.87	0.75	£4,652.14	**£6,210**
SOF+RBV	8.01	£101,108.73	-	-	-

Inc. – incremental; ICER – incremental cost-effectiveness ratio; ext dom – extended dominance; IFN – interferon

Superseded – see erratum

Table 43: Summary of cost-effectiveness acceptability curves presented by the company

Option	Probability optimal at willingness to pay threshold of £20,000 per QALY gained	Probability optimal at willingness to pay threshold of £30,000 per QALY gained
(i) Genotype 1 treatment-naïve		
LDV/SOF	**1.00**	**1.00**
SMV+SOF	0.00	0.00
SOF+PEG-IFN2a+RBV	0.00	0.00
SMV+PEG-IFN2a+RBV	0.00	0.00
TVR+PEG-IFN2a+RBV	0.00	0.00
BOC+PEG-IFN2b+RBV	0.00	0.00
PEG-IFN2a+RBV	0.00	0.00
No treatment	0.00	0.00
(ii) Genotype 4 treatment-naïve		
LDV/SOF	**0.88**	**1.00**
SMV+SOF	0.10	0.00
SOF+PEG-IFN2a+RBV	0.00	0.00
SMV+PEG-IFN2a+RBV	0.00	0.00
PEG-IFN2a+RBV	0.02	0.00
No treatment	0.00	0.00
(iii) Genotype 1/4 treatment-experienced		
LDV/SOF	**0.88**	**1.00**
SMV+SOF	0.00	0.00
SOF+PEG-IFN2a+RBV	0.00	0.00
SMV+PEG-IFN2a+RBV	0.10	0.00
TVR+PEG-IFN2a+RBV	0.01	0.00
BOC+PEG-IFN2b+RBV	0.00	0.00
PEG-IFN2a+RBV	0.01	0.00
No treatment	0.00	0.00
(iv) Genotype 3 treatment-naïve		
LDV/SOF	**0.03**	**0.68**
PEG-IFN2a+RBV	0.97	0.32
No treatment	0.00	0.00
(v) Genotype 3 treatment-naïve with compensated cirrhosis		
LDV/SOF+RBV	**0.02**	**0.08**
SOF+RBV	0.07	0.14
SOF+PEG-IFN2a+RBV	0.91	0.78
(vi) Genotype 3 treatment-experienced, IFN-ineligible		
LDV/SOF+RBV	**0.01**	**0.60**
No treatment	0.99	0.40
(vii) Genotype 3 treatment-experienced IFN-ineligible with compensated cirrhosis		
LDV/SOF+RBV	**0.78**	**0.83**
SOF+RBV	0.22	0.17

(i) Genotype 1 treatment-naïve subgroup

The model suggests that within the genotype 1 treatment-naïve subgroup, LDV/SOF is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All options excluding LDV/SOF, PEG-IFN2a+RBV and no treatment are ruled out due to simple dominance. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £6,548 per QALY

Superseded – see errata

gained. The ICER for LDV/SOF versus PEG-IFN2a+RBV is estimated to be £7,985 per QALY gained.

The probability that LDV/SOF produces the greatest net benefit is approximately 1.0 at willingness to pay thresholds of £20,000 per QALY gained and £30,000 per QALY gained.

(ii) Genotype 4 treatment-naïve subgroup

The model suggests that within the genotype 4 treatment-naïve subgroup, LDV/SOF is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All options excluding LDV/SOF, PEG-IFN2a+RBV and no treatment are ruled out due to simple dominance. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £6,548 per QALY gained. The ICER for LDV/SOF versus PEG-IFN2a+RBV is estimated to be £12,860 per QALY gained. It should be noted that the ERG was unable to replicate the exact ICER for LDV/SOF versus PEG-IFN2a+RBV reported in the CS (company's estimate = £12,715 per QALY gained).

Assuming a willingness to pay threshold of £20,000 per QALY gained, the probability that LDV/SOF produces the greatest net benefit is approximately 0.88. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that LDV/SOF produces the greatest net benefit is approximately 1.0.

(iii) Genotype 1/4 treatment-experienced subgroup

Within the genotype 1/4 treatment-experienced subgroup, the model suggests that LDV/SOF is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All options excluding LDV/SOF and no treatment are expected to be ruled out due to simple or extended dominance. The ICER for LDV/SOF is estimated to be £13,527 per QALY gained.

Assuming a willingness to pay threshold of £20,000 per QALY gained, the probability that LDV/SOF produces the greatest net benefit is approximately 0.88. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that LDV/SOF produces the greatest net benefit is approximately 1.0.

(iv) Genotype 3 treatment-naïve

The model suggests that within the genotype 3 treatment-naïve subgroup, LDV/SOF+RBV is expected to produce the greatest number of QALYs. No treatment is expected to produce fewer QALYs at a higher cost than PEG-IFN2a+RBV hence this option is ruled out due to simple dominance. The ICER for LDV/SOF+RBV versus PEG-IFN2a+RBV is estimated to be £26,491 per QALY gained.

Superseded – see erratum

Assuming a willingness to pay threshold of £20,000 per QALY gained, the probability that LDV/SOF produces the greatest net benefit is approximately 0.03. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that LDV/SOF produces the greatest net benefit is approximately 0.68.

(v) Genotype 3 treatment-naïve cirrhotic

Within the subgroup of patients with genotype 3 compensated cirrhosis who are treatment-naïve, the model suggests that LDV/SOF+RBV is expected to produce the greatest number of QALYs. SOF+PEG-IFN2a+RBV is expected to produce the fewest number of QALYs. SOF+RBV is ruled out of the analysis due to extended dominance. The ICER for LDV/SOF+RBV versus SOF+PEG-IFN2a+RBV is estimated to be £46,491 per QALY gained.

Assuming a willingness to pay threshold of £20,000 per QALY gained, the probability that LDV/SOF+RBV produces the greatest net benefit is approximately 0.02. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that LDV/SOF+RBV produces the greatest net benefit is approximately 0.08.

(vi) Genotype 3 treatment-experienced, IFN ineligible

The model suggests that within the genotype 3 treatment-experienced IFN-ineligible subgroup, LDV/SOF+RBV is expected to produce the greatest number of QALYs. No treatment is expected to be the least effective treatment. The ICER for LDV/SOF+RBV versus no treatment is estimated to be £28,048 per QALY gained.

Assuming a willingness to pay threshold of £20,000 per QALY gained, the probability that LDV/SOF+RBV produces the greatest net benefit is approximately 0.01. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that LDV/SOF+RBV produces the greatest net benefit is approximately 0.60.

(vii) Genotype 3 treatment-experienced IFN-ineligible with compensated cirrhosis

The model suggests that within the Genotype 3 treatment-experienced, IFN-ineligible, compensated cirrhosis subgroup, LDV/SOF+RBV is expected to produce the greatest number of QALYs. SOF+RBV is expected to be the least effective treatment. The ICER for LDV/SOF+RBV versus SOF+RBV is estimated to be £6,210 per QALY gained.

Assuming a willingness to pay threshold of £20,000 per QALY gained, the probability that LDV/SOF+RBV produces the greatest net benefit is approximately 0.78. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that LDV/SOF+RBV produces the greatest net benefit is approximately 0.83.

The company also presents a weighted overall ICER for LDV/SOF+/-RBV versus current treatments; this is estimated to be £12,107 per QALY gained. The ERG does not believe that this weighted ICER approach is appropriate for informing decision-making hence this analysis is not considered further within this report.

5.3.2 Deterministic sensitivity analysis results

Table 44 summarises the findings of the company's deterministic sensitivity analyses; these analyses are based on net monetary benefit assuming a willingness to pay threshold of £20,000 per QALY gained. All analyses are univariate.

Table 44: Summary findings of deterministic sensitivity analyses

Economic comparison (LDV/SOF+/-RBV versus comparator)	**Most influential variables**	**Deterministic sensitivity analysis findings**
*(i) Genotype 1 treatment-naïve**		
SOF+PEG-IFN2a+RBV	• treatment costs for non-cirrhotic patients • discount rates • SVR rate for SOF+PEGIFN2a+RBV in cirrhotic patients	NB positive in all scenarios considered
SMV+PEG-IFN2a+RBV	• discount rates • treatment costs for non-cirrhotic patients • SVR rate for SMV+PEG-IFN2a+RBV in cirrhotic patients	NB positive in all scenarios considered
PEG-IFN2a+RBV	• discount rates • TP from non-cirrhotic to compensated cirrhosis • LDV/SOF treatment costs for non-cirrhotic patients	NB positive in all scenarios considered
TVR+PEG-IFN2a+RBV	• discount rates • variation in treatment costs for non-cirrhotic patients • from non-cirrhotic to compensated cirrhosis	NB positive in all scenarios considered
BOC+PEG-IFN2b+RBV	• discount rates • treatment costs for non-cirrhotic patients • TP from non-cirrhotic to compensated cirrhosis	NB positive in all scenarios considered
No treatment	• discount rates • TP from non-cirrhotic to compensated cirrhosis • utility increment with achieving a SVR	NB positive in all scenarios considered
*(ii) Genotype 4 treatment-naïve**		
SOF+PEG-IFN2a+RBV	• treatment costs for non-cirrhotic patients • discount rates • SVR rate for SOF+PEGIFN2a+RBV in cirrhotic patients	NB negative (a) when the treatment cost (drug acquisition, AE and monitoring costs) of LDV/SOF in non-cirrhotic patients was increased by 25%, and (b) when the treatment cost of SOF+PEG-

Economic comparison (LDV/SOF+/-RBV versus comparator)	Most influential variables	Deterministic sensitivity analysis findings
		IFN2a+RBV in non-cirrhotic patients decreased by 25%
SMV+PEG-IFN2a+RBV	• discount rates • treatment costs for non-cirrhotic patients • SVR rate for SMV+PEG-IFN2a+RBV in cirrhotic patients	NB negative (a) when discount rate is increased to 6%, (b) when the treatment cost of LDV/SOF in non-cirrhotic patients was increased by 25%, and (c) when treatment costs of SMV+PEG-IFN2a+RBV in non-cirrhotic patients decreased by 25%
PEG-IFN2a+RBV	• discount rates • TP from non-cirrhotic to compensated cirrhosis • LDV/SOF treatment costs for non-cirrhotic patients	NB negative when discount rate increased to 6%.
No treatment	• discount rates • TP from non-cirrhotic to compensated cirrhosis • LDV/SOF treatment costs for • non-cirrhotic patients	NB positive in all scenarios considered
(iii) Genotype 1/4 treatment-experienced		
SOF+PEG-IFN2a+RBV	• treatment costs for non-cirrhotic patients • discount rates • SVR rate for SOF+PEGIFN2a+RBV in non-cirrhotic patients	NB negative (a) when treatment cost of LDV/SOF in non-cirrhotic patients was increased by 25% and (b) treatment cost of SOF+PEG-IFN2a+RBV in non-cirrhotic patients was decreased by 25%
SMV+PEG-IFN2a+RBV	• treatment costs for non-cirrhotic patients • discount rates • SVR rate for SMV+PEG-FN2a+RBV in cirrhotic patients	NB negative (a) when the treatment cost of LDV/SOF in non-cirrhotic patients increased by 25% and (b) when the treatment cost of SMV+PEG-IFN2a+RBV in non-cirrhotic patients decreased by 25%
PEG-IFN2a+RBV	• discount rates • TP from non-cirrhotic to compensated cirrhosis • LDV/SOF treatment costs for non-cirrhotic patients	NB negative when discount rate = 6%
TVR+PEG-IFN2a+RB	• discount rates • treatment costs for non-cirrhotic patients • TP from non-cirrhotic to compensated cirrhosis	NB positive in all scenarios considered
BOC+PEG-IFN2b+RBV	• discount rates • treatment costs for non-cirrhotic patients	NB positive in all scenarios considered
No treatment	• discount rates • TP from non-cirrhotic to compensated	NB negative when discount rate = 6%

Economic comparison (LDV/SOF+/-RBV versus comparator)	Most influential variables	Deterministic sensitivity analysis findings
	cirrhosis • LDV/SOF treatment costs for non-cirrhotic patients	
(iv) Genotype 3 treatment-naïve		
PEG-IFN2a+RBV	• discount rates • LDV/SOF+RBV treatment costs for non-cirrhotic patients • TP from non-cirrhotic to compensated cirrhosis	NB negative (a) when discount rate = 6% and (b) when the treatment cost of LDV/SOF+RBV in non-cirrhotic patients was increased by 25%
No treatment	• discount rates • TP from non-cirrhotic to compensated cirrhosis • LDV/SOF+RBV treatment costs for non-cirrhotic patients	NB negative when discount rate = 6%
(v) Genotype 3 treatment-naïve with compensated cirrhosis		
SOF+PEG-IFN2a+RBV	• discount rates • SVR rate for SOF+PEGIFN2a+RBV in cirrhotic patients • LDV/SOF+RBV treatment costs for cirrhotic patients	Base case NB negative. NB of £7,373 recorded when the SVR rate for SOF+PEG-IFN2a+RBV was reduced to the lower bound of the estimated 95% CI.
SOF+RBV	• SVR rate for SMV+PEGIFN2a+RBV in cirrhotic patients • treatment costs for cirrhotic patients	Base case NB close to zero hence all minimum net benefits fell below £0.
(vi) Genotype 3 treatment-experienced, IFN ineligible		
No treatment	• discount rates • TP from non-cirrhotic to compensated cirrhosis • LDV/SOF+RBV treatment costs for non-cirrhotic patients	Base case NB negative hence all minimum net benefits fell below £0. NB positive when discount rate of 0% applied.
(vii) Genotype 3 treatment experienced IFN ineligible with compensated cirrhosis		
SOF+RBV	• treatment costs for cirrhotic patients • SVR rate for SOF+RBV in cirrhotic patients	NB negative (a) when treatment cost of LDV/SOF+RBV in cirrhotic patients was increased by 25%, (b) when treatment cost of SOF+RBV in cirrhotic patients was decreased by 25%, (c) SVR rate for LDV/SOF+RBV was reduced to the lower bound of 58%, and (d) when the SVR rate for SOF+RBV was increased to the upper bound of 74%

NB calculated assuming λ=£20,000 per QALY gained;
** Analysis of LDV/SOF versus SMV+SOF not reported within the CS*[1]

5.3.3 Scenario analysis

The CS[1] also presents three additional scenario analyses.

Scenario 1: Treating all GT1/4 treatment experienced cirrhotic patients with LDV/SOF+RBV for 12 weeks instead of LDV/SOF for 12 or 24 weeks

A scenario analysis was conducted modelling LDV/SOF+RBV for 12 weeks for all treatment-experienced cirrhotic patients with genotype 1/4 disease rather than LDV/SOF for 12 or 24 weeks. In GT1 and GT4 treatment-experienced patients without cirrhosis the LDV/SOF regimen remains unchanged. This analysis produced an ICER for LDV/SOF+RBV versus no treatment of £12,299 per QALY gained.[1]

Scenario 2: Use of GT4 specific clinical data instead of GT1 data

The company presented a separate scenario analysis in which GT4-specific data were used to inform the analysis of treatment options in this subgroup of patients. It should be noted that the actual data used to inform this analysis and the changes from the base case analysis are unclear.

Within the GT4 treatment-naïve group, the efficiency frontier consists of no treatment, PEG-IFN+RBV, SMV+PEG-IFN+RBV and LDV/SOF. LDV/SOF is expected to be the most effective treatment. SMV+SOF is dominated, whilst SOF+PEG-IFN2a+RBV is extendedly dominated. The ICER for SMV+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £4,137 per QALY gained. The ICER for LDV/SOF versus SMV+PEG=IFN2a+RBV is estimated to be £13,213 per QALY gained.

Within the GT4 treatment-experienced group, LDV/SOF is expected to be the most effective treatment. The ICER for LDV/SOF versus no treatment is expected to be £12,313 per QALY gained. All other treatment options are expected to be ruled out due to simple or extended dominance.

Scenario 3: Variation in treatment duration

A third scenario analysis was undertaken in which 15% of patients were assumed to receive 24 weeks LDV/SOF with the remaining 85% patients receiving 12 weeks LDV/SOF.

In the GT1 treatment-naïve subgroup, LDV/SOF is expected to be the most effective treatment. All options except for no treatment, PEG-IFN2a+RBV and LDV/SOF are expected to be ruled out of the analysis due to simple or extended dominance. The ICER for PEG-IFN2a+RBV versus no treatment is expected to be £6,548 per QALY gained. The ICER for LDV/SOF versus PEG-IFN2a+RBV is expected to be £8,453 per QALY gained.

Superseded – see erratum

In the GT4 treatment-naïve subgroup, LDV/SOF is expected to be the most effective treatment. SOF+PEG-IFN2a+RBV and SOF+SMV are expected to be ruled out due to simple or extended dominance. The ICER for LDV/SOF versus SMV+ PEG-IFN2a+RBV is expected to be £13,580 per QALY gained.

In the GT1/4 treatment-experienced subgroup, LDV/SOF is expected to be the most effective treatment. All other treatment options except for no treatment are expected to be ruled out of the analysis due to simple or extended dominance. The ICER for LDV/SOF versus no treatment is estimated to be £14,146 per QALY gained.

5.4 Critical appraisal of the company's model

This section presents a critical appraisal of the company's health economic analysis and the model upon which this analysis is based.

5.4.1 Methods for reviewing the company's economic evaluation and health economic model

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic evaluation and health economic model. These included:

- The use of published economic evaluation and health economic modelling checklists[52,81] to critically appraise the company's model and analysis.
- The use of expert clinical input to judge the clinical credibility of the company's economic evaluation and assumptions underlying the model.
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the ERG team.
- A complete re-build of the deterministic version of the company's model within the genotype 1 subgroup to assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any errors in the implementation of the model.
- A comparison of model structures, evidence sources and parameter inputs used within the company's model against those reported within model-based assessments undertaken to inform previous technology appraisals of antiviral treatments for HCV.
- A comparison of the company's estimates of cost and health outcomes for individual options against those reported within model-based assessments undertaken to inform previous technology appraisals of antiviral treatments for HCV.

5.4.2 Summary of main issues identified through critical appraisal of the company's model

The company's economic analyses are subject to a number of issues, as summarised in Box 1. These issues are discussed in more detail in the subsequent sections.

Box 1: Main issues identified through critical appraisal of the company's model

1. Deviations from the NICE Reference Case[63] and final NICE scope[5]
2. Presentation of base case results using point estimates of parameters rather than the expectation of the mean
3. Omission of relevant health effects on individuals with HCV - possibility of re-infection
4. Omission of health effects between individuals – onward transmission
5. Invalid assumptions regarding disease progression and mortality
6. Use of 'blended' comparisons for LDV/SOF
7. Uncertain and unreliable endpoints for genotype 3 patients
8. Concerns regarding the identification, selection and synthesis of evidence of SVR rates for LDV/SOF and comparators
9. Issues surrounding estimated transition probabilities
10. Questionable assumptions regarding health-related quality of life
11. Issues concerning model implementation

(1) Deviations from the NICE Reference Case[63] and final NICE scope[5]

Table 46 demonstrates the extent to which the company's economic analysis adheres to the NICE Reference Case[63]

Table 45: Adherence of the company's economic analysis to the NICE Reference Case[63]

Element of HTA	Reference Case	ERG comments
Defining the decision problem	The scope developed by NICE	The scope of the company's analysis is partly in line with that developed by NICE (see points below).
Comparator(s)	As listed in the scope developed by NICE	LDV/SOF+RBV treatment duration in GT3 patients is not in line with its marketing authorisation No treatment not included as comparator within the company's analysis of the subgroups of patients with GT3 disease with compensated cirrhosis who are treatment-naïve or patients with GT3 disease with compensated cirrhosis who are treatment-experienced and IFN-ineligible BOC and TVR included in analyses of treatment-experienced GT1/4 patients. Within the treatment-experienced GT3 subgroup, IFN-based treatments are not included as comparators.

Superseded – see erratum

Element of HTA	Reference Case	ERG comments
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health benefits for patients are measured and valued over a lifetime horizon.
Perspective on costs	NHS and PSS	An NHS and PSS perspective was adopted.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The economic analysis takes the form of a cost-utility analysis whereby the primary health economic model is the incremental cost per QALY gained.
Time horizon	Long enough to reflect all important differences between the technologies being compared	A lifetime horizon is used in all of the company's analyses.
Synthesis of evidence on health effects	Based on systematic review	Based on studies selected by the company
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Health outcomes are valued using QALYs. HRQoL was derived from a range of sources and measures (EQ-5D and SF-36).
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	HRQoL estimates valued using public preferences. At least one value (utility increment for achieving SVR) is valued using the US EQ-5D tariff.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs relate to NHS and PSS resource use and are valued using relevant prices.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health outcomes are discounted at 3.5%.

Superseded — see erratum

The company's health economic analysis has been implemented partly in line with NICE's Reference Case[63] (see Table 45). Three deviations from the final NICE scope[5] should be noted. Firstly, the LDV/SOF+RBV treatment duration for genotype 3 patients is not in line with recommendations from the EMA. The company's model assumes that 75% of non-cirrhotic genotype 3 patients receiving LDV/SOF+RBV will receive 12 weeks of treatment . The SmPC recommends 24-weeks of treatment for all patients with genotype 3 disease. Secondly, TVR and BOC are evaluated in the GT1/4

treatment-experienced subgroup however neither product has marketing authorisation in patients with GT4 disease. Whilst this issue is mentioned in the table footnotes on page 206 of the CS,[1] both regimens are still included in the company's analysis without further discussion. Thirdly, no treatment is not considered as an option within the company's analysis of the subgroups of patients with GT3 disease with compensated cirrhosis who are treatment-naïve or patients with GT3 disease with compensated cirrhosis who are treatment-experienced and IFN-ineligible; the reason for this deviation from the NICE scope[5] is unclear from the CS.

In addition, the methods for synthesising evidence on health effects were not based on a full systematic review; this point is further discussed later in this section.

The ERG notes also that the CS presents results only for three genotypes (GT1, GT3 and GT4 patients), no analyses undertaken by the company relate to GT2, GT5 or GT6. The ERG notes that this is consistent with the wording of the EPAR, which only relates to GT1, GT3 and GT4 patients. The CS assumes that GT4 are similar to GT1 patients.

Finally, the ERG notes that most, but not all, of the HRQoL values used in the model are based on the preferences valued by the UK general public. However, the utility increment associated with achieving SVR has been valued using the US EQ-5D tariff.

(2) Presentation of base case results using point estimates of parameters rather than the expectation of the mean

The company's base case analysis uses point estimates of parameters rather than the expectation of the mean. There may be some discrepancy between deterministic and probabilistic results as a consequence of non-linearity between model inputs and outputs. Table 46 summarises the results of the model based on additional probabilistic analysis requested by the ERG and undertaken by the company. It should be noted that the ICERs may be subject to rounding errors as the table has been produced by the ERG using probabilistic estimates of expected QALYs and expected costs provided within the company's clarification response[2] (question C21).

Superseded – see erratum

Table 46: Summary of probabilistic central estimates of cost-effectiveness reported by the company (based on costs and QALYs provided within the company's clarification response[2])

(i) Genotype 1 treatment-naïve					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF	15.69	£38,656	1.71	£13,471	**£7,878**
SMV+SOF	15.60	£65,466	-	-	dominated
SOF+PEG-IFN2a+RBV	15.43	£45,610	-	-	dominated
SMV+PEG-IFN2a+RBV	15.04	£38,586	-	-	ext dom
TVR+PEG-IFN2a+RBV	14.87	£39,890	-	-	dominated
BOC+PEG-IFN2b+RBV	14.68	£41,248	-	-	dominated
PEG-IFN2a+RBV	13.98	£25,185	0.97	£6,345	£6,541
No treatment	13.01	£18,840	-	-	-
(ii) Genotype 4 treatment-naïve					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF	15.69	£46,774	1.69	£21,484	**£12,712**
SMV+SOF	15.57	£65,741	-	-	dominated
SOF+PEG-IFN2a+RBV	15.41	£45,849	-	-	ext dom
SMV+PEG-IFN2a+RBV	15.03	£38,731	-	-	ext dom
PEG-IFN2a+RBV	14.00	£25,290	0.99	£6,159	£6,221
No treatment	13.01	£19,131	-	-	-
(iii) Genotype 1/4 treatment-experienced					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF	14.73	£49,560	2.31	£31,216	**£13,513**
SMV+SOF	14.64	£65,249	-	-	dominated
SOF+PEG-IFN2a+RBV	14.22	£46,875	-	-	ext dom
SMV+PEG-IFN2a+RBV	14.14	£43,646	-	-	ext dom
TVR+PEG-IFN2a+RBV	13.93	£41,922	-	-	ext dom
BOC+PEG-IFN2b+RBV	13.71	£45,872	-	-	dominated
PEG-IFN2a+RBV	12.77	£24,992	-	-	ext dom
No treatment	12.42	£18,344	-	-	-
(iv) Genotype 3 treatment-naïve					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF	15.46	£58,091	1.43	£39,243	**£27,443**
PEG-IFN2a+RBV	14.03	£18,848	-	-	-
No treatment	12.27	£21,485	-	-	dominated
(v) Genotype 3 treatment-naïve with compensated cirrhosis					
Option	QALYs	Cost	Inc QALYs	Inc Cost	ICER
LDV/SOF+RBV	10.25	£102,811	0.74	£39,601	**£53,515**
SOF+RBV	9.97	£95,890	-	-	ext dom
SOF+PEG-IFN2a+RBV	9.51	£63,210	-	-	-
(vi) Genotype 3 treatment-experienced, IFN-ineligible					
Option	QALYs	Cost	Inc QALYs	Inc Cost	ICER
LDV/SOF+RBV	14.17	£89,506	2.43	£69,042	**£28,412**
no treatment	11.74	£20,464	-	-	-
(vii) Genotype 3 treatment-experienced IFN-ineligible with compensated cirrhosis					
Option	QALYs	Cost	Inc QALYs	Inc Cost	ICER
LDV/SOF+RBV	8.8	£105,599	0.73	£4,711	**£6,453**
SOF+RBV	8.07	£100,888	-	-	-

Inc. – incremental; ICER – incremental cost-effectiveness ratio; ext dom – extended dominance; IFN – interferon

As can be seen by comparing the results presented within Tables 42 and 46, the probabilistic results are very similar to those based on point estimates of parameters.

(3) Omission of health effects on individuals with HCV - possibility of re-infection

The company's model is intended to reflect the expected costs and consequences of treatment following infection with HCV. The model does not include the possibility of re-infection with HCV for non-cirrhotic patients; rather, patients who achieve SVR12 following antiviral treatment are assumed to be cured indefinitely, without re-treatment. The probability of re-infection is likely to be dependent on the characteristics of the population under consideration. The consequence of excluding re-infection from the model is that the benefits of more effective treatments are likely to be overestimated, whilst their costs will be underestimated as patients may subsequently require re-treatment with further therapy. Models used to inform previous NICE appraisals have not included such health effects.[12,44,45,73,82-84] The impact of this exclusion on the cost-effectiveness of LDV/SOF is unclear; as such, the ERG has concerns regarding the reliability of cost-effectiveness results produced using the company's model. The adequate resolution of this issue would however require the development of a different model structure.

(4) Omission of health effects between individuals – onward transmission

The company's model does not include the possibility of onward transmission between patients; rather the model approach takes the form of a static Markov model without interactions between individuals. However, as recognised within the CS,[1] achieving a sustained virologic response may reduce rates of transmission between individuals. The CS[1] (page 40) also notes that previous dynamic modelling work suggests that HCV treatment can have an important role in preventing transmission in populations who are at a higher risk of re-infection and that this approach can be a cost-effective policy.[85-87] The consequence of excluding this factor from the model is that the health benefits resulting from the use of more effective treatments with higher SVR rates may be underestimated. The extent of the bias caused by this exclusion is not clear. As with the previous point, the examination of the potential impact of this exclusion would require the development of a different model.

(5) Invalid assumptions regarding disease progression and mortality

The company's model assumes that there are no deaths, either because of HCV or as a consequence of other causes, until at least 9 months after starting treatment. Similarly, patients cannot not experience disease progression whilst on treatment, or during the period 12 to 24 weeks after the end of treatment (see CS[1] Section 7.3.8). Thus, patients are assumed not to develop any of the adverse consequences of

hepatitis C (for example, cirrhosis, cancer or death) until several months after stopping treatment (see Section 5.2.3). These assumptions lack credibility.

(6) Use of 'blended' comparisons for LDV/SOF

Within the analysis of patients with genotype 1 and genotype 4 disease, the costs and effectiveness of LDV/SOF are based on a mix of estimates observed within multiple trial arms using a "blended comparison" approach. This blended comparison involves taking a weighted average of SVR rates and treatment durations for different options given over different treatment durations based on the expected proportion of patients who would receive each. Consequently, the mean treatment duration, SVR rates, costs, treatment-specific HRQoL decrement avoided and ultimately, the cost-effectiveness of LDV/SOF, are dependent upon the proportion of patients in each part of the "blend."

The SVR rate for LDV/SOF within the genotype 1 treatment-naïve non-cirrhotic population was estimated by the company using a weighted average of the efficacy of 8-week and 12-week treatment regimens of LDV/SOF, assuming the use of 8 weeks LDV/SOF for genotype 1 treatment-naïve patients without cirrhosis who have a baseline viral load of <6 million IU/mL, and 12 weeks LDV/SOF in those with a baseline viral load ≥6 million IU/mL. The company uses a 79% to 21% split of 8-week and 12-week treatment regimens of LDV/SOF, stating that patient-level data from the HCV Research UK Database[64] showed that 79% of genotype 1 non-cirrhotic patients (n=408) in the UK had a pre-treatment viral load <6million IU/mL. However, it should be noted that the cut-off of 6 million IU/ml is based on a *post hoc* analysis of the ION-3 study (see CS,[1] Section 6.5.5, page 89) and clinical advice to ERG suggested that there is no clinical significance for this 6 million IU/ml cut-off. Similarly, the efficacy for the genotype 1 treatment-naïve cirrhotic population for LDV/SOF was estimated by the company using a weighted average of the efficacy of 12-week and 24-week treatment regimens of LDV/SOF, assuming a 95% to 5% split, respectively. The efficacy for LDV/SOF within the genotype 1 and genotype 4 treatment-experienced non-cirrhotic populations was estimated by the company using a weighted average of the efficacy of 12-week and 24-week treatment regimens of LDV/SOF, assuming a 95% to 5% split, respectively. The efficacy for LDV/SOF within the genotype 1 and genotype 4 treatment-experienced cirrhotic populations was estimated by the company using a weighted average of the efficacy of 12-week and 24-week treatment regimens of LDV/SOF, assuming a 75% to 25% split, respectively.

It is noteworthy that the baseline viral load ≥6 million IU/mL criterion for guiding treatment duration in patients with genotype 1 disease does not form part of the license recommendations from the EMA.[6] Rather, the EPAR[6] suggests other criteria for guiding treatment duration i.e. pre-treatment

status, perceived risk of clinical disease progression and the availability of subsequent retreatment options. The treatment durations recommended for LDV/SOF are summarised in Table 47.

Table 47: Treatment durations recommended within the EPAR[6]

Patient population*	Treatment	Duration
Patients with genotype 1 or genotype 4 CHC		
Patients without cirrhosis	LDV/SOF	12 weeks. - 8 weeks may be considered in previously untreated genotype 1-infected patients - 24 weeks should be considered for previously treated patients with uncertain subsequent retreatment options
Patients with compensated cirrhosis	LDV/SOF	24 weeks. - 12 weeks may be considered for patients deemed at low risk for clinical disease progression and who have subsequent retreatment options
Patients with decompensated cirrhosis or who are pre-/post-liver transplant	LDV/SOF+RBV	24 weeks
Patients with genotype 3 CHC		
Patients with cirrhosis and/or prior treatment failure	LDV/SOF+RBV	24 weeks

CHC – chronic hepatitis C

In response to a request for clarification from the ERG[2] regarding the use of blended comparisons for LDV/SOF (question C8), the company stated:

"Using a blended comparison allows for the consideration of a representative CHC population receiving treatment, of which some sub-populations may not receive the same duration of LDV/SOF treatment. Modelling the treatment durations separately and subsequently calculating weighted average results for the overall population returns the same results as running a combined analysis (wherein the efficacy and costs inputs are weighted to reflect the proportion receiving each treatment regimen). Running combined analyses reflects the cost-effectiveness of treating a CHC cohort according to the population characteristics, aligns with how the cost-effectiveness of CHC medicines has been assessed in previous appraisals (by subgroup not duration), and reduces the number of results presented in the submission."[2]

The ERG is not satisfied with the company's response. The ERG also notes that consistency with previous appraisals and limiting the number of results presented within the submission do not represent a sufficient justification for the use of blended comparisons.

The ERG would urge caution in interpreting the results of any cost-effectiveness analysis in which the intervention is comprised of a blend of multiple options (in this case, the same drug given over different durations). The ERG would suggest that the key issues concern (a) whether or not there exists a clinical justification for prescribing treatment for one particular duration over another within specific subgroups of patients, and (b) what is known about differences in clinical benefits and costs between different treatment durations within those subgroups. These two issues are related. In the instance whereby there is a clinical justification for using LDV/SOF over a particular duration, for example, due to known characteristics of the patient subgroup and their propensity to benefit from treatment given over a particular duration, this would imply the need for a subgroup analysis of the subset of treatment options that are considered to be relevant only to that subgroup. Such an analysis should be undertaken for all relevant subgroups using a fully incremental approach in which each option is compared against its next best non-dominated alternative. Conversely, if there is no clinical justification for giving LDV/SOF over one particular treatment duration or another, the different durations represent discrete competing treatment options within a common population; each of these options is associated with its individual profile of expected health benefit and cost. Again, such an analysis should be undertaken using a fully incremental approach in which each option is compared against its next best non-dominated alternative. The blending of options within either instance may result in the joint recommendation of some options which are known to be efficient and other options which are known to be inefficient. Of course, there may also exist the situation whereby evidence is not available to quantify the costs and clinical benefits of individual treatment durations and a blended approach is all that is possible given the available evidence; this is not however the case for LDV/SOF. As can be seen from the wording of the recommended treatment durations within the EPAR[6] presented in Table 45, there are clear clinical reasons why particular treatment durations should be considered for particular subgroups of patients. The ERG thus considers that the company's blended comparison approach (genotypes 1/4) and the results reported within the CS are of questionable value for informing decision-making.

(7) Uncertain and unreliable endpoints for genotype 3 patients

For genotype 3 treatment-naïve patients, the SVR rate for LDV/SOF+RBV is based on data from 26 patients in ELECTRON-2[24], an ongoing, open-label Phase II study in New Zealand. Furthermore, for genotype 3 treatment-experienced IFN-ineligible patients, the SVR rate for LDV/SOF+RBV is based on preliminary SVR4 data from ELECTRON-2.[24] Clinical advice received by the ERG suggests that SVR4 is not a robust end point, as a proportion of the patients who achieved SVR4 do not

subsequently achieve SVR12. The use of SVR4 data would therefore likely overestimate the effectiveness of LDV/SOF+RBV. Given the small numbers of patients and use of SVR4 data, the results for GT3 treatment-experienced patients should be treated with caution.

(8) Concerns regarding the identification, selection and synthesis of evidence of SVR rates for LDV/SOF and comparators

The CS states that a systematic review of the literature was conducted to identify studies for comparators as part of the submission to NICE for the SOF appraisal. However, 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. Most of the SVR estimates are from single arms of RCTs, observational studies and subgroup analyses. Some SVR estimates are sourced from pooled studies and no justification was provided for the studies selected. This selective approach to study choice deviates from the NICE Reference Case which suggests that estimates of effectiveness should be based on a systematic review of evidence.

The ERG requested clarification on the methods used by the company to select studies to inform the estimates of effectiveness within the model (see clarification response,[2] question B6). However, the ERG could not identify a clear set of selection methods from the company's responses as the criteria used to select studies appear to vary between different populations.

Furthermore, it should be noted that the estimates for each treatment are not evaluated within a formal network meta-analysis. As noted in Section 4.4, the use of naïve estimates of response rates between studies breaks randomisation and fails to fully reflect uncertainty surrounding these parameters. The ERG considers that a coherent synthesis of the evidence associated with the comparator treatments would have been preferable. It should be noted that, in their response to clarification queries (see clarification response,[2] question B9), the company acknowledged that meta-analysis is feasible for estimating the SVR in GT1 patients for PEG-IFN+RBV, BOC, TVR and SMV.

Given the lack of consistent selection criteria and the absence of meta-analysis, the ERG suggests that appropriate caution should be applied in the interpretation of the results of the company's analyses, as the cost-effectiveness results may be biased by the selection of individual studies and confounded by the impact of other factors such as differences in study design, patient characteristics and trial protocols on the estimated effectiveness of each comparator.

(9) Issues surrounding estimated transition probabilities

The ERG has several concerns regarding the reliability of the transition probabilities used within the company's model.

(i) Questionable methods for estimating transition probabilities from the non-cirrhotic state to the compensated cirrhosis state

The company's model estimates transition probabilities using the Microsoft Excel Solver add-in (see CS[1] Section 7.3.2). However, as noted in Section 5.2.3.3, the CS does not provide sufficient detail regarding the calculations and the assumptions used to inform this fitting process. During clarification, the ERG requested details of the calculations used to derive these transition probabilities (see clarification response,[2] question C12). This additional information was not provided by the company. Thus, the ERG has concerns regarding the reliability of the methods for deriving transition probabilities from the non-cirrhotic state to the compensated cirrhosis state. Notwithstanding the lack of detail, the ERG believes that there may be problems associated with this approach as the transition probability depends on the starting distribution of patients in the mild and moderate states, and the time period used. It is further unclear how the fitting process captures the uncertainty surrounding these parameters. It should also be noted that these transition probabilities are marginally different to those used in the model used to inform the recent appraisal of sofosbuvir[12] (see Table 48).

Table 48: Transition probabilities from non-cirrhotic state to compensated cirrhosis

	Transition probabilities used in the CS[1]	**Transition probabilities used in the Sofosbuvir appraisal**
Annual transition probabilities from non-cirrhotic state to compensated cirrhosis	*Genotype 1/4* 30 years: 0.006 40 years: 0.009 50 years: 0.016 *Genotype 3* 30 years: 0.008 40 years: 0.013 50 years: 0.024	*Mono-infected* *HCV genotype 1:* 30 years: 0.006 40 years: 0.010 50 years: 0.016 *HCV genotype non-1:* 30 years: 0.009 40 years: 0.014 50 ears: 0.025

CS – company's submission

(ii) Sources of transition probabilities used in the model

The other transition probabilities used in the model are assumed to be common across all patient populations and comparators. Table 49 compares these probabilities to those used in the appraisal of sofosbuvir. It should be noted that during the sofosbuvir appraisal, the ERG stated that the model parameters were reasonable and consistent with previous economic evaluations (Shepherd *et al*, 2007[58] and Hartwell *et al*, 2011[55]).

Table 49: Annual transition probabilities

From	To	Probability used in CS[1]	Source used in CS[1]	Probability used in Sofosbuvir appraisal[12]	Source used in Sofosbuvir appraisal[12]
Non-cirrhotic, SVR	Non-cirrhotic (recurrence)	For both health states: Base case: 0 Min: 0 Max: 0.01	Expert opinion	For both health states: Base case: 0 Min: 0 Max: 0.01	External expert opinion
	Non-cirrhotic (re-infection)				
Compensated cirrhosis	Decompensated cirrhosis	0.0438	Cardoso *et al*[68]	0.039	Fattovich *et al*[70]
	HCC	0.0631		0.014	
Compensated cirrhosis with SVR	Compensated cirrhosis (recurrence)	For both health states: Base case: 0 Min: 0 Max: 0.01	Expert opinion	For both health states: Base case: 0 Min: 0 Max: 0.01	External expert opinion
	Compensated cirrhosis (re-infection)				
	Decompensated cirrhosis	0.0064	Cardoso *et al*[68]	N/A	N/A
	HCC	0.0128		N/A	N/A
Decompensated cirrhosis	HCC	0.0631	Cardoso *et al*[68]	0.014	Fattovich *et al*[70]
	Liver transplant	0.022	Siebert *et al*[69]	0.02	
	Death	0.13	Fattovich *et al*[70]	0.13	
HCC	Liver transplant	Base case: 0 Min: 0 Max: 0.01	Expert opinion	Base case: 0 Min: 0 Max: 0.01	External expert opinion
	Death	0.43	Fattovich *et al*[70]	0.43	Fattovich *et al*[70]
Liver transplant	Death, Year1	0.21	Shepherd *et al*[58]	0.21	Shepherd *et al*[58]
Post-liver transplant	Death, Year2+	0.057		0.057	

GT - genotype; HCC - hepatocellular carcinoma; SVR,- sustained virologic response

The transition probabilities from compensated cirrhosis or decompensated cirrhosis to HCC used in the company's model are considerably higher (probability = 0.0631) than those used in the sofosbuvir model (probability = 0.014). Also, some transitions (e.g. compensated cirrhosis with SVR to decompensated cirrhosis or HCC) that were not considered in the previous sofosbuvir model are included in the company's LDV/SOF model. The probability of transiting from compensated cirrhosis and compensated cirrhosis with SVR to decompensated cirrhosis was estimated from data reported by Cardoso *et al.*[68] The ERG notes that the clinical outcome defined as liver-related complications in Cardoso *et al*[68] is used as a proxy for decompensated cirrhosis in the CS i.e. the transition probabilities to decompensated cirrhosis used in the company's model were the transition

probabilities to liver-related complications in Cardoso *et al*.[68] The potential impact of using different transition probabilities on the cost-effectiveness results is not clear from the CS.

The remaining transition probabilities used in the company's model are the same (or very similar to, in the case of compensated cirrhosis with SVR to decompensated cirrhosis) as those used in the model used to inform the appraisal of sofosbuvir.

The annual probabilities of moving from non-cirrhotic SVR and cirrhotic SVR to recurrence and re-infection and the probability of obtaining a liver transplant whilst in the HCC state were based on external expert opinion (see Table 49). Clinical expert advice received by the ERG suggests that the value used for these probabilities (0.01 in scenario analysis) is reasonable.

(10) Questionable assumptions regarding health-related quality of life

The ERG also has several concerns regarding the methods and assumptions used by the company to estimate HRQoL.

(i) The utility increment for SVR is based on the US EQ-5D tariff

The company's model uses an increment of 0.04 to reflect the utility gain associated with achieving SVR; this value was sourced from an analysis reported by Vera-Llonch *et al*, 2013.[65] This value however has been derived using the US EQ-5D tariff. This estimate may not reflect the preferences of the general public in England and Wales and represents a deviation from the NICE Reference Case.[63]

(ii) Treatment disutility used in model not related to incidence of adverse events

Utilities during treatment are estimated by applying treatment-related utility decrements to the baseline utility for the on-treatment health states (i.e. non-cirrhotic and compensated cirrhotic states). These utility decrements differ depending on treatment (see CS[1] Tables 73-76) as shown in Table 36. It should be noted that these disutilities are not explicitly linked to the frequency of AEs modelled for the treatments i.e. whilst AE costs are dependent on the frequency of these events, treatment-specific disutilities are independent of frequency.

(iii) Treatment disutility applied to entire time in state rather than time receiving drug

The company's model uses the treatment disutility for the entire time in the state rather than the time receiving the drug. For example, if the treatment duration was 8.1 months, the treatment disutility is applied for the whole 9 months (i.e. the duration of time spent in the state). The ERG believes that the impact of this bias is likely to be minor.

(11) Issues concerning model implementation

In order to assess the integrity of the model implementation, the ERG scrutinised the company's model and also re-built a deterministic version of the model within the genotype 1/4 subgroups. These processes did not identify any serious programming errors in the implementation of the company's model, however a number of issues were identified, as discussed below.

(i) Unwieldy model structure and unnecessary complexity in model implementation

The company's model is very large. The executable model itself includes 59 worksheets, which for a 12-state time-invariant Markov model seems somewhat excessive and unnecessary. Upon receipt of the model, 27 of the model's worksheets were hidden, whilst within the unhidden worksheets, important cells (e.g. live transition probabilities, costs and QALYs) were also hidden. The company's model also features a number of default settings which are applied automatically (for example, when moving between worksheets); the consequence is that the user may define a scenario for analysis but in attempting to view the model results for that scenario, the model then automatically undermines those settings and presents results for an alternative default scenario. This makes it difficult to verify whether the results correspond to the inputs specified. During the clarification stage (see clarification response[2] question C2), the ERG asked the company to provide a version of the economic model in which these automated settings are disabled. This request was not fulfilled by the company.

In addition, within the genotype 1/4 treatment-naïve subgroups, the company's model can only evaluate options for the cirrhotic and non-cirrhotic populations separately; the results for each group are then weighted according to the probability of a patient being cirrhotic. This is unusual since the model structure explicitly includes health states for patients with cirrhotic and non-cirrhotic disease, and since within the genotype 3 subgroups and the genotype 1/4 treatment-experienced subgroup, the model does evaluate both cirrhotic/non-cirrhotic groups simultaneously. The ERG sought clarification from the company regarding why the economic model does not allow for a mix of cirrhotic and non-cirrhotic to flow through the states simultaneously (see clarification response[2] question C20). The company stated that at the beginning of model development different treatment durations were expected for the treatment-naive non-cirrhotic and cirrhotic cohorts and therefore it was decided to separate them into two different indications.

Furthermore, despite the size and complexity of the company's model, it only has the functionality to compare two options simultaneously. Producing a fully incremental analysis using the probabilistic version of the model is laborious.

Whilst these issues do not make the model incorrect, they do serve to limit the transparency of the model and ultimately hindered the ability of the ERG to interrogate the model programming and data inputs.

(ii) Use of a different model structure according to treatment duration

As discussed in Section 5.2.3, the company's model assumes that patients cannot progress or die until 12-24 weeks following the completion of treatment. The implication of this assumption is that the point at which the risks of disease progression and death apply are dependent on the duration of treatment. For example, in the evaluation of genotype 1 non-cirrhotic patients, LDV/SOF is given for a mean duration of 8.84 weeks (corresponding to three 1-month cycles). Risks of disease progression and death then apply from cycle 10 onwards (0.83 years after model entry). Before this point, the risk of disease progression or death is assumed to be zero. However, for PEG-IFN+RBV (48 weeks), treatment is assumed to be given for an average duration of 38.4 weeks (corresponding to ten 1-month cycles). Risks of disease progression and death then apply from cycle 17 onwards (1.42 years after model entry). Before this point, the risk of disease progression or death is assumed to be zero. This means (a) patients receive a "grace" period in which they are assumed to be invulnerable to disease progression and death, and (b) the duration of that grace period depends on how long the patient receives treatment for. The consequence is that the model structure itself is different for every comparator. The ERG does not consider this to be appropriate. However, the ERG also recognises that the magnitude of the bias is likely to be small and will favour treatment options given over a longer mean duration. Further to this point, the ERG believes that there is little point in modelling time on treatment if the model does not also consider the risks of progression and death during that period. The assumed grace period in which patients cannot progress or die is clearly not a credible representation of reality.

(iii) Unnecessary adjustment of the model cycle length

Over the course of the time horizon, the company's model uses three different cycle lengths (monthly for 18 cycles, 3-monthly for 2 cycles and annual for all subsequent cycles). As all patients have discontinued antiviral treatment before 18 months, and subsequent prognosis is state- rather than treatment-dependent, the adjustment of the cycle length is unnecessary and adds little to the model. The ERG also notes that the half-cycle correction is applied from year 3 onwards; prior to this point, the costs and QALYs for each cycle are not corrected. This approach is unusual. If a single cycle duration had been adopted, a more consistent approach to half-cycle correction could have been applied. Again, these issues do not have a substantive impact upon the model results but simply increase the size of the model unnecessarily.

(iv) Issues concerning the characterisation of uncertainty within the company's probabilistic analysis

The characterisation of uncertainty within the company's model is problematic. Most notably, the central estimates of cost-effectiveness presented within the base case analysis are based on point estimates of parameters rather than the expectation of the mean (refer to Table 46 for probabilistic ICERs derived from results produced by the company during clarification). In addition, where implemented, the reliability of the probabilistic analysis itself is limited due to (a) key uncertain parameters (e.g. SVR rates) being pre-sampled outside of the model and (b) the use of inappropriate distributions for some uncertain parameters.

The company's health economic model holds sampled SVR rates as fixed between different probabilistic analyses i.e. pre-sampled values of SVR rates are used within the model rather than sampling from a distribution. The ERG was unable to identify the parametric distributions used to derive the samples of SVR rates in the model and thus, cannot comment on the appropriateness of the sampled SVR rates. However, the ERG notes that LDV/SOF appears to be more effective (i.e. has a higher SVR rate) than the comparators in each of the probabilistic sensitivity analysis (PSA) runs (except for GT1 TE patients where SMV+SOF has better SVR rates than LDV/SOF in some of the PSA runs). Given that SVR is the key parameter in the model, this may be inappropriate. Further to this point, the SVR rates for LDV/SOF+RBV in genotype 3 patients in particular are based on a Phase II study with a very small sample size hence the SVR rates derived from these studies are very uncertain. It is not clear how this uncertainty is captured within the company's analysis. In addition, where uncertainty has been recognised, some of the distributions are inappropriate as they include zero as a parameter. For example, gamma distributions are used to reflect uncertainty around parameters for the HRQoL decrement on treatment (in the "PSA inputs" worksheet). However, these gamma distributions use a parameter value of zero. The ERG notes that gamma distribution is represented by two parameters that must take values greater than zero and thus the distributions used by the company may not be appropriate as these probability distributions are not defined when one of the parameters is exactly zero (and can also be poorly defined when parameters are close to zero).

It is also noteworthy that the company's model does not use a common set of random numbers. Since only two options can be compared simultaneously, this will introduce Monte Carlo sampling bias when comparing all options incrementally. The ERG advises further caution in the interpretation of the probabilistic cost-effectiveness results presented in Table 46.

(v) Issues surrounding LDV/SOF treatment duration and costs

The company's model is inconsistent in how treatment duration is calculated for LDV/SOF and for some of the comparators. Whilst the model calculates mean duration for some options by taking into

account dropouts, the same approach has not been adopted for other options (in these instances, treatment duration reflects the maximum planned treatment course). This is a pessimistic assumption for LDV/SOF.

5.5 Exploratory and sensitivity analyses undertaken by the ERG

This section presents the additional analyses undertaken by the ERG, including the development of an ERG-preferred base case.

5.5.1 Description of additional analyses undertaken by the ERG

Based on the issues identified within the critical appraisal of the company's model (see Section 5.4), the following sets of additional analyses were undertaken:

1. Development of an ERG-preferred base case using "unblended" EMA-recommended treatment durations for LDV/SOF
2. Examination of alternative EMA-recommended treatment durations for LDV/SOF
3. Use of alternative transition probabilities based on the sofosbuvir STA model[12]
4. Use of UK valued utility increment derived by Wright *et al*[71]
5. Use of shorter time horizons (5-years and 10-years) to dampen assumptions regarding no re-infection
6. Threshold analysis for SVR rates of the comparators

It should be noted that additional analyses 3-6 use the ERG-preferred base case analysis as a starting point. All analyses were undertaken using point estimates of parameters due to the excessive computation time and complexity associated with running the probabilistic version of the model. The methods used to implement these additional analyses are detailed in Appendix 2.

5.5.1.1 ERG analysis 1: Development of an ERG-preferred base case using "unblended" EMA-recommended treatment durations for LDV/SOF

In the company's analysis of subgroups of patients with genotype 1 and genotype 4, the costs and outcomes of LDV/SOF are based on a mix of estimates SVR rates and treatment durations observed within multiple trial arms using a "blended comparison" approach. As discussed in Section 5.4, the ERG considers that the "blended" analyses presented by the company are of limited value for decision-making as these may result in the simultaneous recommendation of some options which are known to be efficient and other options which are known to be inefficient. The ERG performed "unblended" analyses using the company's model based on EMA[6] recommended treatment durations for LDV/SOF+/-RBV (see Table 47); this analysis forms the ERG's preferred base case. The SVR rates used for LDV/SOF correspond to the treatment duration and the population based on genotype

Superseded — see erratum

and cirrhotic status. The SVR rates of 24 week LDV/SOF for GT3 patients are assumed to be the same as 12 week LDV/SOF. The costs of LDV/SOF treatment were estimated using the unit costs of £12,993.33 per 28-day course presented by the company (see CS[1] Table 77). The treatment costs, SVR rates used and the sources used for their derivation within this analysis are presented in Table 50. No other model parameters were amended. It should be noted that since the EMA recommendations are specific to cirrhotic status, results are presented separately for cirrhotic and non-cirrhotic subgroups.

Table 50: SVR rates, treatment duration and costs used within the ERG base case analysis (EMA-recommended unblended LDV/SOF treatment)

Subgroup	Duration	Treatment costs	SVR	Source
GT1/4 treatment-naïve				
non-cirrhotic	12 weeks	£38,979.99	97.7%	ION-1[13] and ION-3[14]
cirrhotic	24 weeks	£77,959.98	97.0%	ION-1[13]
GT1/4 treatment-experienced				
non-cirrhotic	12 weeks	£38,979.99	93.6%	ION-2[15]
cirrhotic	24 weeks	£77,959.98	97.4%	SIRIUS[28]
GT3 treatment-naïve				
non-cirrhotic	24 weeks	£77,959.98	100%	ELECTRON-2[24]
cirrhotic	24 weeks	£77,959.98	100%	ELECTRON-2[24]
GT3 treatment-experienced				
non-cirrhotic	24 weeks	£77,959.98	89.3%	ELECTRON-2[24]
cirrhotic	24 weeks	£77,959.98	77.3%	ELECTRON-2[24]

GT – genotype; SVR – sustained virologic response

5.5.1.2 ERG analysis 2: Examination of alternative EMA-recommended treatment durations for LDV/SOF

As shown in Table 47, the SmPC for LDV/SOF mentions the use of alternative treatment durations for specific subgroups of GT1/4 patients based on prior treatment, risk of disease progression and the availability of subsequent treatment options. Within this exploratory analysis, the ERG undertook an "unblended" analysis of these alternative treatment durations. As with the ERG-preferred base case, the SVR rates used for LDV/SOF correspond to the treatment duration and the population (genotype and cirrhotic status). The costs of LDV/SOF treatment were estimated using the unit costs presented by the company.[1] The treatment costs, SVR rates used and the sources used for their derivation within this analysis are presented in Table 51. No other model parameters were amended. It should be noted that since the EMA recommendations are specific to cirrhotic status, results are presented separately for cirrhotic and non-cirrhotic subgroups.

Table 51: ERG scenario analysis using unblended LDV/SOF treatment

Subgroup	Duration	Treatment costs	SVR	Source
GT1/4 treatment-naïve				
non-cirrhotic	8 weeks	£25,986.66	94.0%	ION-3[14]
cirrhotic	12 weeks	£38,979.99	94.1%	ION-1[13]
GT1/4 treatment-experienced				
non-cirrhotic	24 weeks	£77,959.98	99.1%	ION-2[15]

GT – genotype; SVR – sustained virologic response

5.5.1.3 ERG analysis 3: Use of alternative transition probabilities based on the sofosbuvir STA model

The transition probabilities from compensated cirrhosis or decompensated cirrhosis to HCC used in the company's model are considerably higher (probability = 0.0631) than those used in the model used to inform the sofosbuvir appraisal (probability = 0.014). An exploratory analysis was undertaken whereby transition probabilities used with the ERG base case analysis were replaced with those taken from the previous sofosbuvir model.[12]

5.5.1.4 ERG analysis 4: Use of UK valued utility increment derived by Wright et al[71]

The HRQoL gain associated with achieving SVR (0.04) in the company's model was derived using the US EQ-5D tariff (Vera-Llonch *et al*, 2013[65]). This value may not reflect the preferences of the general public in England and Wales. An exploratory analysis was undertaken using the estimate of 0.05 based on a UK analysis of the UK HCV mild trial reported by Wright *et al.*[71]

5.5.1.5 ERG analysis 5: Use of shorter time horizons (5-years and 10-years) to dampen assumptions regarding no re-infection

A key structural assumption within the company's model is that non-cirrhotic patients who achieve SVR12 following antiviral treatment are cured indefinitely; the possibility of re-infection is not captured within the analysis. A small risk of progression to decompensated cirrhosis is included for cirrhotic patients. Retreatment with antiviral therapies is not captured further either non-cirrhotic or cirrhotic patients. The consequence of this exclusion is that the benefits of more effective treatments are likely to be overestimated, whilst their costs will be underestimated as patients may subsequently require re-treatment with further therapy if re-infected with HCV. The full resolution of this issue would require the development of a different model structure; however, an exploratory analysis was undertaken by the ERG using shorter time horizons of 5-years and 10-years. This assumes that the patients gain QALYs from achieving SVR only until the end of the time horizon; this approach therefore "dampens" the benefits associated with achieving SVR. The ERG acknowledges however that this analysis is limited in that the upfront costs of antiviral treatment are captured, yet the benefits of avoiding decompensated cirrhosis, HCC and death due to HCV are truncated for all patients irrespective of whether they would become re-infected or not. The ERG also notes that in reality the

probability of re-infection is likely to be time-dependent; this is not reflected as the analysis assumes that achieving SVR provides a fixed period of cure. Given these limitations associated with implementing this exploratory analysis, the results should be interpreted with some caution.

5.5.1.6 ERG analysis 6: Threshold analysis for SVR rates of comparators

As noted in Section 5.4.2, the ERG has several concerns regarding the identification, selection and synthesis of evidence of SVR rates for comparators within the company's model. In particular, the company's analyses may be biased due to the lack of consistent selection criteria for comparator studies and the absence of a formal evidence synthesis to estimate SVR rates for comparators. In order to estimate the extent of this potential bias, the ERG undertook threshold analyses to identify the magnitude of change in SVR rate for the comparator (the next best intervention to LDV/SOF on the efficiency frontier) required in order for LDV/SOF to achieve an ICER of £30,000 per QALY gained against that comparator. The ERG acknowledges that are limitations to this approach as there may be multiple interventions on the efficiency frontier within each subgroup and the frontier itself may change when different SVR rates for comparator are assumed. Again, this exploratory analysis should be interpreted with some degree of caution.

5.5.2 Results of additional analyses undertaken by the ERG

5.5.2.1 Results of additional analysis 1 - central estimates of cost-effectiveness (ERG-preferred base case)

Table 52 presents the central estimates of cost-effectiveness for the ERG-preferred base case using the company's model. These results are summarised below.

Table 52: Central estimates of cost-effectiveness (ERG-preferred base case)

(i) Genotype 1 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	17.20	£42,160.45	0.39	£8,843.83	**£22,676**
SMV+SOF	17.09	£61,415.79	-	-	dominated
SOF+PEG-IFN2a+RBV	17.04	£41,081.62	-	-	ext dom
SMV+PEG-IFN2a+RBV	16.81	£33,316.62	0.85	£14,111.22	£16,601
TVR+PEG-IFN2a+RBV	16.69	£34,631.46	-	-	dominated
BOC+PEG-IFN2b+RBV	16.41	£35,002.22	-	-	dominated
PEG-IFN2a+RBV	15.96	£19,205.40	0.89	£6175.99	£6,939
No treatment	15.07	£13,029.41	-	-	-
(ii) Genotype 1 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	10.08	£101,051.95	0.2	£19,567.23	**£97,836**
SMV+SOF	9.88	£81,484.72	0.63	£18,051.21	£28,653
SOF+PEG-IFN2a+RBV	9.25	£63,433.51	2.71	£15,167.91	£5,597
SMV+PEG-IFN2a+RBV	8.28	£59,097.68	-	-	ext dom
BOC+PEG-IFN2b+RBV	8.09	£64,985.45	-	-	dominated
TVR+PEG-IFN2a+RBV	7.95	£61,326.36	-	-	ext dom
PEG-IFN2a+RBV	6.54	£48,265.60	1.29	£7,012.58	£5,436
No treatment	5.25	£41,253.02	-	-	-
(iii) Genotype 4 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	17.20	£42,160.45	0.39	£8,843.83	**£22,676**
SMV+SOF	17.09	£61,415.79	-	-	dominated
SOF+PEG-IFN2a+RBV	17.04	£41,081.62	-	-	ext dom
SMV+PEG-IFN2a+RBV	16.81	£33,316.62	0.85	£14,111.22	£16,601
PEG-IFN2a+RBV	15.96	£19,205.40	0.89	£6,175.99	£6,939
No treatment	15.07	£13,029.41	-	-	-
(iv) Genotype 4 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	10.08	£101,051.95	0.2	£19,567.23	**£97,836**
SMV+SOF	9.88	£81,484.72	0.63	£18,051.21	£28,653
SOF+PEG-IFN2a+RBV	9.25	£63,433.51	2.71	£15,167.91	£5,597
SMV+PEG-IFN2a+RBV	8.28	£59,097.68	-	-	ext dom
PEG-IFN2a+RBV	6.54	£48,265.60	1.29	£7,012.58	£5,436
No treatment	5.25	£41,253.02	-	-	-
(v) Genotype 1/4 treatment-experienced non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	16.11	£41,978.77	1.80	£29,819.05	**£16,566**
SMV+SOF	16.09	£60,723.61	-	-	dominated
SOF+PEG-IFN2a+RBV	15.71	£42,386.90	-	-	dominated
SMV+PEG-IFN2a+RBV	15.67	£38,729.70	-	-	ext dom
TVR+PEG-IFN2a+RBV	15.62	£36,459.92	-	-	ext dom
BOC+PEG-IFN2b+RBV	15.48	£39,911.38	-	-	dominated
PEG-IFN2a+RBV	14.61	£18,984.11	-	-	ext dom
No treatment	14.31	£12,159.72	-	-	-
(vi) Genotype 1/4 treatment-experienced cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	9.70	£99,222.17	0.21	£19,467.86	**£92,704**
SMV+SOF	9.49	£79,754.31	0.90	£16,560.88	£18,401
SOF+PEG-IFN2a+RBV	8.59	£63,193.43	3.4	£22,542.63	£6,630

SMV+PEG-IFN2a+RBV	8.31	£62,045.65	-	-	ext dom
TVR+PEG-IFN2a+RBV	7.46	£63,324.53	-	-	dominated
BOC+PEG-IFN2b+RBV	6.95	£68,413.45	-	-	dominated
PEG-IFN2a+RBV	5.74	£47,441.22	-	-	ext dom
No treatment	5.19	£40,650.80	-	-	-
(vii) Genotype 3 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	17.24	£83,330.76	0.81	£71,970.90	**£88,853**
PEG-IFN2a+RBV	16.43	£11,359.86	-	-	-
No treatment	14.57	£14,928.01	-	-	dominated
(viii) Genotype 3 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	10.23	£102,644.92	0.85	£39,226.39	**£46,149**
SOF+RBV	9.87	£95,947.03	-	-	ext dom
SOF+PEG-IFN2a+RBV	9.38	£63,418.53	4.13	£22,165.51	£2,363
No treatment	5.25	£41,253.02	-	-	-
(ix) Genotype 3 treatment-experienced IFN-ineligible non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	15.97	£84,108.64	0.06	£7,899.24	**£131,654**
SOF+RBV	15.91	£76,209.40	2.03	£62,273.69	£30,677
No treatment	13.88	£13,935.71	-	-	-
(x) Genotype 3 treatment-experienced IFN-ineligible cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	8.76	£105,760.87	3.57	£65,110.07	**£18,238**
SOF+RBV	8.01	£101,108.73	-	-	ext dom
No treatment	5.19	£40,650.80	-	-	-

Inc. – incremental; ICER – incremental cost-effectiveness ratio; ext dom – extended dominance; IFN – interferon

(i) Genotype 1 treatment-naïve non-cirrhotic subgroup

The model suggests that within the genotype 1 treatment-naïve non-cirrhotic subgroup, LDV/SOF (12 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All options excluding LDV/SOF (12-weeks), SMV+PEG-IFN2a+RBV, PEG-IFN2a+RBV and no treatment are ruled out due to simple dominance or extended dominance. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £6,939 per QALY gained. The ICER for SMV+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £16,601 per QALY gained. The ICER for LDV/SOF versus SMV+PEG-IFN2a+RBV is estimated to be £22,676 per QALY gained.

(ii) Genotype 1 treatment-naïve cirrhotic subgroup

Within the genotype 1 treatment-naïve cirrhotic subgroup, LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. BOC+PEG-IFN2b+RBV is expected to be ruled out due to simple dominance, whilst SMV+PEG-IFN2a+RBV and TVR+PEG-IFN2a+RBV are expected to be ruled out due to extended dominance. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £5,436 per QALY gained. The ICER for SOF+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £5,597 per QALY

gained. The ICER for SMV+SOF versus SOF+PEG-IFN2a+RBV is estimated to be £28,653 per QALY gained. The ICER for LDV/SOF (24 weeks) versus SMV+SOF is estimated to be £97,836 per QALY gained.

(iii) Genotype 4 treatment-naïve non-cirrhotic subgroup

The model suggests that within the genotype 4 treatment-naïve non-cirrhotic subgroup, LDV/SOF (12 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest number of QALYs. SMV+SOF and SOF+PEG-IFN2a+RBV are expected to be ruled out due to simple dominance and extended dominance, respectively. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £6,939 per QALY gained. The ICER for SMV+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £16,601 per QALY gained. The ICER for LDV/SOF (12 weeks) versus SMV+PEG-IFN2a+RBV is estimated to be £22,676 per QALY gained.

(iv) Genotype 4 treatment-naïve cirrhotic subgroup

The model suggests that within the genotype 4 treatment-naïve cirrhotic subgroup, LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. SMV+PEG-IFN2a+RBV is expected to be ruled out due to extended dominance. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £5,436 per QALY gained. The ICER for SOF+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £5,597 per QALY gained. The ICER for SMV+SOF versus SOF+PEG-IFN2a+RBV is estimated to be £28,653 per QALY gained. The ICER for LDV/SOF (24 weeks) versus SMV+SOF is estimated to be £97,836 per QALY gained.

(v) Genotype 1/4 treatment-experienced non-cirrhotic subgroup

Within the genotype 1/4 treatment-experienced non-cirrhotic subgroup, the model suggests that LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All options excluding LDV/SOF (24 weeks) and no treatment are expected to be ruled out due to simple or extended dominance. The ICER for LDV/SOF is estimated to be £16,566 per QALY gained.

TVR and BOC are not licensed for use in patients with genotype 4 disease. However, since both options are ruled out of the analysis due to simple or extended dominance, the ICER in the GT4 treatment-experienced subgroup is unaffected.

(vi) Genotype 1/4 treatment-experienced cirrhotic subgroup

Within the genotype 1/4 treatment-experienced cirrhotic subgroup, the model suggests that LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to

produce the fewest QALYs. All options excluding LDV/SOF (24 weeks), SMV+SOF, SOF+PEG-IFN2a+RBV and no treatment are expected to be ruled out due to simple or extended dominance. The ICER for SOF+PEG-IFN2a+RBV versus no treatment is estimated to be £6,630 per QALY gained. The ICER for SMV+SOF versus SOF+PEG-IFN2a+RBV is estimated to be £18,401 per QALY gained. The ICER for LDV/SOF (24 weeks) versus SMV+SOF is estimated to be £92,704 per QALY gained.

It should be noted that TVR and BOC are not licensed for use in patients with genotype 4 disease. However, since both options are ruled out of the analysis due to simple dominance, the ICER in the GT4 treatment-experienced subgroup is unaffected.

(vii) Genotype 3 treatment-naïve non-cirrhotic subgroup

The model suggests that within the genotype 3 treatment-naïve non-cirrhotic subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs albeit at a higher cost than PEG-IFN2a+RBV hence this option is ruled out due to simple dominance. The ICER for LDV/SOF+RBV (24 weeks) versus PEG-IFN2a+RBV is estimated to be £88,853 per QALY gained.

(viii) Genotype 3 treatment-naïve cirrhotic subgroup

The model suggests that within the genotype 3 treatment-naïve cirrhotic subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce fewest QALYs. SOF+RBV is ruled out of the analysis due to extended dominance. The ICER for SOF+PEG-IFN2a+RBV versus no treatment is estimated to be £2,363 per QALY gained. The ICER for LDV/SOF+RBV (24 weeks) versus SOF+PEG-IFN2a+RBV is estimated to be £46,149 per QALY gained.

(ix) Genotype 3 treatment-experienced IFN-ineligible non-cirrhotic

The model suggests that within the genotype 3 treatment-experienced non-cirrhotic subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to be the least effective treatment. The ICER for SOF+RBV versus no treatment is estimated to be £30,677 per QALY gained. The ICER for LDV/SOF+RBV (24 weeks) versus SOF+RBV is estimated to be £131,654 per QALY gained.

(x) Genotype 3 treatment-experienced IFN-ineligible cirrhotic

The model suggests that within the Genotype 3 treatment-experienced, IFN-ineligible, compensated cirrhosis subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of

QALYs. No treatment is expected to produce fewest QALYs. SOF+RBV is ruled out due to extended dominance. The ICER for LDV/SOF+RBV (24 weeks) versus no treatment is estimated to be £18,238 per QALY gained.

5.5.2.2 Results of additional analysis 2 - examination of alternative EMA-recommended treatment durations for LDV/SOF

Table 53 presents the central estimates of cost-effectiveness results of the additional ERG analysis which includes "unblended" analyses based on treatment durations for LDV/SOF as suggested by EMA (see Section 5.5.1.2).

Table 53: Central estimates of cost-effectiveness (additional analysis 2, alternative EMA-recommended LDV/SOF treatment durations)

(i) Genotype 1 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 8 weeks	17.12	£29,522.69	1.16	£10,317.29	**£8,894**
SMV+SOF	17.09	£61,415.79	-	-	dominated
SOF+PEG-IFN2a+RBV	17.04	£41,081.62	-	-	dominated
SMV+PEG-IFN2a+RBV	16.81	£33,316.62	-	-	dominated
TVR+PEG-IFN2a+RBV	16.69	£34,631.46	-	-	dominated
BOC+PEG-IFN2b+RBV	16.41	£35,002.22	-	-	dominated
PEG-IFN2a+RBV	15.96	£19,205.40	0.89	£6,175.99	£6,939
No treatment	15.07	£13,029.41	-	-	-
(ii) Genotype 1 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	9.94	£62,440.44	4.69	£21,187.42	**£4,518**
SMV+SOF	9.88	£81,484.72	-	-	dominated
SOF+PEG-IFN2a+RBV	9.25	£63,433.51	-	-	dominated
SMV+PEG-IFN2a+RBV	8.28	£59,097.68	-	-	ext dom
BOC+PEG-IFN2b+RBV	8.09	£64,985.45	-	-	dominated
TVR+PEG-IFN2a+RBV	7.95	£61,326.36	-	-	ext dom
PEG-IFN2a+RBV	6.54	£48,265.60	-	-	ext dom
No treatment	5.25	£41,253.02	-	-	-
(iii) Genotype 1/4 treatment-experienced non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	16.21	£80,577.05	0.12	19853.44	**£165,445**
SMV+SOF	16.09	£60,723.61	0.42	21993.91	£52,366
SOF+PEG-IFN2a+RBV	15.71	£42,386.90	-	-	ext dom
SMV+PEG-IFN2a+RBV	15.67	£38,729.70	0.05	£2,269.78	£45,396
TVR+PEG-IFN2a+RBV	15.62	£36,459.92	1.31	£24,300.20	£18,550
BOC+PEG-IFN2b+RBV	15.48	£39,911.38	-	-	dominated
PEG-IFN2a+RBV	14.61	£18,984.11	-	-	ext dom
No treatment	14.31	£12,159.72	-	-	-

Inc. – incremental; ICER – incremental cost-effectiveness ratio; ext dom – extended dominance; IFN – interferon

(i) Genotype 1 treatment-naïve non-cirrhotic subgroup

The model suggests that within the genotype 1 treatment-naïve non-cirrhotic subgroup, LDV/SOF (8 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All options excluding LDV/SOF, PEG-IFN2a+RBV and no treatment are ruled out due to simple dominance. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £6,939 per QALY gained. The ICER for LDV/SOF versus PEG-IFN2a+RBV is estimated to be £8,894 per QALY gained.

(ii) Genotype 1 treatment-naïve cirrhotic subgroup

The model suggests that within the genotype 1 treatment-naïve cirrhotic subgroup, LDV/SOF (12 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All options excluding LDV/SOF and no treatment are ruled out due to simple dominance or extended dominance. The ICER for LDV/SOF (12 weeks) versus no treatment is estimated to be £4,518 per QALY gained.

(iii) Genotype 1/4 treatment-experienced non-cirrhotic subgroup

Within the genotype 1/4 treatment-experienced non-cirrhotic subgroup, the model suggests that LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All options excluding LDV/SOF, SMV+PEG-IFN2a+RBV, TVR+PEG-IFN2a+RBV and no treatment are expected to be ruled out due to simple or extended dominance. The ICER for TVR+PEG-IFN2a+RBV versus no treatment is estimated to be £18,550 per QALY gained. The ICER for SMV+PEG-IFN2a+RBV versus TVR+PEG-IFN2a+RBV is estimated to be £45,396 per QALY gained. The ICER for SMV+SOF versus SMV+PEG-IFN2a+RBV is estimated to be £52,366 per QALY gained. The ICER for LDV/SOF (24 weeks) versus SMV+SOF is estimated to be £165,445 per QALY gained.

It should be noted that TVR and BOC are not licensed for use in patients with genotype 4 disease. Excluding TVR and BOC from the analysis for GT4 treatment-experienced patients results in an ICER for SMV+PEG-IFN2a+RBV versus no treatment of £19,537 per QALY gained. The ICER for LDV/SOF is unaffected.

5.5.2.3 Results of additional analysis 3 - use of alternative transition probabilities based on the sofosbuvir STA model

Table 54 presents the central estimates of cost-effectiveness results of the exploratory analysis 3 (see Section 5.5.1.3); this analysis uses the ERG-preferred base case analysis in combination with transition probabilities taken from the model used within the previous sofosbuvir STA.[12]

Table 54: Central estimates of cost-effectiveness (additional analysis 3, use of alternative transition probabilities based on the sofosbuvir STA model)

(i) Genotype 1 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	17.20	£42,184.89	0.34	£8,678.81	**£25,526**
SMV+SOF	17.11	£61,492.38	-	-	dominated
SOF+PEG-IFN2a+RBV	17.06	£41,170.98	-	-	ext dom
SMV+PEG-IFN2a+RBV	16.86	£33,506.08	0.75	£13,725.14	£18,300
TVR+PEG-IFN2a+RBV	16.75	£34,867.92	-	-	dominated
BOC+PEG-IFN2b+RBV	16.51	£35,371.57	-	-	dominated
PEG-IFN2a+RBV	16.11	£19,780.94	0.75	£5,679.23	£7,572
No treatment	15.36	£14,101.71	-	-	-
(ii) Genotype 1 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	10.18	£102,305.63	0.11	£19,142.54	**£174,023**
SMV+SOF	10.07	£83,163.09	0.34	£16,812.09	£49,447
SOF+PEG-IFN2a+RBV	9.73	£66,351.00	1.46	£9,632.22	£6,597
SMV+PEG-IFN2a+RBV	9.20	£64,023.82	-	-	ext dom
BOC+PEG-IFN2b+RBV	9.12	£70,316.26	-	-	dominated
TVR+PEG-IFN2a+RBV	9.03	£66,927.05	-	-	dominated
PEG-IFN2a+RBV	8.27	£56,718.78	0.71	£4,268.64	£6,012
No treatment	7.56	£52,450.14	-	-	-
(iii) Genotype 4 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	17.20	£42,184.89	0.34	£8,678.81	**£25,526**
SMV+SOF	17.11	£61,492.38	-	-	dominated
SOF+PEG-IFN2a+RBV	17.06	£41,170.98	-	-	ext dom
SMV+PEG-IFN2a+RBV	16.86	£33,506.08	0.75	£13,725.14	£18,300
PEG-IFN2a+RBV	16.11	£19,780.94	0.75	£5,679.23	£7,572
No treatment	15.36	£14,101.71	-	-	-
(iv) Genotype 4 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	10.18	£102,305.63	0.11	£19,142.54	**£174,023**
SMV+SOF	10.07	£83,163.09	0.34	16812.09	£49,447
SOF+PEG-IFN2a+RBV	9.73	£66,351.00	1.46	£9,632.22	£6,597
SMV+PEG-IFN2a+RBV	9.20	£64,023.82	-	-	ext dom
PEG-IFN2a+RBV	8.27	£56,718.78	0.71	£4,268.64	£6,012
No treatment	7.56	£52,450.14	-	-	-
(v) Genotype 1/4 treatment-experienced non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF12 weeks	16.12	£42,032.16	1.56	£29,038.36	**£18,614**
SMV+SOF	16.11	£60,783.18	-	-	dominated
SOF+PEG-IFN2a+RBV	15.77	£42,603.76	-	-	dominated
SMV+PEG-IFN2a+RBV	15.73	£38,911.81	-	-	ext dom
TVR+PEG-IFN2a+RBV	15.68	£36,678.99	-	-	ext dom
BOC+PEG-IFN2b+RBV	15.57	£40,189.27	-	-	dominated
PEG-IFN2a+RBV	14.81	£19,643.16	-	-	ext dom
No treatment	14.56	£12,993.80	-	-	-
(vi) Genotype 1/4 treatment-experienced cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	9.78	£100,330.45	0.11	£19,046.32	**£173,148**

SMV+SOF	9.67	£81,284.13	0.48	£14,811.09	£30,856
SOF+PEG-IFN2a+RBV	9.19	£66,473.04	1.81	£15,676.01	£8,660
SMV+PEG-IFN2a+RBV	9.03	£65,803.66	-	-	ext dom
TVR+PEG-IFN2a+RBV	8.59	£68,854.52	-	-	dominated
BOC+PEG-IFN2b+RBV	8.33	£74,964.16	-	-	dominated
PEG-IFN2a+RBV	7.68	£56,386.16	-	-	ext dom
No treatment	7.38	£50,797.03	-	-	-
(vii) Genotype 3 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	17.24	£83,330.76	0.7	£71,547.68	**£102,210**
PEG-IFN2a+RBV	16.54	£11,783.08	-	-	-
No treatment	14.97	£16,429.60	-	-	dominated
(viii) Genotype 3 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	10.26	£103,591.07	0.47	£37,517.89	**£79,825**
SOF+RBV	10.08	£97,657.23	-	-	ext dom
SOF+PEG-IFN2a+RBV	9.79	£66,073.18	2.23	£13,623.04	£1,392
No treatment	7.56	£52,450.14	-	-	-
(ix) Genotype 3 treatment-experienced IFN-ineligible non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	16.01	£84,234.47	0.06	£7,876.10	**£131,268**
SOF+RBV	15.95	£76,358.37	1.72	£61,248.26	£35,609
No treatment	14.23	£15,110.11	-	-	-
(x) Genotype 3 treatment-experienced IFN-ineligible cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	9.28	£108,736.80	1.9	£57,939.77	**£30,495**
SOF+RBV	8.89	£105,607.67	-	-	ext dom
No treatment	7.38	£50,797.03	-	-	-

Inc. – incremental; ICER – incremental cost-effectiveness ratio; ext dom – extended dominance; IFN – interferon

(i) Genotype 1 treatment-naïve non-cirrhotic subgroup

The model suggests that within the genotype 1 treatment-naïve non-cirrhotic subgroup, LDV/SOF (12 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest number of QALYs. All options excluding LDV/SOF (12 weeks), SMV+PEG-IFN2a+RBV, PEG-IFN2a+RBV and no treatment are ruled out due to simple dominance or extended dominance. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £7,572 per QALY gained. The ICER for SMV+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £18,300 per QALY gained. The ICER for LDV/SOF (12 weeks) versus SMV+PEG-IFN2a+RBV is estimated to be £25,526 per QALY gained.

(ii) Genotype 1 treatment-naïve cirrhotic subgroup

The model suggests that within the genotype 1 treatment-naïve cirrhotic subgroup, LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. TVR+PEG-IFN2a+RBV and BOC+PEG-IFN2b+RBV are ruled out due to simple dominance whilst SMV+PEG-IFN2a+RBV is ruled out due to extended dominance. The ICER for

PEG-IFN2a+RBV versus no treatment is estimated to be £6,012 per QALY gained. The ICER for SOF+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £6,597 per QALY gained. The ICER for SMV+SOF versus SOF+PEG-IFN2a+RBV is estimated to be £49,447 per QALY gained. The ICER for LDV/SOF (24 weeks) versus SMV+SOF is estimated to be £174,023 per QALY gained.

(iii) Genotype 4 treatment-naïve non-cirrhotic subgroup

The model suggests that within the genotype 4 treatment-naïve non-cirrhotic subgroup, LDV/SOF (12 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. SMV+SOF is expected to be dominated whilst SOF+PEG-IFN2a+RBV is expected to be extendedly dominated. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £7,572 per QALY gained. The ICER for SMV+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £18,300 per QALY gained. The ICER for LDV/SOF (12 weeks) versus SMV+PEG-IFN2a+RBV is estimated to be £25,526 per QALY gained.

(iv) Genotype 4 treatment-naïve cirrhotic subgroup

The model suggests that within the genotype 4 treatment-naïve cirrhotic subgroup, LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. SMV+PEG-IFN2a+RBV is ruled out due to extended dominance. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £6,012 per QALY gained. The ICER for SOF+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £6,597 per QALY gained. The ICER for SMV+SOF versus SOF+PEG-IFN2a+RBV is estimated to be £49,447 per QALY gained. The ICER for LDV/SOF (24 weeks) versus SMV+SOF is estimated to be £174,023 per QALY gained.

(v) Genotype 1/4 treatment-experienced non-cirrhotic subgroup

Within the genotype 1/4 treatment-experienced non-cirrhotic subgroup, the model suggests that LDV/SOF (12 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All options excluding LDV/SOF and no treatment are expected to be ruled out due to simple or extended dominance. The ICER for LDV/SOF (12 weeks) is estimated to be £18,614 per QALY gained.

TVR and BOC are not licensed for use in patients with genotype 4 disease. However, since both options are ruled out of the analysis due to simple or extended dominance, the ICER for LDV/SOF in the GT4 treatment-experienced subgroup is unaffected.

(vi) Genotype 1/4 treatment-experienced cirrhotic subgroup

Within the genotype 1/4 treatment-experienced cirrhotic subgroup, the model suggests that LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All options excluding LDV/SOF, SMV+SOF, SOF+PEG-IFN2a+RBV and no treatment are expected to be ruled out due to simple or extended dominance. The ICER for SOF+PEG-IFN2a+RBV versus no treatment is estimated to be £8,660 per QALY gained. The ICER for SMV+SOF versus SOF+PEG-IFN2a+RBV is estimated to be £30,856 per QALY gained. The ICER for LDV/SOF (24 weeks) versus SMV+SOF is estimated to be £173,148 per QALY gained.

TVR and BOC are not licensed for use in patients with genotype 4 disease. However, since both options are ruled out of the analysis due to simple dominance, the ICER for LDV/SOF in the GT4 treatment-experienced subgroup is unaffected.

(vii) Genotype 3 treatment-naïve non-cirrhotic subgroup

The model suggests that within the genotype 3 treatment-naïve non-cirrhotic subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce fewer QALYs at a higher cost than PEG-IFN2a+RBV hence this option is ruled out due to simple dominance. The ICER for LDV/SOF+RBV (24 weeks) versus PEG-IFN2a+RBV is estimated to be £102,210 per QALY gained.

(viii) Genotype 3 treatment-naïve cirrhotic subgroup

The model suggests that within the genotype 3 treatment-naïve cirrhotic subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce fewest QALYs. SOF+RBV is ruled out of the analysis due to extended dominance. The ICER for SOF+PEG-IFN2a+RBV versus no treatment is estimated to be £1,392 per QALY gained. The ICER for LDV/SOF+RBV (24 weeks) versus SOF+PEG-IFN2a+RBV is estimated to be £79,285 per QALY gained.

(ix) Genotype 3 treatment-experienced IFN-ineligible non-cirrhotic

The model suggests that within the genotype 3 treatment-experienced non-cirrhotic subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to be the least effective treatment. The ICER for SOF+RBV versus no treatment is estimated to be £35,609 per QALY gained. The ICER for LDV/SOF+RBV (24 weeks) versus SOF+RBV is estimated to be £131,268 per QALY gained.

(x) Genotype 3 treatment-experienced IFN-ineligible cirrhotic

The model suggests that within the genotype 3 treatment-experienced, IFN-ineligible cirrhotic subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce fewest QALYs. SOF+RBV is ruled out due to extended dominance. The ICER for LDV/SOF+RBV (24 weeks) versus no treatment is estimated to be £30,495 per QALY gained.

5.5.2.4 Results of additional analysis 4 - use of UK valued utility increment derived by Wright et al[71]

Table 55 presents the central estimates of cost-effectiveness results of the exploratory analysis 4 (see Section 5.5.1.4); this analysis uses the ERG-preferred base case analysis in combination with the utility gain associated with achieving SVR as reported by Wright *et al*, 2006.[71]

Table 55: Central estimates of cost-effectiveness (additional analysis 4, use of UK-valued HRQoL increment for achieving SVR[71])

(i) Genotype 1 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	17.38	£42,160.45	0.41	£8,843.83	**£21,570**
SMV+SOF	17.27	£61,415.79	-	-	dominated
SOF+PEG-IFN2a+RBV	17.21	£41,081.62	-	-	ext dom
SMV+PEG-IFN2a+RBV	16.97	£33,316.62	0.93	£14,111.22	£15,173
TVR+PEG-IFN2a+RBV	16.83	£34,631.46	-	-	dominated
BOC+PEG-IFN2b+RBV	16.53	£35,002.22	-	-	dominated
PEG-IFN2a+RBV	16.04	£19,205.40	0.97	£6175.99	£6,367
No treatment	15.07	£13,029.41	-	-	-
(ii) Genotype 1 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	10.22	£101,051.95	0.21	£19,567.23	**£93,177**
SMV+SOF	10.01	£81,484.72	0.64	£18,051.21	£28,205
SOF+PEG-IFN2a+RBV	9.37	£63,433.51	2.79	£15,167.91	£5,437
SMV+PEG-IFN2a+RBV	8.36	£59,097.68	-	-	ext dom
BOC+PEG-IFN2b+RBV	8.17	£64,985.45	-	-	dominated
TVR+PEG-IFN2a+RBV	8.02	£61,326.36	-	-	ext dom
PEG-IFN2a+RBV	6.58	£48,265.60	1.33	£7,012.58	£5,273
No treatment	5.25	£41,253.02	-	-	-
(iii) Genotype 4 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	17.38	£42,160.45	0.41	£8,843.83	**£21,570**
SMV+SOF	17.27	£61,415.79	-	-	dominated
SOF+PEG-IFN2a+RBV	17.21	£41,081.62	-	-	ext dom
SMV+PEG-IFN2a+RBV	16.97	£33,316.62	0.93	£14,111.22	£15,173
PEG-IFN2a+RBV	16.04	£19,205.40	0.97	£6,175.99	£6,637
No treatment	15.07	£13,029.41	-	-	-
(iv) Genotype 4 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	10.22	£101,051.95	0.21	£19,567.23	**£93,177**
SMV+SOF	10.01	£81,484.72	0.64	£18,051.21	£28,205
SOF+PEG-IFN2a+RBV	9.37	£63,433.51	2.79	£15,167.91	£5,437
SMV+PEG-IFN2a+RBV	8.36	£59,097.68	-	-	ext dom
PEG-IFN2a+RBV	6.58	£48,265.60	1.33	£7,012.58	£5,273
No treatment	5.25	£41,253.02	-	-	-
(v) Genotype 1/4 treatment-experienced non-cirrhotic12 weeks					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF12 weeks	16.28	£41,978.77	1.97	£29,819.05	**£15,137**
SMV+SOF	16.26	£60,723.61	-	-	dominated
SOF+PEG-IFN2a+RBV	15.84	£42,386.90	-	-	dominated
SMV+PEG-IFN2a+RBV	15.80	£38,729.70	-	-	ext dom
TVR+PEG-IFN2a+RBV	15.75	£36,459.92	-	-	ext dom
BOC+PEG-IFN2b+RBV	15.60	£39,911.38	-	-	dominated
PEG-IFN2a+RBV	14.64	£18,984.11	-	-	ext dom
No treatment	14.31	£12,159.72	-	-	-
(vi) Genotype 1/4 treatment-experienced cirrhotic 24 weeks					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	9.83	£99,222.17	0.21	£19,467.86	**£92,704**

SMV+SOF	9.62	£79,754.31	0.92	£16,560.88	£18,001
SOF+PEG-IFN2a+RBV	8.70	£63,193.43	3.51	£22,542.63	£6,422
SMV+PEG-IFN2a+RBV	8.40	£62,045.65	-	-	ext dom
TVR+PEG-IFN2a+RBV	7.52	£63,324.53	-	-	dominated
BOC+PEG-IFN2b+RBV	7.00	£68,413.45	-	-	dominated
PEG-IFN2a+RBV	5.76	£47,441.22	-	-	ext dom
No treatment	5.19	£40,650.80	-	-	-
(vii) Genotype 3 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	17.43	£83,330.76	0.87	£71,970.90	**£82,725**
PEG-IFN2a+RBV	16.56	£11,359.86	-	-	-
No treatment	14.57	£14,928.01	-	-	dominated
(viii) Genotype 3 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	10.37	£102,644.92	0.87	£39,226.39	**£45,088**
SOF+RBV	10.01	£95,947.03	-	-	ext dom
SOF+PEG-IFN2a+RBV	9.50	£63,418.53	4.25	£22,165.51	£2,333
No treatment	5.25	£41,253.02	-	-	-
(ix) Genotype 3 treatment-experienced IFN-ineligible non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	16.13	£84,108.64	0.07	£7,899.24	**£112,846**
SOF+RBV	16.06	£76,209.40	2.18	£62,273.69	£28,566
No treatment	13.88	£13,935.71	-	-	-
(x) Genotype 3 treatment-experienced IFN-ineligible cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	8.87	£105,760.87	3.68	£65,110.07	**£17,693**
SOF+RBV	8.09	£101,108.73	-	-	ext dom
No treatment	5.19	£40,650.80	-	-	-

Inc. – incremental; ICER – incremental cost-effectiveness ratio; ext dom – extended dominance; IFN – interferon

(i) Genotype 1 treatment-naïve non-cirrhotic subgroup

The model suggests that within the genotype 1 treatment-naïve non-cirrhotic subgroup, LDV/SOF (12 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All options excluding LDV/SOF, SMV+PEG-IFN2a+RBV, PEG-IFN2a+RBV and no treatment are ruled out due to simple dominance or extended dominance. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £6,637 per QALY gained. The ICER for SMV+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £15,173 per QALY gained. The ICER for LDV/SOF (12 weeks) versus SMV+PEG-IFN2a+RBV is estimated to be £21,570 per QALY gained.

(ii) Genotype 1 treatment-naïve cirrhotic subgroup

The model suggests that within the genotype 1 treatment-naïve cirrhotic subgroup, LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. BOC+PEG-IFN2b+RBV is expected to be ruled out due to simple dominance, whilst SMV+PEG-IFN2a+RBV and TVR+PEG-IFN2a+RBV are expected to be ruled out due to

extended dominance. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £5,273 per QALY gained. The ICER for SOF+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £5,437 per QALY gained. The ICER for SMV+SOF versus SOF+PEG-IFN2a+RBV is estimated to be £28,205 per QALY gained. The ICER for LDV/SOF (24 weeks) versus SMV+SOF is estimated to be £93,177 per QALY gained.

(iii) Genotype 4 treatment-naïve non-cirrhotic subgroup

The model suggests that within the genotype 4 treatment-naïve non-cirrhotic subgroup, LDV/SOF (12 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. SMV+SOF is expected to be ruled out of the analysis due to simple dominance whilst SOF+PEG-IFN2a+RBV is expected to be ruled out due to extended dominance. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £6,637 per QALY gained. The ICER for SMV+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £15,173 per QALY gained. The ICER for LDV/SOF (12 weeks) versus SMV+PEG-IFN2a+RBV is estimated to be £21,570 per QALY gained.

(iv) Genotype 4 treatment-naïve cirrhotic subgroup

The model suggests that within the genotype 4 treatment-naïve cirrhotic subgroup, LDV/SOF is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. SMV+PEG-IFN2a+RBV is expected to be ruled out due to extended dominance. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £5,273 per QALY gained. The ICER for SOF+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £5,437 per QALY gained. The ICER for SMV+SOF versus SOF+PEG-IFN2a+RBV is estimated to be £28,205 per QALY gained. The ICER for LDV/SOF (24 weeks) versus SMV+SOF is estimated to be £93,177 per QALY gained.

(v) Genotype 1/4 treatment-experienced non-cirrhotic subgroup

Within the genotype 1/4 treatment-experienced non-cirrhotic subgroup, the model suggests that LDV/SOF (12 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All options excluding LDV/SOF and no treatment are expected to be ruled out due to simple or extended dominance. The ICER for LDV/SOF (12 weeks) is estimated to be £15,137 per QALY gained.

TVR and BOC are not licensed for use in patients with genotype 4 disease. However, since both options are ruled out of the analysis due to simple dominance, the ICER in the GT4 treatment-experienced subgroup is unaffected.

(vi) Genotype 1/4 treatment-experienced cirrhotic subgroup

Within the genotype 1/4 treatment-experienced cirrhotic subgroup, the model suggests that LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All options excluding LDV/SOF, SMV+SOF, SOF+PEG-IFN2a+RBV and no treatment are expected to be ruled out due to simple or extended dominance. The ICER for SOF+PEG-IFN2a+RBV versus no treatment is estimated to be £6,422 per QALY gained. The ICER for SMV+SOF versus SOF+PEG-IFN2a+RBV is estimated to be £18,001 per QALY gained. The ICER for LDV/SOF (24 weeks) versus SMV+SOF is estimated to be £92,704 per QALY gained.

TVR and BOC are not licensed for use in patients with genotype 4 disease. However, since both options are ruled out of the analysis due to simple dominance, the ICER in the GT4 treatment-experienced subgroup is unaffected.

(vii) Genotype 3 treatment-naïve non-cirrhotic subgroup

The model suggests that within the genotype 3 treatment-naïve non-cirrhotic subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce fewer QALYs at a higher cost than PEG-IFN2a+RBV hence this option is ruled out due to simple dominance. The ICER for LDV/SOF+RBV versus PEG-IFN2a+RBV is estimated to be £82,725 per QALY gained.

(viii) Genotype 3 treatment-naïve cirrhotic subgroup

The model suggests that within the genotype 3 treatment-naïve cirrhotic subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce fewest QALYs. SOF+RBV is ruled out of the analysis due to extended dominance. The ICER for SOF+PEG-IFN2a+RBV versus no treatment is estimated to be £2,333 per QALY gained. The ICER for LDV/SOF+RBV (24 weeks) versus SOF+PEG-IFN2a+RBV is estimated to be £45,088 per QALY gained.

(ix) Genotype 3 treatment-experienced IFN-ineligible non-cirrhotic

The model suggests that within the genotype 3 treatment-experienced non-cirrhotic subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to be the least effective treatment. The ICER for SOF+RBV versus no treatment is estimated to be £28,566 per QALY gained. The ICER for LDV/SOF+RBV (24 weeks) versus SOF+RBV is estimated to be £112,846 per QALY gained.

(x) Genotype 3 treatment-experienced IFN-ineligible cirrhotic

The model suggests that within the genotype 3 treatment-experienced, IFN-ineligible cirrhotic subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce fewest QALYs. SOF+RBV is ruled out due to extended dominance. The ICER for LDV/SOF+RBV versus no treatment is estimated to be £17,693 per QALY gained.

5.5.2.5 Results of additional analysis 5 - central estimates of cost-effectiveness using short time horizons

This section presents the results of the exploratory analysis 5 (see Section 5.5.1.5); this analysis uses the ERG-preferred base case analysis in combination with short time horizons. Table 56 presents the central estimates of cost-effectiveness using the company's model using a 5-year time horizon.

Table 56: Central estimates of cost-effectiveness (additional analysis 5, 5-year time horizon)

(i) Genotype 1 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	4.32	£41,914.72	0.22	£39,662	**£180,286**
SMV+SOF	4.31	£60,645.96	-	-	dominated
SOF+PEG-IFN2a+RBV	4.28	£40,183.49	-	-	ext dom
SMV+PEG-IFN2a+RBV	4.24	£31,377.72	-	-	ext dom
TVR+PEG-IFN2a+RBV	4.20	£32,196.85	-	-	dominated
BOC+PEG-IFN2b+RBV	4.17	£31,153.45	-	-	ext dom
PEG-IFN2a+RBV	4.10	£13,171.87	-	-	dominated
No treatment	4.10	£2,251.75	-	-	-
(ii) Genotype 1 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	3.15	£85,390.04	0.02	£20,010	**£1,000,548**
SMV+SOF	3.13	£65,379.09	0.07	£19,345	£276,370
SOF+PEG-IFN2a+RBV	3.06	£46,033.18	0.22	£22,227	£101,033
SMV+PEG-IFN2a+RBV	2.97	£39,286.64	-	-	ext dom
BOC+PEG-IFN2b+RBV	2.95	£44,142.20	-	-	dominated
TVR+PEG-IFN2a+RBV	2.94	£40,647.15	-	-	dominated
PEG-IFN2a+RBV	2.84	£23,805.99	0.09	£8,604	£95,602
No treatment	2.75	£15,201.77	-	-	-
(iii) Genotype 4 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	4.32	£41,914.72	0.22	£39,662	**£180,286**
SMV+SOF	4.31	£60,645.96	-	-	dominated
SOF+PEG-IFN2a+RBV	4.28	£40,183.49	-	-	ext dom
SMV+PEG-IFN2a+RBV	4.24	£31,377.72	-	-	ext dom
PEG-IFN2a+RBV	4.10	£13,171.87	-	-	dominated
No treatment	4.10	£2,251.75	-	-	-
(iv) Genotype 4 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	3.15	£85,390.04	0.02	£20,010	**£1,000,548**
SMV+SOF	3.13	£65,379.09	0.07	£19,345	£276,370
SOF+PEG-IFN2a+RBV	3.06	£46,033.18	0.22	£22,227	£101,033
SMV+PEG-IFN2a+RBV	2.97	£39,286.64	-	-	ext dom
PEG-IFN2a+RBV	2.84	£23,805.99	0.09	£8,604	£95,602
No treatment	2.75	£15,201.77	-	-	-
(v) Genotype 1/4 treatment-experienced non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	4.31	£41,344.45	0.22	£39,096	**£177,710**
SMV+SOF	4.31	£60,015.65	-	-	dominated
SOF+PEG-IFN2a+RBV	4.24	£39,809.94	-	-	ext dom
TVR+PEG-IFN2a+RBV	4.16	£33,721.87	-	-	ext dom
BOC+PEG-IFN2b+RBV	4.15	£36,412.90	-	-	dominated
SMV+PEG-IFN2a+RBV	4.13	£36,420.48	-	-	dominated
No treatment	4.09	£2,248.32	-	-	-
PEG-IFN2a+RBV	4.06	£10,865.23	-	-	dominated
(vi) Genotype 1/4 treatment-experienced cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	3.15	£84,518.46	0.02	£19,970	**£998,514**
SMV+SOF	3.13	£64,548.18	0.10	£18,646	£186,463
SOF+PEG-IFN2a+RBV	3.03	£45,901.79	0.28	£30,726	£109,738

SMV+PEG-IFN2a+RBV	2.93	£43,352.62	-	-	ext dom
TVR+PEG-IFN2a+RBV	2.91	£42,402.75	-	-	dominated
BOC+PEG-IFN2b+RBV	2.88	£45,930.36	-	-	dominated
PEG-IFN2a+RBV	2.78	£22,309.01	-	-	ext dom
No treatment	2.75	£15,175.13	-	-	-
(vii) Genotype 3 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	4.32	£83,330.76	0.12	£75,578	**£629,814**
PEG-IFN2a+RBV	4.20	£7,753.04	0.11	£5,400	£49,091
No treatment	4.09	£2,352.98	-	-	-
(viii) Genotype 3 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	3.16	£87,304.33	0.09	£41,012	**£455,683**
SOF+RBV	3.12	£79,700.16	-	-	ext dom
SOF+PEG-IFN2a+RBV	3.07	£46,292.83	0.32	£31,091	£10,127
No treatment	2.75	£15,201.77	-	-	-
(ix) Genotype 3 treatment-experienced IFN-ineligible non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	4.29	£82,867.24	0.02	£8,159	**£407,936**
SOF+RBV	4.27	£74,708.52	0.19	£72,359	£380,838
No treatment	4.08	£2,349.29	-	-	-
(x) Genotype 3 treatment-experienced IFN-ineligible cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	3.06	£88,831.18	0.31	£73,656	**£237,600**
SOF+RBV	2.99	£82,041.08	-	-	ext dom
No treatment	2.75	£15,175.13	-	-	-

Inc. – incremental; ICER – incremental cost-effectiveness ratio; ext dom – extended dominance; IFN – interferon

(i) Genotype 1 treatment-naïve non-cirrhotic subgroup

The model suggests that within the genotype 1 treatment-naïve non-cirrhotic subgroup, LDV/SOF is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All other options are ruled out due to simple or extended dominance. The ICER for LDV/SOF versus no treatment is estimated to be £180,286 per QALY gained.

(ii) Genotype 1 treatment-naïve cirrhotic subgroup

Within the genotype 1 treatment-naïve cirrhotic subgroup, LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. BOC+PEG-IFN2b+RBV and TVR+PEG-IFN2a+RBV are expected to be ruled out due to simple dominance, whilst SMV+PEG-IFN2a+RBV is expected to be ruled out due to extended dominance. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £95,602 per QALY gained. The ICER for SOF+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £101,033 per QALY gained. The ICER for SMV+SOF versus SOF+PEG-IFN2a+RBV is estimated to be £276,370 per QALY gained. The ICER for LDV/SOF (24 weeks) versus SMV+SOF is estimated to be in excess of £1million per QALY gained.

(iii) Genotype 4 treatment-naïve non-cirrhotic subgroup

The model suggests that within the genotype 4 treatment-naïve non-cirrhotic subgroup, LDV/SOF (12 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All other options are ruled out due to simple dominance or extended dominance. The ICER for LDV/SOF versus no treatment is estimated to be £180,286 per QALY gained.

(iv) Genotype 4 treatment-naïve cirrhotic subgroup

The model suggests that within the genotype 4 treatment-naïve cirrhotic subgroup, LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. SMV+PEG-IFN2a+RBV is expected to be ruled out due to extended dominance. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £95,602 per QALY gained. The ICER for SOF+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £101,033 per QALY gained. The ICER for SMV+SOF versus SOF+PEG-IFN2a+RBV is estimated to be £276,370 per QALY gained. The ICER for LDV/SOF (24 weeks) versus SMV+SOF is estimated to be £1,000,548 per QALY gained.

(v) Genotype 1/4 treatment-experienced non-cirrhotic subgroup

Within the genotype 1/4 treatment-experienced non-cirrhotic subgroup, the model suggests that LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. PEG-IFN2a+RBV is expected to produce the fewest QALYs. All other options are expected to be ruled out due to simple or extended dominance. The ICER for LDV/SOF is estimated to be £177,710 per QALY gained.

TVR and BOC are not licensed for use in patients with genotype 4 disease. However, since both options are ruled out of the analysis due to dominance, the ICER for LDV/SOF in the GT4 treatment-experienced subgroup is unaffected.

(vi) Genotype 1/4 treatment-experienced cirrhotic subgroup

Within the genotype 1/4 treatment-experienced cirrhotic subgroup, the model suggests that LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All options excluding LDV/SOF (24 weeks), SMV+SOF, SOF+PEG-IFN2a+RBV and no treatment are expected to be ruled out due to simple or extended dominance. The ICER for SOF+PEG-IFN2a+RBV versus no treatment is estimated to be £109,738 per QALY gained. The ICER for SMV+SOF versus SOF+PEG-IFN2a+RBV is estimated to be £186,463 per QALY gained. The ICER for LDV/SOF (24 weeks) versus SMV+SOF is estimated to be £998,514 per QALY gained.

Superseded – see erratum

TVR and BOC are not licensed for use in patients with genotype 4 disease. However, since both options are ruled out of the analysis due to simple dominance, the ICER for LDV/SOF in the GT4 treatment-experienced subgroup is unaffected.

(vii) Genotype 3 treatment-naïve non-cirrhotic subgroup

The model suggests that within the genotype 3 treatment-naïve non-cirrhotic subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £49,091 per QALY gained. The ICER for LDV/SOF+RBV (24 weeks) versus PEG-IFN2a+RBV is estimated to be £629,814 per QALY gained.

(viii) Genotype 3 treatment-naïve cirrhotic subgroup

The model suggests that within the genotype 3 treatment-naïve cirrhotic subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce fewest QALYs. SOF+RBV is ruled out of the analysis due to extended dominance. The ICER for SOF+PEG-IFN2a+RBV versus no treatment is estimated to be £10,127 per QALY gained. The ICER for LDV/SOF+RBV (24 weeks) versus SOF+PEG-IFN2a+RBV is estimated to be £455,683 per QALY gained.

(ix) Genotype 3 treatment-experienced IFN-ineligible non-cirrhotic

The model suggests that within the genotype 3 treatment-experienced non-cirrhotic subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to be the least effective treatment. The ICER for SOF+RBV versus no treatment is estimated to be £380,838 per QALY gained. The ICER for LDV/SOF+RBV (24 weeks) versus SOF+RBV is estimated to be £407,936 per QALY gained.

(x) Genotype 3 treatment-experienced IFN-ineligible cirrhotic

The model suggests that within the Genotype 3 treatment-experienced, IFN-ineligible, compensated cirrhosis subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce fewest QALYs. SOF+RBV is ruled out due to extended dominance. The ICER for LDV/SOF+RBV (24 weeks) versus no treatment is estimated to be £237,600 per QALY gained.

Table 57 presents the central estimates of cost-effectiveness using the company's model using 10 year time horizon. These results are summarised below.

Table 57: Central estimates of cost-effectiveness (additional analysis 5, 10 year time horizon)

(i) Genotype 1 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	7.28	£41,961.63	0.11	10216.65	**£92,879**
SMV+SOF	7.26	£60,792.95	-	-	dominated
SOF+PEG-IFN2a+RBV	7.23	£40,354.98	-	-	ext dom
SMV+PEG-IFN2a+RBV	7.17	£31,744.98	0.33	27435.36	£83,137
TVR+PEG-IFN2a+RBV	7.12	£32,656.74	-	-	dominated
BOC+PEG-IFN2b+RBV	7.06	£31,876.48	-	-	dominated
PEG-IFN2a+RBV	6.95	£14,302.16	-	-	ext dom
No treatment	6.84	£4,309.62	-	-	-
(ii) Genotype 1 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	5.13	£89,706.51	0.05	£19,676	**£393,527**
SMV+SOF	5.08	£70,030.16	0.16	£18,370	£114,810
SOF+PEG-IFN2a+RBV	4.92	£51,660.57	0.61	£17,291	£28,347
SMV+PEG-IFN2a+RBV	4.69	£46,629.45	-	-	ext dom
BOC+PEG-IFN2b+RBV	4.66	£52,062.29	-	-	dominated
TVR+PEG-IFN2a+RBV	4.62	£48,594.48	-	-	dominated
PEG-IFN2a+RBV	4.31	£34,369.08	0.32	£7,016	£21,926
No treatment	3.99	£27,352.76	-	-	-
(iii) Genotype 4 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	7.28	£41,961.63	0.11	10216.65	**£92,879**
SMV+SOF	7.26	£60,792.95	-	-	dominated
SOF+PEG-IFN2a+RBV	7.23	£40,354.98	-	-	ext dom
SMV+PEG-IFN2a+RBV	7.17	£31,744.98	0.33	27435.36	£83,137
PEG-IFN2a+RBV	6.95	£14,302.16	-	-	ext dom
No treatment	6.84	£4,309.62	-	-	-
(iv) Genotype 4 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	5.13	£89,706.51	0.05	£19,676	**£393,527**
SMV+SOF	5.08	£70,030.16	0.16	£18,370	£114,810
SOF+PEG-IFN2a+RBV	4.92	£51,660.57	0.61	£17,291	£28,347
SMV+PEG-IFN2a+RBV	4.69	£46,629.45	-	-	ext dom
PEG-IFN2a+RBV	4.31	£34,369.08	0.32	£7,016	£21,926
No treatment	3.99	£27,352.76	-	-	-
(v) Genotype 1/4 treatment-experienced non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	7.24	£41,475.24	0.42	£37,183	**£88,532**
SMV+SOF	7.24	£60,161.62	-	-	dominated
SOF+PEG-IFN2a+RBV	7.12	£40,341.28	-	-	ext dom
TVR+PEG-IFN2a+RBV	7.05	£34,276.23	-	-	ext dom
SMV+PEG-IFN2a+RBV	7.03	£36,885.49	-	-	dominated
BOC+PEG-IFN2b+RBV	7.02	£37,119.31	-	-	dominated
PEG-IFN2a+RBV	6.83	£12,517.82	-	-	dominated
No treatment	6.82	£4,291.96	-	-	-
(vi) Genotype 1/4 treatment-experienced cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	5.12	£88,773.59	0.06	£19,606	**£326,762**
SMV+SOF	5.06	£69,167.84	0.24	£17,133	£71,389
SOF+PEG-IFN2a+RBV	4.82	£52,034.60	0.84	£24,789	£29,510

SMV+PEG-IFN2a+RBV	4.71	£50,247.87	-	-	ext dom
TVR+PEG-IFN2a+RBV	4.55	£50,905.48	-	-	dominated
BOC+PEG-IFN2b+RBV	4.44	£55,478.84	-	-	dominated
PEG-IFN2a+RBV	4.13	£33,852.22	-	-	ext dom
No treatment	3.98	£27,245.91	-	-	-
(vii) Genotype 3 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	7.29	£83,330.76	0.2	£74,909	**£374,545**
PEG-IFN2a+RBV	7.09	£8,421.67	0.29	£3,713	£12,805
No treatment	6.80	£4,708.22	-	-	-
(viii) Genotype 3 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	5.16	£91,378.49	0.21	£39,665	**£188,883**
SOF+RBV	5.07	£84,407.71	-	-	ext dom
SOF+PEG-IFN2a+RBV	4.95	£51,713.13	0.96	£24,360	£4,921
No treatment	3.99	£27,352.76	-	-	-
(ix) Genotype 3 treatment-experienced IFN-ineligible non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	7.21	£83,117.83	0.03	£8,109	**£270,310**
SOF+RBV	7.18	£75,008.52	0.41	£70,320	£171,513
No treatment	6.77	£4,688.17	-	-	-
(x) Genotype 3 treatment-experienced IFN-ineligible cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	4.87	£94,701.38	0.89	£67,455	**£75,793**
SOF+RBV	4.70	£89,370.24	-	-	ext dom
No treatment	3.98	£27,245.91	-	-	-

Inc. – incremental; ICER – incremental cost-effectiveness ratio; ext dom – extended dominance; IFN – interferon

(i) Genotype 1 treatment-naïve non-cirrhotic subgroup

The model suggests that within the genotype 1 treatment-naïve non-cirrhotic subgroup, LDV/SOF is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All other options except LDV/SOF, SMV+PEG-IFN2a+RBV and no treatment are ruled out due to simple dominance or extended dominance. The ICER for SMV+PEG-IFN2a+RBV versus no treatment is estimated to be £83,137 per QALY gained. The ICER for LDV/SOF versus SMV+PEG-IFN2a+RBV is estimated to be £92,879 per QALY gained.

(ii) Genotype 1 treatment-naïve cirrhotic subgroup

Within the genotype 1 treatment-naïve cirrhotic subgroup, LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. BOC+PEG-IFN2b+RBV and TVR+PEG-IFN2a+RBV are expected to be ruled out due to simple dominance, whilst SMV+PEG-IFN2a+RBV is expected to be ruled out due to extended dominance. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £21,926 per QALY gained. The ICER for SOF+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £28,347 per QALY gained. The ICER for SMV+SOF versus SOF+PEG-IFN2a+RBV is estimated to be £114,810

per QALY gained. The ICER for LDV/SOF (24 weeks) versus SMV+SOF is estimated to be £393,527 per QALY gained.

(iii) Genotype 4 treatment-naïve non-cirrhotic subgroup

The model suggests that within the genotype 4 treatment-naïve non-cirrhotic subgroup, LDV/SOF (12 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All other options except LDV/SOF, SMV+PEG-IFN2a+RBV and no treatment are ruled out due to simple dominance or extended dominance. The ICER for SMV+PEG-IFN2a+RBV versus no treatment is estimated to be £83,137 per QALY gained. The ICER for LDV/SOF versus SMV+PEG-IFN2a+RBV is estimated to be £92,879 per QALY gained.

(iv) Genotype 4 treatment-naïve cirrhotic subgroup

The model suggests that within the genotype 4 treatment-naïve cirrhotic subgroup, LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. SMV+PEG-IFN2a+RBV is expected to be ruled out due to extended dominance. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £21,926 per QALY gained. The ICER for SOF+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £28,347 per QALY gained. The ICER for SMV+SOF versus SOF+PEG-IFN2a+RBV is estimated to be £114,810 per QALY gained. The ICER for LDV/SOF (24 weeks) versus SMV+SOF is estimated to be £393,527 per QALY gained.

(v) Genotype 1/4 treatment-experienced non-cirrhotic subgroup

Within the genotype 1/4 treatment-experienced non-cirrhotic subgroup, the model suggests that LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All other options are expected to be ruled out due to simple or extended dominance. The ICER for LDV/SOF (24 weeks) is estimated to be £88,532 per QALY gained.

TVR and BOC are not licensed for use in patients with genotype 4 disease. However, since both options are ruled out of the analysis due to dominance, the ICER for LDV/SOF in the GT4 treatment-experienced subgroup is unaffected.

(vi) Genotype 1/4 treatment-experienced cirrhotic subgroup

Within the genotype 1/4 treatment-experienced cirrhotic subgroup, the model suggests that LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. All options excluding LDV/SOF (24 weeks), SMV+SOF, SOF+PEG-

IFN2a+RBV and no treatment are expected to be ruled out due to simple or extended dominance. The ICER for SOF+PEG-IFN2a+RBV versus no treatment is estimated to be £29,510 per QALY gained. The ICER for SMV+SOF versus SOF+PEG-IFN2a+RBV is estimated to be £71,389 per QALY gained. The ICER for LDV/SOF (24 weeks) versus SMV+SOF is estimated to be £326,762 per QALY gained.

TVR and BOC are not licensed for use in patients with genotype 4 disease. However, since both options are ruled out of the analysis due to simple dominance, the ICER for LDV/SOF in the GT4 treatment-experienced subgroup is unaffected.

(vii) Genotype 3 treatment-naïve non-cirrhotic subgroup

The model suggests that within the genotype 3 treatment-naïve non-cirrhotic subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce the fewest QALYs. The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £12,805 per QALY gained. The ICER for LDV/SOF+RBV (24 weeks) versus PEG-IFN2a+RBV is estimated to be £374,545 per QALY gained.

(viii) Genotype 3 treatment-naïve cirrhotic subgroup

The model suggests that within the genotype 3 treatment-naïve cirrhotic subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce fewest QALYs. SOF+RBV is ruled out of the analysis due to extended dominance. The ICER for SOF+PEG-IFN2a+RBV versus no treatment is estimated to be £4,921 per QALY gained. The ICER for LDV/SOF+RBV (24 weeks) versus SOF+PEG-IFN2a+RBV is estimated to be £188,883 per QALY gained.

(ix) Genotype 3 treatment-experienced IFN-ineligible non-cirrhotic

The model suggests that within the genotype 3 treatment-experienced non-cirrhotic subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to be the least effective treatment. The ICER for SOF+RBV versus no treatment is estimated to be £171,513 per QALY gained. The ICER for LDV/SOF+RBV (24 weeks) versus SOF+RBV is estimated to be £270,310 per QALY gained.

(x) Genotype 3 treatment-experienced IFN-ineligible cirrhotic

The model suggests that within the Genotype 3 treatment-experienced, IFN-ineligible, compensated cirrhosis subgroup, LDV/SOF+RBV (24 weeks) is expected to produce the greatest number of QALYs. No treatment is expected to produce fewest QALYs. SOF+RBV is ruled out due to extended

dominance. The ICER for LDV/SOF+RBV (24 weeks) versus no treatment is estimated to be £75,793 per QALY gained.

5.5.2.6 Results of additional analysis 6: Threshold analysis for SVR rates of the comparators

Table 58 presents the results for exploratory analysis 6; these show the SVR rate for the next best non-dominated comparator to LDV/SOF required in order for LDV/SOF to achieve an ICER of £30,000 per QALY gained relative to that comparator (see Section 5.5.1.6).

Table 58: Comparator SVR rates required for LDV/SOF to achieve ICER of £30,000 per QALY gained (additional analysis 6, threshold analysis)

Subgroup	Next best non-dominated comparator	SVR needed required to achieve ICER of £30,000/QALY gained	SVR (company base case)
GT1/4 treatment-naïve			
Non-cirrhotic	SMV+PEG-IFN2a+RBV	85.4%	82.0%
Cirrhotic	SMV+SOF	85.1%	92.9%
GT1/4 treatment-experienced			
Non-cirrhotic	No treatment	N/A	0%
Cirrhotic	SMV+SOF	84.7%	92.9%
GT3 treatment-naïve			
Non-cirrhotic	PEG-IFN2a+RBV	21%	71.2%
Cirrhotic	SOF+PEG-IFN2a+RBV	75%	83.3%
GT3 treatment-experienced			
Non-cirrhotic	SOF+RBV	79.6%	87.0%
Cirrhotic	No treatment	N/A	0%

GT – genotype; SVR – sustained virologic response; N/A – not applicable

For the genotype 1/4 treatment-naïve non-cirrhotic subgroup, the SVR rate for SMV+PEG-IFN2a+RBV, the next best comparator to LDV/SOF on the efficiency frontier, would need to increase from the company's estimate of 82% to 85.4% in order for LDV/SOF to achieve an ICER of £30,000 per QALY gained.

For the genotype 1/4 treatment-naïve cirrhotic subgroup, the SVR rate for SMV+SOF, the next best comparator to LDV/SOF on the efficiency frontier, would need to decrease from the company's estimate of 92.9% to 85.1% in order for LDV/SOF to achieve an ICER of £30,000 per QALY gained.

For the genotype 1/4 treatment-experienced non-cirrhotic subgroup, the next best non-dominated comparator to LDV/SOF is no treatment. Given that no treatment is assumed to have an SVR rate of zero, it is not possible for LDV/SOF to achieve an ICER of £30,000 per QALY gained within this subgroup.

For the genotype 1/4 treatment-experienced cirrhotic subgroup, the SVR rate for SMV+SOF, the next best comparator to LDV/SOF on the efficiency frontier, would need to decrease from the company's estimate of 92.9% to a rate of 84.7% in order for LDV/SOF to achieve an ICER of £30,000 per QALY gained.

For the genotype 3 treatment-naïve non-cirrhotic subgroup, the SVR rate for PEG-IFN2a+RBV, the next best comparator to LDV/SOF on the efficiency frontier, would need to decrease from the company's estimate of 71.2% to a rate of 21% in order for LDV/SOF to achieve an ICER of £30,000 per QALY gained.

For the genotype 3 treatment-naïve cirrhotic subgroup, the SVR rate for SOF+PEG-IFN2a+RBV, the next best comparator to LDV/SOF on the efficiency frontier, would need to decrease from the company's estimate of 83.3% to a rate of 75% in order for LDV/SOF to achieve an ICER of £30,000 per QALY gained.

For the genotype 3 treatment-experienced non-cirrhotic subgroup, the SVR rate for SOF+RBV, the next best comparator to LDV/SOF on the efficiency frontier, would need to decrease from the company's estimate of 87% to a rate of 79.6% in order for LDV/SOF to achieve an ICER of £30,000 per QALY gained.

For the genotype 3 treatment-experienced cirrhotic subgroup, the next best comparator to LDV/SOF on the efficiency frontier is no treatment. Given that no treatment is assumed to have an SVR rate of zero, it is not possible for LDV/SOF to achieve an ICER of £30,000 per QALY gained within this subgroup.

5.6 Discussion of the company's submitted cost-effectiveness evidence and additional analyses undertaken by the ERG

As part of their submission to NICE, the company submitted a static state transition model to evaluate the cost-effectiveness of LDV/SOF compared against other antiviral treatment options and no treatment for the treatment of chronic hepatitis C genotypes 1,3 and 4. The company's model includes a total of twelve health states, including two death states to represent the progression of liver disease and the costs and health benefits associated with curing HCV. All analyses adopt a lifetime horizon. The effectiveness of treatment is driven by SVR12 rates which are assumed to determine whether the disease cure is achieved, whilst the cost-effectiveness of antiviral treatment is driven by the costs and benefits of the antiviral treatment and the avoidance of long-term costs and consequences associated with disease progression. Relative treatment benefits are modelled using naïve indirect comparisons between individual trial arms from multiple studies. The company's base case analysis includes

separate economic comparisons for seven subgroups of patients: (i) genotype 1 treatment-naïve; (ii) genotype 4 treatment-naïve; (iii) genotype 1/4 treatment-experienced; (iv) genotype 3 treatment-naïve; (v) genotype 3 treatment-naïve with compensated cirrhosis; (vi) genotype 3 treatment-experienced, IFN ineligible; and, (vii) genotype 3 treatment-experienced IFN-ineligible with compensated cirrhosis. The set of comparator therapies differs by subgroup.

The company's model suggests that within all seven subgroups, LDV/SOF is expected to be the most effective treatment option. Within the genotype 1 treatment-naïve subgroup, the ICER for LDV/SOF versus PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £7,985 per QALY gained. Within the genotype 4 treatment-naïve subgroup, the ICER for LDV/SOF versus PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £12,860.18 per QALY gained. Within the genotype 1/4 treatment-experienced subgroup, the ICER for LDV/SOF versus no treatment (the next most effective non-dominated option) is estimated to be £13,527 per QALY gained. Within the genotype 3 treatment-naïve subgroup, the ICER for LDV/SOF versus PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £26,491 per QALY gained. Within the genotype 3 treatment-naïve with compensated cirrhosis subgroup, the ICER for LDV/SOF+RBV versus SOF+PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £46,491 per QALY gained. Within the genotype 3 treatment-experienced, IFN ineligible subgroup, the ICER for LDV/SOF+RBV versus no treatment (the next most effective non-dominated option) is estimated to be £28,048 per QALY gained. Within the genotype 3 treatment-experienced IFN-ineligible with compensated cirrhosis subgroup, the ICER for LDV/SOF +RBV versus SOF+RBV (the next most effective non-dominated option) is estimated to be £6,210 per QALY gained.

The ERG's critical appraisal of the company's economic evaluation highlighted a number of concerns. These include: (i) deviations from the final NICE scope; (ii) the exclusion of relevant health effects relating to disease transmission and re-infection from the model, (iii) the use of naïve indirect comparisons to inform estimates of effectiveness which may be subject to bias and confounding, (iv) the use of "blended comparisons" which take a weighted average of efficacy and treatment duration for LDV/SOF, (v) uncertainty regarding the HRQoL benefits of LDV/SOF whilst receiving treatment and (vi) discordance between some of the transition probabilities assumed within the company's model and those used within previous models to inform appraisals of other antiviral therapies for the treatment of HCV. In addition, the company's analysis of LDV/SOF in treatment-experienced patients with genotype 3 disease assumes a treatment duration of 15 weeks; this is inconsistent with the recommended 24-week duration stated within the EPAR published by the EMA.

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Following the critical appraisal, the ERG undertook additional analyses to address issues regarding the inappropriate use of blended comparisons and violations of the LDV/SOF license. This additional analysis forms the ERG's base case. In order to examine uncertainty surrounding some of the inputs to the model, additional exploratory analyses were undertaken to examine the impact of alternative assumptions regarding transition probabilities and health gains associated with achieving SVR. It should be noted that all the analyses undertaken by the ERG are deterministic.

The ERG-preferred base case analysis suggests the following results. Within the genotype 1/4 treatment-naïve subgroup, in the non-cirrhotic population, the ICER for LDV/SOF versus SMV+PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £22,676 per QALY gained; within the cirrhotic population, the ICER for LDV/SOF versus SMV+SOF (the next most effective non-dominated option) is estimated to be £97,836 per QALY gained. Within the genotype 1/4 treatment-experienced subgroup, in the non-cirrhotic population, the ICER for LDV/SOF versus no treatment (the next most effective non-dominated option) is estimated to be £16,566 per QALY gained; within the cirrhotic population, the ICER for LDV/SOF versus SMV+SOF (the next most effective non-dominated option) is £92,704 per QALY gained. Within the genotype 3 treatment-naïve subgroup, in the non-cirrhotic population, the ICER for LDV/SOF versus PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £88,853 per QALY gained; within the cirrhotic population, the ICER for LDV/SOF versus SOF+PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £46,149 per QALY gained. Within the genotype 3 treatment-experienced subgroup, in the non-cirrhotic population, the ICER for LDV/SOF versus SOF+RBV (the next most effective non-dominated option) is estimated to be £131,654 per QALY gained; within the cirrhotic population, the ICER for LDV/SOF versus no treatment (the next most effective non-dominated option) is estimated to be £18,238 per QALY gained.

The use of alternative EMA-recommended treatment durations has a substantial impact upon the cost-effectiveness of LDV/SOF. Assuming an alternative treatment duration of 8 weeks LDV/SOF in the genotype 1/4 treatment-naïve non-cirrhotic population, the ICER for LDV/SOF versus PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £8,894 per QALY gained. Assuming an alternative treatment duration of 12 weeks LDV/SOF within the genotype 1/4 treatment-naïve cirrhotic population, the ICER for LDV/SOF versus no treatment (the next most effective non-dominated option) is estimated to be £4,518 per QALY gained. In the treatment experienced GT1/4 subgroup, using an alternative treatment duration of 24 weeks for LDV/SOF, the ICER for LDV/SOF versus SMV+SOF is estimated to be £165,445 per QALY gained.

The ERG base case analyses suggest that when using the treatment durations recommended by the EMA within an "unblended" analysis, the ICERs for LDV/SOF within the non-cirrhotic and cirrhotic populations are very different. Within genotypes 1 and 4, the economic profile of LDV/SOF appears considerably more favourable for non-cirrhotic rather than cirrhotic subgroups. This finding is masked by the company's use of blended comparisons which not only combine efficient and inefficient uses of LDV/SOF (some of which do not reflect the marketing authorisation for the drug). This issue can be illustrated by considering different treatment durations of LDV/SOF within the same population. For example, in an analysis performed by the ERG, within the genotype 1 treatment-naïve subgroup, the ICER for 12-weeks LDV/SOF versus 8-weeks LDV/SOF is estimated to be £157,972 per QALY gained in the non-cirrhotic population, whilst in the cirrhotic population, the ICER for 24-weeks LDV/SOF versus 12-weeks LDV/SOF is approximately £275,796 per QALY gained. The ERG would urge caution in using any analyses which combine multiple indications of LDV/SOF.

The ERG's additional analyses surrounding the company's transition probabilities and the HRQoL increment associated with achieving SVR produces different ICERs; however the overall economic conclusions remain unaffected.

The ERG's analyses which use shorter time horizons result in an increase in the ICERs for LDV/SOF (all of which are higher than £75,000 per QALY gained) compared to those estimated in the ERG-preferred base case analyses. This is unsurprising since the benefits are curtailed to a short time horizon yet the costs of treatment are incurred upfront.

The ERG's threshold analyses around comparator SVR rates suggest that for the GT1/4 treatment naïve non-cirrhotic subgroup, the SVR rate for SMV+PEG-IFN2a+RBV (the next best non-dominated comparator) would need to increase by 3.4% (from 82% to 85.4%) in order for LDV/SOF to achieve an ICER of £30,000 per QALY gained. However, in the other subgroups where ICERs of LDV/SOF are currently greater than £30,000 per QALY gained, the SVR rates of the comparators (the next best non-dominated options) would need to be lower than the company's current estimates in order for LDV/SOF to achieve an ICER of £30,000 per QALY gained.

The ERG notes that based on the company's analysis, the budget impact for the NHS will be substantial in the short-term. Clinical advisors to the ERG suggest that a treatment approach using a highly effective therapy has the possibility to eradicate HCV infection from the UK. Based on clinical advice received by the ERG, the patient numbers needed to treat in order to have a significant impact on disease prevalence is higher than the estimates reported within the CS[1] (around 6000-10000 per year).

6. CONCLUSIONS

6.1 Conclusions on the clinical effectiveness evidence for LDV/SOF

Ten trials of LDV/SOF were included in the CS. These were comprised of three Phase III trials and seven Phase II trials. Trials compared different durations of LDV/SOF, with and without ribavirin (RBV). There were no head-to-head trials comparing LDV/SOF with any of the comparators listed in the final NICE scope. The Phase III trials were designed to compare different durations of LDV/SOF with or without RBV, with only historical controls for comparison.

Data from the trials were mostly from populations with genotype 1 (GT1) disease, although some limited data were available for populations with genotypes 3 and 4. Treatment-naïve and treatment-experienced patients were represented within the trials. All ten trials reported sustained virologic response outcomes at 12-week post-treatment (SVR12). The Phase III trials provided data on resistance, health-related quality of life (HRQoL), and adverse events (AEs). One of the Phase II trials also contributed AE data.

For LDV/SOF treated patients, SVR12 rates ranged from 93% to 99% across all treatment arms for GT1 treatment-naïve patients. SVR12 rates of 93.1% to 99.4% were reported for subgroups of patients with GT1 treatment-naïve non-cirrhotic disease, whilst SVR rates of 94.1% to 100% were reported for subgroups of patients with compensated cirrhosis.

SVR12 rates for LDV/SOF treated GT1 treatment-experienced patients ranged from 94% to 99%. SVR rates ranging from 95.4% to 100% were reported for subgroups of GT1 treatment-experienced non-cirrhotic patients. Within subgroups of patients with compensated cirrhosis, reported SVR rates ranged from 81.8% to 100%

The most common AEs for LDV/SOF-treated patients were fatigue, headache, insomnia, and nausea. Across the treatment arms of the Phase III trials, 67% to 93% of patients experienced at least one AE. Of these, the majority were mild to moderate in severity.

The ERG has several concerns regarding the available evidence base, as presented within the CS:

- Comparator data were not searched systematically as part of the submission, but were based on the company's previous NICE submission of sofosbuvir, with additional targeted searches. Network meta-analyses were not conducted.
- The approach to searching the evidence base for comparator terms and AEs was not systematic, especially given the use of targeted searches and the absence of a full systematic review. Whilst it is unlikely that there are any major omissions in the studies retrieved, there

is potential for evidence to have been missed and the overall reporting of the searches is such that the ERG could not make a fully informed critique of this element of the appraisal.

- The main source of clinical evidence was from three phase III studies. Although open-label, the three Phase III LDV/SOF trials were generally at low risk of bias. However, they were designed to compare different durations of LDV/SOF. SVR12 rates were high across all LDV/SOF treatment arms. AEs were generally mild to moderate, with fatigue and headache being very common.
- The ERG consider that it may have been useful for the company to attempt to analyse the six active interventions from ION-1 and ION-3 in a coherent model and generate the joint posterior distribution of treatment effect for these. Similarly, the ERG believes that a coherent synthesis of the evidence associated with the comparator treatments may have been useful.

6.2 Conclusions on the cost-effectiveness evidence for LDV/SOF

The company's model suggests that within all seven subgroups, LDV/SOF is expected to be the most effective treatment option. Within the genotype 1 treatment-naïve subgroup, the ICER for LDV/SOF versus PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £7,985 per QALY gained. Within the genotype 4 treatment-naïve subgroup, the ICER for LDV/SOF versus PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £12,860.18 per QALY gained. Within the genotype 1/4 treatment-experienced subgroup, the ICER for LDV/SOF versus no treatment (the next most effective non-dominated option) is estimated to be £13,527 per QALY gained. Within the genotype 3 treatment-naïve subgroup, the ICER for LDV/SOF versus PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £26,491 per QALY gained. Within the genotype 3 treatment-naïve with compensated cirrhosis subgroup, the ICER for LDV/SOF+RBV versus SOF+PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £46,491 per QALY gained. Within the genotype 3 treatment-experienced, IFN ineligible subgroup, the ICER for LDV/SOF+RBV versus no treatment (the next most effective non-dominated option) is estimated to be £28,048 per QALY gained. Within the genotype 3 treatment-experienced IFN-ineligible with compensated cirrhosis subgroup, the ICER for LDV/SOF +RBV versus SOF+RBV (the next most effective non-dominated option) is estimated to be £6,210 per QALY gained.

The ERG's critical appraisal of the company's economic evaluation highlighted a number of concerns:

- Deviations from the final NICE scope
- The exclusion of relevant health effects relating to disease transmission and re-infection from the model

- The use of naïve indirect comparisons to inform estimates of effectiveness which may be subject to bias and confounding
- The use of "blended comparisons" which take a weighted average of efficacy and treatment duration for LDV/SOF
- Uncertainty regarding the HRQoL benefits of LDV/SOF whilst receiving treatment
- Discordance between some of the transition probabilities assumed within the company's model and those used within previous models to inform appraisals of other antiviral therapies for the treatment of HCV.
- The company's analysis of LDV/SOF in treatment-experienced patients with genotype 3 disease assumes a treatment duration of 15 weeks; this is inconsistent with the recommended 24-week duration stated within the EPAR published by the EMA.

The ERG-preferred base case analysis suggests the following results. Within the genotype 1/4 treatment-naïve subgroup, in the non-cirrhotic population, the ICER for LDV/SOF versus SMV+PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £22,676 per QALY gained; within the cirrhotic population, the ICER for LDV/SOF versus SMV+SOF (the next most effective non-dominated option) is estimated to be £97,836 per QALY gained. Within the genotype 1/4 treatment-experienced subgroup, in the non-cirrhotic population, the ICER for LDV/SOF versus no treatment (the next most effective non-dominated option) is estimated to be £16,566 per QALY gained; within the cirrhotic population, the ICER for LDV/SOF versus SMV+SOF (the next most effective non-dominated option) is £92,704 per QALY gained. Within the genotype 3 treatment-naïve subgroup, in the non-cirrhotic population, the ICER for LDV/SOF versus PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £88,853 per QALY gained; within the cirrhotic population, the ICER for LDV/SOF versus SOF+PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £46,149 per QALY gained. Within the genotype 3 treatment-experienced subgroup, in the non-cirrhotic population, the ICER for LDV/SOF versus SOF+RBV (the next most effective non-dominated option) is estimated to be £131,654 per QALY gained; within the cirrhotic population, the ICER for LDV/SOF versus no treatment (the next most effective non-dominated option) is estimated to be £18,238 per QALY gained.

The ERG base case analyses suggest that when using the treatment durations recommended by the EMA within an "unblended" analysis, the ICERs for LDV/SOF within the non-cirrhotic and cirrhotic populations are very different. Within genotypes 1 and 4, the economic profile of LDV/SOF appears considerably more favourable for non-cirrhotic rather than cirrhotic subgroups (<£23,000 per QALY gained for non-cirrhotic patients; >£93,000 per QALY gained for cirrhotic patients). Within the

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genotype 3 subgroups, however, the economic profile of LDV/SOF appears considerably more favourable for cirrhotic rather than non-cirrhotic subgroups. The ERG would urge caution in interpreting the results of GT3 treatment experienced patients as they are based on small numbers of patients and use of SVR4 data.

6.3 Implications for research

It is unlikely that head-to-head trials will be undertaken given that LDV/SOF has been licensed based on current Phase III trials and given the high response rates observed within these studies.

The ERG considers that observational data may be useful to assess re-infection rates for patients who have achieved SVR.

Further data on SVR12 outcomes for treatment-experienced genotype 3 patients would add to the existing evidence base.

7. REFERENCES

1. Gilead Sciences Ltd. Manufacturer/sponsor submission of evidence for Single Technology Appraisal (STA) of Ledipasvir-sofosbuvir for treating chronic hepatitis C [ID742]; Gilead Sciences Ltd, Cambridge. 2014.

2. Gilead Sciences Ltd. Responses to ERG clarification questions for Single Technology Appraisal (STA) of ledipasvir-sofosbuvir for treating chronic hepatitis C [ID742]; Gilead Sciences Ltd, Cambridge. 2014.

3. European Association for the Study of the Liver. EASL clinical practice guidelines: Management of hepatitis C virus infection. *Journal of Hepatology* 2014; 60(2):392-420.

4. Miller MH, Agarwal K, Austin A, Brown A, Barclay ST, Dundas P *et al*. Review article: 2014 UK consensus guidelines - hepatitis C management and direct-acting anti-viral therapy. *Alimentary Pharmacology & Therapeutics* 2014; 39(12):1363-1375.

5. National Institute for Health and Care Excellence. Single Technology Appraisal - Ledipasvir-sofosbuvir for treating chronic hepatitis C. Final scope. NICE, London. 2014.

6. European Medicines Agency. European Public Assessment Report - Harvoni. EMA, London. 2014.

7. Wyles DL, Rodriguez-Torres M, Lawitz E, Shiffman ML, Pol S, Herring RW *et al*. All-oral combination of ledipasvir, vedroprevir, tegobuvir, and ribavirin in treatment-naive patients with genotype 1 HCV infection. *Hepatology* 2014; 60(1):56-64.

8. Thompson A, Shiffman ML, Pianko S, Kanwar B, McHutchison JG, Muir AJ *et al*. Ledipasvir + GS-9451 + peginterferon and ribavrin (PR) for six or 12 weeks achieves a high SVR12 in treatment naive genotype 1 IL28B CC patients. *Journal of Gastroenterology and Hepatology* 2013; 28(Supplement S2):173.

9. Thompson A, Han S, Shiffman ML, Rossaro L, Ghalib R, Beavers K *et al*. GS-5885 + GS-9451 + peginterferon and ribavirin (PR) for six or twelve weeks achieves high SVR12 rates in treatment-naive genotype 1 IL28B CC patients. *Journal of Hepatology* 2014; 48th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress, Amsterdam, Netherlands.

10. Mizokami M, Takehara T, Yokosuka O, Sakamoto S, Korenaga M, Mochizuki H, *et al*. 100% SVR12 in Japanese Patients With Chronic Genotype 1 Hepatitis C Virus Infection Receiving Ledipasvir/Sofosbuvir Fixed-Dose Combination for 12 Weeks: Results From a Multicenter Phase 3 Study. *65th Annual Meeting of the American Association for the Study of Liver Diseases Boston, MA Nov 7-11 2014*.

11. Gilead Sciences Inc. Final synoptic clinical study report: GS-US-337-0108 (ION-3): A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination +/- Ribavirin for 8 Weeks and Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks in Treatment-Naive Subjects with Chronic Genotype 1 HCV Infection. 2014.

12. National Instiute for Health and Care Excellence. Hepatitis C (chronic) - sofosbuvir: consultation document. 2014; ID654; NICE, London.

13. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M *et al*. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *New England Journal of Medicine* 2014; 370(20):1889-1898.

14. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, *et al*. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *New England Journal of Medicine* 2014; 370(20):1879-1888.

15. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, *et al*. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *New England Journal of Medicine* 2014; 370(16):1483-1493.

16. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. 2008; http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf:i-281. CRD, University of York.

17. Gilead Sciences Inc. Final clinical study report: GS-US-337-0102 (ION-1): A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination +/- Ribavirin for 12 and 24 Weeks in Treatment-Naive Subjects with Chronic Genotype 1 HCV Infection. 2014.

18. ClinicalTrials.gov. 2014.

19. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, *et al*. Telaprevir for previously untreated chronic hepatitis C virus infection. *New England Journal of Medicine* 2011; 364(25):2402-2416.

20. Poordad F, Lawitz E, Reddy KR, Afdhal NH, Hezode C, Zeuzem S, *et al*. Effects of ribavirin dose reduction vs erythropoietin for boceprevir-related anemia in patients with chronic hepatitis C virus genotype 1 infection--a randomized trial. *Gastroenterology* 2013; 145(5):1035-1044.

21. European Medicines Agency. Summary of product characteristics - Incivo (telaprevir). 2014;1-60.

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

23. Gane EJ, Hyland RH, An D, Pang PS, Symonds WT, McHutchison JG. Ledipasvir/sofosbuvir fixed-dose combination is safe and effective in difficult-to-treat populations including GT 3 patients, decompensated GT 1 patients, and GT 1 patients with prior sofosbuvir experience. *49th Annual Meeting of the European Association for the Study of the Liver London, United Kingdom* April 9-13, 2014.

24. Gilead Sciences Inc. Interim synoptic clinical study report: GS-US-337-0122 (ELECTRON 2): A Phase 2, Multicenter, Open-Label Study to Assess the Efficacy and Safety of Sofosbuvir Containing Regimens for the Treatment of Chronic HCV Infection. 2014.

25. Flamm SL, Everson GT, Charlton M, Denning JM, Arterburn S, Brandt-Sarif T. Ledipasvir/sofosbuvir with ribavirin for the treatment of HCV in patients with decompensated cirrhosis: Preliminary results of a prospective, multicenter study. Abstract 239. *65th Annual Meeting of the American Association for the Study of Liver DiseasesBoston, MA* Nov 7-11 2014.

26. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Subramanian GM, *et al*. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. *Gastroenterology* 2014; 146(3):736-743.

27. Lawitz E, Poordad F, Membreno FE, Hyland RH, Ding X, Hebner C. Once daily sofosbuvir/ledipasvir fixed dose combination with or without ribavirin resulted in 97% sustained virologic response in patients with HCV genotype 1, including patients with cirrhosis: The LONESTAR trial. *Oral Presentation at AASLD* 2013.

28. Bourliere M, Bronowicki J, de Ledinghen V, Hezode C., Zoulim F., Mathurin P. Ledipasvir/sofosbuvir fixed dose combination is safe and efficacious in cirrhotic patients who have previously failed protease-inhibitor based triple therapy. *65th Annual Meeting of the American Association for the Study of Liver Diseases, Boston, MA Nov 7-11 2014*.

29. Osinusi A, Marti M, Townsend K, Nelson A, Kohli A, Silk R, *et al*. Retreatment of relapsers to sofosbuvir/ribavirin with sofosbuvir/ledipasvir: Complete and rapid virologic suppression by Week 4. *Journal of Hepatology Conference: 49th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress 2014*.

30. Osinusi A, Townsend K, Kohli A, Nelson A, Seamon C, Meissner E. A pilot study to evaluate the safety and efficacy of ledipasvir/sofosbuvir in HCV genotype 1 subjects coinfected with HIV infection. 2014.

31. Lawitz E, Lalezari JP, Hassanein T, Kowdley KV, Poordad FF, Sheikh AM, *et al*. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *Lancet Infectious Diseases* 2013; 13(5):401-408.

32. European Medicines Agency. Summary of product characteristics - Sovaldi (sofosbuvir). EMA, London, 2014.

33. Lawitz E, Gane EJ. Sofosbuvir for previously untreated chronic hepatitis C infection. *New England Journal of Medicine* 2013; 369(7):678-679.

34. European Medicines Agency. Summary of product characteristics - Olysio. EMA, London, 2014.

35. Jacobson IM, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, *et al*. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2014; 384(9941):403-413.

36. Manns M, Marcellin P, Poordad F, de Araujo ESA, Buti M., Horsmans Y, *et al*. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2014; 384(9941):414-426.

37. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, *et al*. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *New England Journal of Medicine* 2009; 361(6):580-593.

38. Lawitz E, Sulkowski M, Ghalib R, Rodriguez-Torres M, Younossi SM, Corregidor A, *et al*. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis

C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. *Lancet* 2014; 384(9956):1756-1765.

39. Forns X, Lawitz E, Zeuzem S, Gane E, Bronowicki JP, Andreone P, *et al*. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: a phase 3 trial. *Gastroenterology* 2014; 146(7):1669-1679.

40. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, *et al*. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *New England Journal of Medicine* 2014; 370(21):1993-2001.

41. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, *et al*. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *New England Journal of Medicine* 2013; 368(1):34-44.

42. Gilead Sciences Inc. Final clinical study report: P7977-0422 (PROTON). A multi-center, placebo-controlled, dose ranging study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics following oral administration of PSI-7977 in combination with pegylated interferon and ribavirin in treatment-naive patients with chronic HCV infection genotype 1, and an open label assessment of PSI-7977 in patients with HCV genotypes 2 or 3. Data on file 2013.

43. National Institute for Health and Care Excellence. Hepatitis C (chronic) - simeprevir evaluation report (ID668); NICE, London, 2014.

44. National Institute for Health and Care Excellence. Boceprevir for the treatment of genotype 1 chronic hepatitis C - final appraisal determination. NICE, London, 2012.

45. National Institute for Health and Care Excellence. Telaprevir for the treatment of genotype 1 chronic hepatitis C - final appraisal determination. NICE, London, 2012.

46. Gilead Sciences Inc. Clinical study protocol: GS-US-334-0151. A phase 2, open-label study of sofosbuvir in combination with PEG and ribavirin for 12 weeks in treatment experienced subjects with chronic HCV infection genotype 2 or 3. Data on file 2013.

47. Gane EJ, Hyland RH, Pang PS, Symonds WT, McHutchison JG, Stedman CA. High efficacy of LDV/SOF regimens for 12 weeks for patients with HCV genotype 3 or 6 infection. Abstract LB-11. *65th Annual Meeting of the American Association for the Study of Liver Diseases Boston, MA Nov 7-11 2014*.

48. Kohli A, Sims Z, Marti M, Nelson A, Osinusi A, Bon D. Combination oral, hepatitis C antiviral therapy for 6 or 12 weeks: Results of the SYNERGY trial. *Poster Presented at CROI; March 3-6 2014*.

49. Reddy KR, Everson GT, Flamm SL, Denning JM, Arterburn S, Brandt-Sarif T. Ledipasvir/sofosbuvir with ribavirin for the treatment of HCV in patients with post transplant recurrence: Preliminary results of a prospective, multicenter study. Abstract 8. *2014. Presented at AASLD 2014, November 7-11, Boston, MA, USA.*

50. Martinot-Peignoux M, Stern C, Maylin S, Ripault MP, Boyer N, Leclere L, *et al*. Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin. *Hepatology* 2010; 51(4):1122-1126.

51. Chen J, Florian J, Carter W, Fleischer RD, Hammerstrom TS, Jadhav PR, *et al*. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. *Gastroenterology* 2013; 144(7):1450-1455.

52. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *British Medical Journal* 1996; 313(7052):275-283.

53. McGinnis JJ, Hay JW. The cost effectiveness of hepatitis C treatments in treatment naive genotype 1 patients. *Value in Health* 2014; 17:A274.

54. Jones J, Hartwell D, Baxter L, Harris P. Telaprevir for the treatment of genotype 1 chronic hepatitis C - Evidence Review Group Report commissioned by the NHS R&D HTA Programme on behalf of NICE. 2011; 10/148/01:1-74.

55. Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. *Health Technology Assessment* 2011; 15(17):i-210.

56. Hartwell D, Jones J, Baxter L, Shepherd J. Shortened peginterferon and ribavirin treatment for chronic hepatitis C. *International Journal of Technology Assessment in Health Care* 2012; 28(4):398-406.

57. Grishchenko M, Grieve RD, Sweeting MJ, De Angelis D, Thomson BJ, Ryder SD, *et al*. Cost-effectiveness of pegylated interferon and ribavirin for patients with chronic hepatitis C treated in routine clinical practice. *International Journal of Technology Assessment in Health Care* 2009; 25(2):171-180.

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

59. Mendes D, White K, Cooper K, Bryant J. Boceprevir for the treatment of genotype 1 chronic hepatitis C. Evidence Review Group Report Commissioned by the NHS R&D HTA Programme on Behalf of NICE 2011.

60. Cure S, Bianic F, Gavart S, Curtis S, Lee S, Dusheiko G. Cost-effectiveness of telaprevir in combination with pegylated interferon alpha and ribavirin in treatment-experienced chronic hepatitis C genotype 1 patients. *Journal of Medical Economics* 2014; 17(1):77-87.

61. McEwan P, Kim R, Yuan Y. Assessing the cost utility of response-guided therapy in patients with chronic hepatitis C genotype 1 in the UK using the MONARCH model. *Applied Health Economics and Health Policy* 2013; 11(1):53-63.

62. Miners AH, Martin NK, Ghosh A, Hickman M, Vickerman P. Assessing the cost-effectiveness of finding cases of hepatitis C infection in UK migrant populations and the value of further research. *Journal of Viral Hepatology* 2014; 21(9):616-623.

63. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. NICE, London.

64. HCV UK Research Database. 2014.

65. Vera-Llonch M, Martin M, Aggarwal J, Donepudi M, Bayliss M, Goss T, *et al*. Health-related quality of life in genotype 1 treatment-naive chronic hepatitis C patients receiving telaprevir

combination treatment in the ADVANCE study. *Alimentary Pharmacology & Therapeutics* 2013; 38(2):124-133.

66. Pol S, Sulkowski M, Hassanein T, Gane E, Li N, Mo H, *et al*. Successful retreatment of HCV genotype-1 infected patients who failed prior therapy with peginterferon + ribavirin plus 1 or 2 other direct-acting antiviral agents with sofosbuvir. *49th Annual Meeting of the European Association for the Study of the Liver* 2014; April 9-13, 2014.

67. Thomson BJ, Kwong G, Ratib S, Sweeting M, Ryder SD, De Angelis D, *et al*. Response rates to combination therapy for chronic HCV infection in a clinical setting and derivation of probability tables for individual patient management. *Journal of Viral Hepatology* 2008; 15(4):271-278.

68. Cardoso AC, Moucari R, Figueiredo-Mendes C, Ripault MP, Giuily N, Castelnau C, *et al*. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *Journal of Hepatology* 2010; 52(5):652-657.

69. Siebert U, Sroczynski G, Wasem J, Greiner W, Ravens-Sieberer U, Aidelsburger P, *et al*. Using competence network collaboration and decision-analytic modeling to assess the cost-effectiveness of interferon alpha-2b plus ribavirin as initial treatment of chronic hepatitis C in Germany. *European Journal of Health Economics* 2005; 6(2):112-123.

70. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, *et al*. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997; 112(2):463-472.

71. Wright M, Grieve R, Roberts J, Main J, Thomas HC. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technology Assessment* 2006; 10(21):1-113, iii.

72. Janssen Pharmaceuticals. Simeprevir for the treatment of genotype 1 and genotype 4 chronic hepatitis C: NICE Single Technology Appraisal (STA). 2014.

73. National Institute for Health and Care Excellence. NICE Technology Appraisal Guidance TA 253: Boceprevir for the treatment of genotype 1 chronic hepatitis C. Clinical Drug Investigation. 2012; TA253.

74. Younossi ZM, Sepanova M, Lawits E, Nelson DR, Jacobson IM, Gane EJ, *et al*. Health utilities in patients with chronic hepatitis C treated with sofosbuvir (SOF) containing regimens: Results from positron, fisson, fusion and neutrino studies. *64th Annual Meeting of the American Association for the Study of Liver Diseases* 2013;(various pages).

75. BMJ Group, RCPCH Publications Ltd and the Royal Pharmaceutical Society of Great Britain. British National Formulary (BNF). 2014; August.

76. Department of Health. NHS Reference Costs. 2013. DH, London.

77. Stevenson M, Lloyd-Jones M, Morgan MY, Wong R. Non-invasive diagnostic assessment tools for the detection of liver fibrosis in patients with suspected alcohol-related liver disease: a systematic review and economic evaluation. *Health Technology Assessment* 2012; 16(4):1-174.

78. Longworth L, Singh J. Estimating the cost of liver transplantation in patients diagnosed with chronic hepatitis C and B in the UK. 2014.

79. Gao X, Stephens JM, Carter JA, Haider S, Rustgi VK. Impact of adverse events on costs and quality of life in protease inhibitor-based combination therapy for hepatitis C. *Expert Review of Pharmacoeconomics & Outcomes Research* 2012; 12(3):335-343.

80. Office for National Statistics. National Life Tables, United Kingdom, 2010-2012. 2014.

81. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, *et al*. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value in Health* 2013; 16(2):231-250.

82. National Institute for Health and Care Excellence. Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. 2006; TA200. NICE, London.

83. National Institute for Health and Care Excellence. Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. 2006; TA106. NICE, London.

84. National Institute for Health and Care Excellence. Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C. 2004; TA75. NICE, London.

85. Martin NK, Vickerman P, Miners A, Foster GR, Hutchinson SJ, Goldberg DJ et al. The cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. *Hepatology* 2012; 55(1):49-57.

86. Martin NK, Vickerman P, Hickman M. Mathematical modelling of hepatitis C treatment for injecting drug users. *Journal of Theoretical Biology* 2011; 274(1):58-66.

87. Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. *Journal of Hepatology* 2011; 54(6):1137-1144.

8. APPENDICES

Appendix 1: Ongoing studies of ledipasvir/sofosbuvir for chronic hepatitis C

Study 1:
NCT Number: NCT01768286
Title: Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed-Dose Combination ± Ribavirin for the Treatment of HCV
Recruitment: Completed
Study Results: No Results Available
Conditions: Chronic Hepatitis C Virus
Interventions: Drug: Ledipasvir/sofosbuvir|Drug: RBV
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 3
Enrollment: 441
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-337-0109
First Received: January 10, 2013
Start Date: January 2013
Completion Date: February 2014
Last Updated: April 23, 2014
Last Verified: April 2014
Acronym: ION-2
Results First Received: No Study Results Posted
Primary Completion Date: November 2013
Outcome Measures: Proportion of participants with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)|Incidence of adverse events leading to permanent discontinuation of study drug(s)|Proportion of participants with sustained virologic response at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)|Proportion of participants with HCV RNA < LLOQ on treatment|Change in HCV RNA from Baseline|Proportion of participants with virologic failure
URL: http://ClinicalTrials.gov/show/NCT01768286

Study 2:
NCT Number: NCT02125500
Title: Pilot Study to Assess Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-dose Combination in Treatment Experienced Subjects With Hepatitis C Virus (HCV) Genotype 1 - HIV Co-infection
Recruitment: Not yet recruiting
Study Results: No Results Available
Conditions: Viral Hepatitis C|HIV
Interventions: Drug: Sofosbuvir/Ledipasvir fixed dose
Sponsor/Collaborators: French National Institute for Health and Medical Research-French National Agency for Research on AIDS and Viral Hepatitis (Inserm-ANRS)
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 70
Funded Bys: Other

Study Types: Interventional
Study Designs: Endpoint Classification: Safety/Efficacy Study|Intervention Model: Single Group Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: ANRS HC31 SOFTRIH
First Received: April 24, 2014
Start Date: September 2014
Completion Date: November 2015
Last Updated: July 30, 2014
Last Verified: July 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: November 2015
Outcome Measures: Sustained virologic response 12 weeks after discontinuation of therapy (SVR12), i.e. at week 36.|Adverse clinical and biological events that occur during the treatment and up to 24 weeks after the end of the treatment|Number and causes of poor adherence and treatment interruptions|SVR rate 24 weeks (i.e. W48) after the end of treatment and according to the HCV sub-type|Number of patients with HCV resistance mutations to Sofosbuvir and/or Ledipasvir|HCV viral load|Plasma HIV RNA levels|Assess drug-drug interactions between HCV et HIV drugs|Patient's reported outcomes evaluation
URL: http://ClinicalTrials.gov/show/NCT02125500

Study 3:
NCT Number: NCT01193478
Title: A Multiple Ascending Dose Study of GS 5885 in Previously Untreated Subjects With Genotype 1 Chronic Hepatitis C
Recruitment: Completed
Study Results: No Results Available
Conditions: HCV Infection
Interventions: Drug: GS-5885|Drug: Placebo|Drug: GS-5885|Drug: Placebo|Drug: GS-5885|Drug: Placebo|Drug: GS-5885|Drug: Placebo|Drug: GS-5885|Drug: Placebo|Drug: GS-5885|Drug: Placebo
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult
Phases: Phase 1
Enrollment: 71
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Randomized|Endpoint Classification: Pharmacodynamics Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Double Blind (Subject, Investigator)
Other IDs: GS-US-256-0102
First Received: August 31, 2010
Start Date: August 2010
Completion Date: December 2011
Last Updated: January 18, 2013
Last Verified: January 2013
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: January 2011
Outcome Measures: Number of subjects reporting an adverse event or experiencing a laboratory abnormality|Antiviral activity measures: measured by change in plasma HCV RNA levels form baseline|Measure of GS-5885 plasma concentration over time|Emergence of viral resistance
URL: http://ClinicalTrials.gov/show/NCT01193478

Study 4:
NCT Number: NCT01353248
Title: GS 5885 Administered Concomitantly With GS-9451, Tegobuvir and Ribavirin (RBV) in Chronic Genotype 1 Hepatitis C Virus (HCV) Infection
Recruitment: Completed
Study Results: No Results Available
Conditions: Hepatitis C, Chronic
Interventions: Drug: GS-5885|Drug: Tegobuvir|Drug: GS-9451|Drug: ribavirin tablet|Drug: GS-5885
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 141
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Randomized|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-248-0120
First Received: April 22, 2011
Start Date: May 2011
Completion Date: March 2013
Last Updated: November 26, 2013
Last Verified: November 2013
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: October 2012
Outcome Measures: Sustained virologic response (SVR)|Safety and tolerability|HCV RNA < Lower Limit Of Quantification|Rescue Therapy Substudy SVR|Emergence of viral resistance|Viral dynamics of GS-5885, GS-9451 and Tegobuvir when administered in combination with RBV|Pharmacokinetics of GS-5885, GS-9451 and Tegobuvir when administered in combination with RBV
URL: http://ClinicalTrials.gov/show/NCT01353248

Study 5:
NCT Number: NCT01356160
Title: GS-5885 Alone or in Combination With GS-9451 With Peginterferon Alfa 2a and Ribavirin in Treatment Chronic Genotype 1 Hepatitis C Virus
Recruitment: Completed
Study Results: No Results Available
Conditions: Hepatitis C, Chronic
Interventions: Drug: GS-5885|Drug: GS-9451|Biological: peginterferon alfa-2a|Drug: ribavirin tablet|Drug: GS-9451 Placebo
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 351
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Randomized|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Double Blind (Subject, Investigator)
Other IDs: GS-US-256-0148
First Received: May 2, 2011
Start Date: July 2011
Completion Date: June 2013

Last Updated: January 2, 2014
Last Verified: January 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: June 2013
Outcome Measures: To evaluate the antiviral efficacy of response guided therapy.|To evaluate the safety and tolerability of each regimen.|To characterize viral dynamics of GS-5885 and GS-9451 when administered with PEG and RBV.|To characterize the viral resistance to GS-5885 and GS-9451 when administered in combination with PEG and RBV.|To characterize steady state pharmacokinetics of GS-5885 and GS-9451 when administered with PEG and RBV.
URL: http://ClinicalTrials.gov/show/NCT01356160

Study 6:
NCT Number: NCT01435226
Title: GS-5885, GS-9451, Tegobuvir and Ribovirin in Treatment-Experienced Subjects With Chronic Genotype 1a Or 1b Hepatitis C Virus (HCV) Infection
Recruitment: Completed
Study Results: No Results Available
Conditions: Hepatitis C, Chronic
Interventions: Drug: GS-5885|Drug: GS-9451|Drug: tegobuvir|Drug: placebo to match tegobuvir|Drug: placebo to match RBV|Drug: Ribavirin
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 170
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Other IDs: GS-US-248-0131
First Received: September 13, 2011
Start Date: September 2011
Completion Date: July 2013
Last Updated: November 22, 2013
Last Verified: November 2013
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: January 2013
Outcome Measures: Safety and Tolerability|Antiviral Activity|Viral Dynamics|Composite (or Profile) of Pharmacokinetics Composite (or Profile) of Pharmacokinetics|Antiviral Efficacy
URL: http://ClinicalTrials.gov/show/NCT01435226

Study 7:
NCT Number: NCT01371578
Title: Oral Antivirals (GS-5885, Tegobuvir, and/or GS-9451) With Peginterferon Alfa 2a and Ribavirin in Treatment Experienced Subjects With Chronic Genotype 1 Hepatitis C Virus Infection
Recruitment: Completed
Study Results: No Results Available
Conditions: Hepatitis C, Chronic
Interventions: Drug: GS-5885 tablet|Drug: GS-9451 tablet|Biological: peginterferon alfa-2a|Drug: ribavirin tablet

Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 163
Funded Bys: Industry
Study Types: Interventional
Study Designs: Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-256-0124
First Received: June 9, 2011
Start Date: July 2011
Completion Date: March 2013
Last Updated: January 14, 2014
Last Verified: January 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: March 2013
Outcome Measures: Sustained Virologic Response (SVR)|Sustained Virologic Response(SVR) of each regimen administered for 24 to 48 weeks|Safety and Tolerability|Characterize the viral dynamics of GS-5885, GS-9451 when administered in combination with PEG and RBV|Characterize the pharmacokinetics of GS-5885 and GS-9451 when administered in combination with PEG and RBV|Emergence of Viral Resistance
URL: http://ClinicalTrials.gov/show/NCT01371578

Study 8:
NCT Number: NCT01434498
Title: GS-5885, GS-9451, Tegobuvir and Ribavirin (RBV) in Interferon Ineligible or Intolerant Subjects With Chronic Genotype 1a or 1b Hepatitis C Virus (HCV) Infection
Recruitment: Completed
Study Results: No Results Available
Conditions: Chronic Genotype 1a or 1b HCV Infection
Interventions: Drug: GS-5885 tablet|Drug: GS-9451 tablet|Drug: tegobuvir capsule|Drug: ribavirin tablet|Drug: placebo matching ribavirin tablet|Device: placebo matching tegobuvir capsule
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 163
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Other IDs: GS-US-248-0132
First Received: September 9, 2011
Start Date: September 2011
Completion Date: January 2013
Last Updated: November 26, 2013
Last Verified: November 2013
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: January 2013

Outcome Measures: Safety and Tolerability|Antiviral Activity|Viral Dynamics|Composite (or Profile) of Pharmacokinetics
URL: http://ClinicalTrials.gov/show/NCT01434498

Study 9:
NCT Number: NCT01701401
Title: Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed-Dose Combination (FDC) With and Without Ribavirin for the Treatment of HCV
Recruitment: Completed
Study Results: No Results Available
Conditions: Chronic Hepatitis C Virus
Interventions: Drug: LDV/SOF|Drug: RBV
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 3
Enrollment: 870
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-337-0102|2012-003387-43
First Received: October 2, 2012
Start Date: September 2012
Completion Date: April 2014
Last Updated: May 12, 2014
Last Verified: May 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: February 2014
Outcome Measures: Proportion of participants with sustained virologic response (SVR) 12 weeks after discontinuation of study drug|Incidence of any AE leading to permanent discontinuation of study|Proportion of participants with SVR at 4 and 24 weeks after discontinuation of study drug|Proportion of participants with HCV RNA < LLOQ on treatment|Change from baseline in HCV RNA|Proportion of participants with virologic failure
URL: http://ClinicalTrials.gov/show/NCT01701401

Study 10:
NCT Number: NCT01384383
Title: GS-5885, GS-9451 With Peginterferon Alfa 2a (PEG) and Ribavirin in Treatment-Naïve Subjects With Chronic Genotype 1 Hep C Virus Infection and IL28B CC Genotype
Recruitment: Terminated
Study Results: No Results Available
Conditions: Chronic Hepatitis C
Interventions: Drug: GS-5885|Drug: GS-9451|Drug: RBV|Drug: PEG
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 248
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label

Other IDs: GS-US-248-0121
First Received: June 22, 2011
Start Date: August 2011
Completion Date: June 2013
Last Updated: January 2, 2014
Last Verified: January 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: June 2013
Outcome Measures: Sustained virologic response (SVR)|Safety and tolerability of therapy|Virologic response|Compare SVR|Viral resistance
URL: http://ClinicalTrials.gov/show/NCT01384383

Study 11:
NCT Number: NCT01878799
Title: Study of A Combination Pill With GS-7977 and GS-5885 for Hepatitis C in People With HIV
Recruitment: Completed
Study Results: No Results Available
Conditions: Hepatitis C|HIV
Interventions: Drug: GS-7977/GS- 5885 FDC
Sponsor/Collaborators: National Institute of Allergy and Infectious Diseases (NIAID)|National Institutes of Health Clinical Center (CC)
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 63
Funded Bys: NIH
Study Types: Interventional
Study Designs: Allocation: Non-Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Single Group Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: 130159|13-I-0159
First Received: June 14, 2013
Start Date: June 2013
Completion Date: September 2014
Last Updated: September 20, 2014
Last Verified: September 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: September 2014
Outcome Measures: To assess the safety, tolerability and efficacy of a fixed dose combination (FDC) of GS-7977/GS-5885 tablets for 12 weeks in HIV/HCV GT-1 coinfected subjects who are IFN-treatment na(SqrRoot) ve.|To assess the fitness of NS5A/B viral mutants in vivo in the presence or absence of a fixed dose combination of GS-7977/ GS-5885 in vitro by performing NS5A/B site directed mutagenesis.|To compare HCV quasispecies evolution from baseline and throughout 12 weeks of treatment (especially during relapse or viral breakthrough) and assess the influence on virologic response to treatment in HIV/HCV GT-1 coinfected patients.|To compare the immunologic, virologic and host genetic/proteomic predictors of response to treatment with a fixed dose combination of GS-7977/GS-5885 in subjects treated for 12 weeks.
URL: http://ClinicalTrials.gov/show/NCT01878799

Study 12:
NCT Number: NCT01924949
Title: An Open-Label Study of Ledipasvir/Sofosbuvir Fixed-Dose Combination in Subjects With Nosocomial Genotype 1 HCV Infection.
Recruitment: Completed
Study Results: No Results Available
Conditions: Hepatitis C
Interventions: Drug: LDV/SOF
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 5
Funded Bys: Industry
Study Types: Interventional
Study Designs: Endpoint Classification: Safety/Efficacy Study|Intervention Model: Single Group Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-337-0125
First Received: August 14, 2013
Start Date: July 2013
Completion Date: August 2014
Last Updated: August 20, 2014
Last Verified: August 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: May 2014
Outcome Measures: Proportion of participants with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)|Proportion of participants who permanently discontinue study drug due to an adverse event|Proportion of participants with sustained virologic response at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)|Proportion of participants with HCV RNA < LLOQ while on treatment|HCV RNA change from Baseline|Proportion of participants with virologic failure
URL: http://ClinicalTrials.gov/show/NCT01924949

Study 13:
NCT Number: NCT01851330
Title: Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed-Dose Combination ± Ribavirin for the Treatment of HCV (ION-3)
Recruitment: Completed
Study Results: No Results Available
Conditions: Chronic Hepatitis C Virus
Interventions: Drug: LDV/SOF|Drug: RBV
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 3
Enrollment: 647
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-337-0108
First Received: May 3, 2013
Start Date: May 2013

Completion Date: March 2014
Last Updated: March 10, 2014
Last Verified: March 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: November 2013
Outcome Measures: Proportion of participants with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)|Incidence of adverse events leading to permanent discontinuation of study drug(s)|Proportion of participants with sustained virologic response at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)|Proportion of participants with HCV RNA < LLOQ on treatment|Change in HCV RNA from Baseline|Proportion of participants with virologic failure
URL: http://ClinicalTrials.gov/show/NCT01851330

Study 14:
NCT Number: NCT01984294
Title: Ledipasvir/Sofosbuvir Fixed-Dose Combination With Ribavirin or GS-9669 in Subjects With Chronic Genotype 1 HCV Infection
Recruitment: Completed
Study Results: No Results Available
Conditions: Chronic HCV Infection
Interventions: Drug: LDV/SOF|Drug: RBV|Drug: GS-9669
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 101
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-337-0133
First Received: November 8, 2013
Start Date: October 2013
Completion Date: July 2014
Last Updated: August 1, 2014
Last Verified: August 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: April 2014
Outcome Measures: Proportion of participants with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)|Proportion of participants who discontinue study drug due to an adverse event|Proportion of participants with sustained virologic response (SVR) at 2, 4, 8, and 24 weeks after discontinuation of therapy (SVR2, SVR4, SVR8, and SVR24)|Proportion of participants experiencing viral breakthrough|Proportion of participants experiencing viral relapse
URL: http://ClinicalTrials.gov/show/NCT01984294

Study 15:
NCT Number: NCT01726517
Title: Safety and Efficacy of LDV/SOF Fixed-Dose Combination (FDC) ± Ribavirin in HCV Genotype 1 Subjects
Recruitment: Completed
Study Results: No Results Available
Conditions: Chronic Hepatitis C Virus
Interventions: Drug: LDV/SOF|Drug: RBV

Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 100
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-337-0118
First Received: November 10, 2012
Start Date: October 2012
Completion Date: January 2014
Last Updated: March 17, 2014
Last Verified: March 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: July 2013
Outcome Measures: Proportion of participants with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)|Incidence of adverse events leading to permanent discontinuation of study drug(s)|Proportion of participants with sustained virologic response at 2, 4, 8, and 24 weeks after discontinuation of therapy (SVR2, SVR4, SVR8, and SVR24)|Proportion of participants experiencing viral breakthrough|Proportion of participants experiencing viral relapse
URL: http://ClinicalTrials.gov/show/NCT01726517

Study 16:
NCT Number: NCT01965535
Title: Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination ± Ribavirin in Cirrhotic Subjects With Chronic Genotype 1 HCV Infection
Recruitment: Active, not recruiting
Study Results: No Results Available
Conditions: HCV Infection
Interventions: Drug: SOF/LDV|Drug: RBV|Drug: Placebo to match SOF/LDV|Drug: Placebo to match RBV
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 150
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Other IDs: GS-US-337-0121|2013-002296-17
First Received: October 16, 2013
Start Date: October 2013
Completion Date: December 2014
Last Updated: June 19, 2014
Last Verified: June 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: September 2014

Outcome Measures: Proportion of participants with sustained virologic response (SVR) at 12 weeks post-treatment (SVR12)|Proportion of participants with HCV RNA < LLOQ at 4 weeks (SVR4) and 24 weeks (SVR24) post-treatment.|Proportion of participants with HCV RNA < LLOQ while on treatment|Change in HCV RNA|The proportion of patients with virologic failure
URL: http://ClinicalTrials.gov/show/NCT01965535

Study 17:
NCT Number: NCT02249182
Title: Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination in Adolescents and Children With Chronic HCV-Infection
Recruitment: Not yet recruiting
Study Results: No Results Available
Conditions: Hepatitis C Virus Infection
Interventions: Drug: LDV/SOF
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Child
Phases: Phase 2
Enrollment: 200
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Non-Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-337-1116
First Received: September 23, 2014
Start Date: October 2014
Completion Date: June 2018
Last Updated: September 23, 2014
Last Verified: September 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: June 2018
Outcome Measures: For the PK Lead-in Phase, PK parameters of GS-331007 and LDV as measured by AUCtau to determine the appropriate LDV/SOF FDC dose.|For the Treatment Phase, any adverse event leading to permanent discontinuation of study drug(s)|For the Treatment Phase, proportion of participants with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)|For the PK Lead-in Phase, early viral kinetics and PK profiles of GS-331007, sofosbuvir, and ledipasvir|For the PK Lead-in Phase, adverse events leading to permanent discontinuation of study drug(s)|For the Treatment Phase, growth and development measurements such as height, weight, and Tanner Stage Assessment|For the Treatment Phase, proportion of participants with sustained virologic response (SVR) at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)|For the Treatment Phase, proportion of participants experiencing viral breakthrough|For the Treatment Phase, proportion of participants experiencing viral relapse|For the Treatment Phase, HCV RNA change from baseline|For the Treatment Phase, alanine aminotransferase (ALT) normalization|For the Treatment Phase, viral kinetic parameters
URL: http://ClinicalTrials.gov/show/NCT02249182

Study 18:
NCT Number: NCT02226549
Title: Ledipasvir/Sofosbuvir Fixed-Dose Combination and Vedroprevir With or Without Ribavirin in Treatment-Experienced Participants With Chronic Genotype 1 HCV Infection and Cirrhosis
Recruitment: Active, not recruiting
Study Results: No Results Available

Conditions: Hepatitis C Virus Infection
Interventions: Drug: LDV/SOF|Drug: VDV|Drug: RBV
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 50
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-337-1512
First Received: August 25, 2014
Start Date: July 2014
Completion Date: July 2015
Last Updated: October 7, 2014
Last Verified: October 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: July 2015
Outcome Measures: Proportion of participants with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)|Incidence of any adverse event leading to permanent discontinuation of study drug(s)|Proportion of participants with sustained virologic response 4 weeks after discontinuation of therapy (SVR4)
URL: http://ClinicalTrials.gov/show/NCT02226549

Study 19:
NCT Number: NCT02251717
Title: Safety and Efficacy of Ledipasvir/Sofosbuvir (LDV/SOF) Fixed Dose Combination (FDC) for 12 or 24 Weeks in Kidney Transplant Recipients With Chronic HCV Infection
Recruitment: Not yet recruiting
Study Results: No Results Available
Conditions: Hepatitis C Virus Infection
Interventions: Drug: LDV/SOF
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 150
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-337-1406|2014-002121-35
First Received: September 25, 2014
Start Date: September 2014
Completion Date: March 2016
Last Updated: September 25, 2014
Last Verified: September 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: January 2016
Outcome Measures: Proportion of participants with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)|Incidence of any adverse events leading to permanent

discontinuation of study drug|Proportion of participants with sustained virologic response 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)|Proportion of participants with virologic failure
URL: http://ClinicalTrials.gov/show/NCT02251717

Study 20:
NCT Number: NCT02219685
Title: Ledipasvir/Sofosbuvir Fixed-Dose Combination on Cerebral Metabolism and Neurocognition in Treatment-Naive and Treatment-Experienced Participants With Chronic Genotype 1 HCV Infection
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Hepatitis C Virus Infection
Interventions: Drug: LDV/SOF|Drug: Placebo to match LDV/SOF
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult
Phases: Phase 2
Enrollment: 40
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Other IDs: GS-US-337-1445
First Received: August 15, 2014
Start Date: August 2014
Completion Date: February 2016
Last Updated: October 6, 2014
Last Verified: October 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: November 2015
Outcome Measures: Change from pretreatment assessment in MRS metabolic ratios at 4 weeks after discontinuation of therapy|Change from pretreatment assessment in neurocognitive function at 4 weeks after discontinuation of therapy|Proportion of participants with sustained virologic response (SVR) at 4, 12, and 24 weeks after discontinuation of therapy (SVR4, SVR12, and SVR24)|Change from pretreatment assessment in neurocognitive function at 24 weeks after discontinuation of therapy|Change from pretreatment assessment in health-related quality of life at 4 and 24 weeks after discontinuation of therapy|Change from pretreatment assessment in mood-related assessment at 4 and 24 weeks after discontinuation of therapy
URL: http://ClinicalTrials.gov/show/NCT02219685

Study 21:
NCT Number: NCT01938430
Title: Ledipasvir/Sofosbuvir Fixed-Dose Combination + Ribavirin in Subjects With Chronic HCV With Advanced Liver Disease or Post-Liver Transplant
Recruitment: Active, not recruiting
Study Results: No Results Available
Conditions: Chronic HCV Infection
Interventions: Drug: LDV/SOF FDC|Drug: RBV
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior

Phases: Phase 2
Enrollment: 400
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Non-Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-337-0123
First Received: September 5, 2013
Start Date: September 2013
Completion Date: February 2015
Last Updated: May 15, 2014
Last Verified: May 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: November 2014
Outcome Measures: Proportion of participants with sustained virologic response (SVR12), defined as HCV RNA < lower limit of quantitation (LLOQ) 12 weeks after last dose of study drug|Proportion of participants who discontinue study drug due to an adverse event|Proportion of participants with sustained virologic response (SVR) at 2, 4, 8 and 24 weeks after discontinuation of therapy (SVR2, SVR4, SVR8 and SVR24)|Proportion of participants who have HCV RNA < LLOQ by visit while on treatment|HCV RNA levels and change from Day 1 through Week 8|Proportion of participants with virologic failure|Change in model for end-stage liver disease (MELD) and Child-Pugh-Turcotte (CPT) scores|Proportion of participants with post-transplant virologic response
URL: http://ClinicalTrials.gov/show/NCT01938430

Study 22:
NCT Number: NCT02010255
Title: Ledipasvir/Sofosbuvir Fixed-Dose Combination Plus Ribavirin in Subjects With Chronic HCV With Advanced Liver Disease or Post-Liver Transplant
Recruitment: Active, not recruiting
Study Results: No Results Available
Conditions: Chronic HCV Infection
Interventions: Drug: LDV/SOF|Drug: RBV
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 400
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Non-Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-337-0124|2013-002802-30
First Received: December 9, 2013
Start Date: January 2014
Completion Date: August 2015
Last Updated: September 29, 2014
Last Verified: September 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: May 2015
Outcome Measures: Proportion of participants with sustained virologic response 12 weeks after last dose of study drug (SVR12)|Proportion of participants who discontinue study drug due to an adverse event|Proportion of participants with sustained virologic response (SVR) 2, 4, 8, and 24 weeks after

last dose of study drug (SVR2, SVR4, SVR8 and SVR24)|Proportion of participants who have HCV RNA < LLOQ by visit while on treatment|HCV RNA levels and change from Day 1 through Week 8|Proportion of participants with virologic failure|Change in model for end-stage liver disease (MELD) and Child-Pugh-Turcotte (CPT) scores|Proportion of participants with post-transplant virologic response
URL: http://ClinicalTrials.gov/show/NCT02010255

Study 23:
NCT Number: NCT02021656
Title: Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed-Dose Combination in Korean and Taiwanese Participants With Chronic Genotype 1 HCV Infection
Recruitment: Active, not recruiting
Study Results: No Results Available
Conditions: Chronic HCV Infection
Interventions: Drug: LDV/SOF
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 3
Enrollment: 360
Funded Bys: Industry
Study Types: Interventional
Study Designs: Endpoint Classification: Safety/Efficacy Study|Intervention Model: Single Group Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-337-0131
First Received: December 20, 2013
Start Date: December 2013
Completion Date: June 2017
Last Updated: September 2, 2014
Last Verified: September 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: March 2017
Outcome Measures: Proportion of participants with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)|Incidence of adverse events leading to permanent discontinuation of study drug|Proportion of participants with sustained virologic response at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)|Proportion of participants experiencing viral breakthrough|Proportion of participants experiencing viral relapse|HCV RNA change from baseline
URL: http://ClinicalTrials.gov/show/NCT02021656

Study 24:
NCT Number: NCT01975675
Title: Efficacy and Safety of Sofosbuvir/Ledipasvir ± Ribavirin in Japanese Participants With Chronic Genotype 1 HCV Infection
Recruitment: Completed
Study Results: No Results Available
Conditions: Chronic HCV Infection
Interventions: Drug: SOF/LDV|Drug: RBV
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 3
Enrollment: 341
Funded Bys: Industry

Study Types: Interventional
Study Designs: Allocation: Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-337-0113
First Received: October 29, 2013
Start Date: October 2013
Completion Date: August 2014
Last Updated: October 10, 2014
Last Verified: October 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: June 2014
Outcome Measures: Proportion of participants with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)|Proportion of participants who permanently discontinue study drug due to an adverse event|Proportion of participants with sustained virologic response at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)|Proportion of participants experiencing viral breakthrough|Proportion of participants experiencing viral relapse
URL: http://ClinicalTrials.gov/show/NCT01975675

Study 25:
NCT Number: NCT02081079
Title: Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed-Dose Combination in Treatment-Naïve and Treatment-Experienced Subjects With Chronic Genotype 4 or 5 HCV Infection
Recruitment: Active, not recruiting
Study Results: No Results Available
Conditions: Chronic Genotype 4 HCV|Chronic Genotype 5 HCV
Interventions: Drug: LDV/SOF
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 80
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Non-Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-337-1119|2013-003978-27
First Received: March 5, 2014
Start Date: April 2014
Completion Date: March 2015
Last Updated: June 12, 2014
Last Verified: June 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: December 2014
Outcome Measures: Proportion of participants with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)|Incidence of adverse events leading to permanent discontinuation of study drug|Proportion of participants with sustained virologic response at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)|Proportion of participants experiencing viral breakthrough|Proportion of participants experiencing viral relapse|HCV RNA change from baseline
URL: http://ClinicalTrials.gov/show/NCT02081079

Study 26:
NCT Number: NCT02120300
Title: Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed-Dose Combination and Sofosbuvir + Ribavirin for Subjects With Chronic Hepatitis C Virus (HCV) and Inherited Bleeding Disorders
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Chronic HCV Infection
Interventions: Drug: LDV/SOF|Drug: Sofosbuvir|Drug: Ribavirin
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 125
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Non-Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-334-1274
First Received: April 18, 2014
Start Date: April 2014
Completion Date: August 2015
Last Updated: October 20, 2014
Last Verified: October 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: August 2015
Outcome Measures: Proportion of participants with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)|Incidence of adverse events leading to permanent discontinuation of study drug(s)|Proportion of participants with sustained virologic response (SVR) at 4 weeks after discontinuation of therapy (SVR4)|Proportion of participants with HCV RNA < LLOQ on treatment|HCV RNA change from baseline|Proportion of participants with virologic failure|For HIV-1/HCV co-infected participants, the proportion of subjects that maintain HIV-1 RNA < 50 copies/mL while on HCV treatment|For HIV-1/HCV co-infected participants, change from baseline of serum creatinine at the end of treatment|For HIV-1/HCV co-infected participants, change from baseline of serum creatinine at posttreatment Week 12
URL: http://ClinicalTrials.gov/show/NCT02120300

Study 27:
NCT Number: NCT02073656
Title: Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed-Dose Combination for 12 Weeks in Subjects With Chronic Genotype 1 or 4 HCV and HIV-1 Co-infection
Recruitment: Active, not recruiting
Study Results: No Results Available
Conditions: Hepatitis C Virus|HIV
Interventions: Drug: LDV/SOF|Drug: RBV
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 3
Enrollment: 300
Funded Bys: Industry
Study Types: Interventional

Study Designs: Allocation: Non-Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Single Group Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-337-0115
First Received: February 25, 2014
Start Date: February 2014
Completion Date: June 2016
Last Updated: June 11, 2014
Last Verified: June 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: March 2015
Outcome Measures: Proportion of participants with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)|Incidence of adverse events leading to permanent discontinuation of study drug(s)|Proportion of participants with sustained virologic response at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)|Proportion of participants with HCV RNA < LLOQ on treatment|Change in HCV RNA from Baseline|Proportion of participants with virologic failure|For retreatment group only: Proportion of participants with sustained virologic response at 4, 12 and 24 weeks after discontinuation of therapy (SVR4, SVR12, and SVR24)|Proportion of participants that maintain HIV-1 RNA < 50 copies/mL while on treatment|Change from baseline of serum creatinine at end of treatment, posttreatment weeks 12 and 24
URL: http://ClinicalTrials.gov/show/NCT02073656

Study 28:
NCT Number: NCT01987453
Title: Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed-Dose Combination ± Ribavirin in Subjects With Chronic Genotype 1 HCV Who Participated in a Prior Gilead-Sponsored HCV Treatment Study
Recruitment: Enrolling by invitation
Study Results: No Results Available
Conditions: HCV Infection
Interventions: Drug: LDV/SOF|Drug: RBV
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 100
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Non-Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-337-1118|2014-001245-24
First Received: November 12, 2013
Start Date: November 2013
Completion Date: January 2016
Last Updated: October 22, 2014
Last Verified: October 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: October 2015
Outcome Measures: Proportion of participants with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)|Incidence of adverse events leading to permanent discontinuation of study drug|Proportion of participants with sustained virologic response (SVR) at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)|Proportion of participants with HCV RNA <

LLOQ while on treatment|Change in HCV RNA from Baseline|Proportion of participants with virologic failure
URL: http://ClinicalTrials.gov/show/NCT01987453

Study 29:
NCT Number: NCT01826981
Title: Sofosbuvir Containing Regimens for the Treatment of Chronic HCV Infection in Subjects With Chronic Genotype 1, 2, 3, or 6 HCV Infection
Recruitment: Active, not recruiting
Study Results: No Results Available
Conditions: Chronic Hepatitis C
Interventions: Drug: LDV/SOF FDC|Drug: SOF|Drug: RBV|Drug: PEG|Drug: GS-9669|Drug: GS-5816
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 410
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-337-0122
First Received: April 1, 2013
Start Date: April 2013
Completion Date: June 2015
Last Updated: August 14, 2014
Last Verified: August 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: March 2015
Outcome Measures: Proportion of participants with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)|Proportion of participants with adverse events leading to permanent discontinuation of study drug(s)|Proportion of participants with SVR through posttreatment Week 24|Proportion of participants with on-treatment virologic failure and relapse
URL: http://ClinicalTrials.gov/show/NCT01826981

Study 30:
NCT Number: NCT01805882
Title: Combination Therapy for Chronic Hepatitis C Infection
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Hepatitis C, Chronic
Interventions: Drug: Fixed Dose GS-7977/GS-5885|Drug: FDC with GS-9451|Drug: FDC with GS-9669
Sponsor/Collaborators: National Institute of Allergy and Infectious Diseases (NIAID)|National Institutes of Health Clinical Center (CC)
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 325
Funded Bys: NIH
Study Types: Interventional

Study Designs: Allocation: Non-Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: 130066|13-I-0066
First Received: March 5, 2013
Start Date: January 2013
Completion Date: December 2015
Last Updated: September 27, 2014
Last Verified: August 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: December 2015
Outcome Measures: The incidence and severity of adverse events (AEs) during and following treatment with GS-7977 in combination with GS-5885, GS-9669 or GS-9451 and the proportion of subjects who achieve SVR12.|Correlation and comparison of early viral kinetics with response to treatment; host and viral factors influencing response, comparison of HCV viral kinetics and pharmacodynamics in HCV treatment naive vs. null responders.
URL: http://ClinicalTrials.gov/show/NCT01805882

Study 31:
NCT Number: NCT01260350
Title: Open-Labeled Study of PSI-7977 and RBV With and Without PEG-IFN in Treatment-Naïve Patients With HCV GT2 or GT3
Recruitment: Completed
Study Results: No Results Available
Conditions: Chronic Hepatitis C Infection
Interventions: Drug: SOF|Drug: RBV|Drug: PEG|Drug: LDV|Drug: GS-9669|Drug: LDV/SOF
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 292
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: P7977-0523|Medsafe
First Received: December 13, 2010
Start Date: December 2010
Completion Date: December 2013
Last Updated: May 28, 2014
Last Verified: May 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: October 2013
Outcome Measures: Safety and Tolerability|HCV RNA|Sustained Virologic Response (SVR)|Resistance|Duration of PEG-IFN therapy|Pharmacokinetics
URL: http://ClinicalTrials.gov/show/NCT01260350

Study 32:
NCT Number: NCT02202980
Title: Efficacy and Safety of Oral Regimens for the Treatment of Chronic HCV Infection
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Chronic Hepatitis C

Interventions: Drug: LDV/SOF|Drug: RBV
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases: Phase 2
Enrollment: 125
Funded Bys: Industry
Study Types: Interventional
Study Designs: Allocation: Non-Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: GS-US-337-1468
First Received: July 25, 2014
Start Date: August 2014
Completion Date: January 2016
Last Updated: August 14, 2014
Last Verified: August 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: August 2015
Outcome Measures: Proportion of participants with sustained virologic response 12 weeks after discontinuation of therapy (SVR12)|Incidence of any adverse events leading to permanent discontinuation of study drug(s)|Proportion of participants with sustained virologic response 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24)|Proportion of participants with on treatment virologic failure and relapse
URL: http://ClinicalTrials.gov/show/NCT02202980

Study 33:
NCT Number: NCT01457755
Title: Gilead Sustained Virologic Response (SVR) Registry
Recruitment: Enrolling by invitation
Study Results: No Results Available
Conditions: Hepatitis C, Chronic
Interventions:
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases:
Enrollment: 4000
Funded Bys: Industry
Study Types: Observational
Study Designs: Observational Model: Cohort|Time Perspective: Prospective
Other IDs: GS-US-248-0122|2011-000945-19
First Received: October 4, 2011
Start Date: September 2011
Completion Date: July 2023
Last Updated: August 11, 2014
Last Verified: August 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: July 2023
Outcome Measures: Sustained Virologic Response|Subsequent detection of HCV RNA|Clinical Progression of liver disease|Development of hepatocellular carcinoma (HCC)
URL: http://ClinicalTrials.gov/show/NCT01457755

Study 34:
NCT Number: NCT01457768
Title: A Gilead Sequence Registry of Subjects Who Did Not Achieve Sustained Virologic Response
Recruitment: Enrolling by invitation
Study Results: No Results Available
Conditions: Hepatitis C, Chronic
Interventions:
Sponsor/Collaborators: Gilead Sciences
Gender: Both
Age Groups: Adult|Senior
Phases:
Enrollment: 800
Funded Bys: Industry
Study Types: Observational
Study Designs: Observational Model: Cohort|Time Perspective: Prospective
Other IDs: GS-US-248-0123|2011-000946-39
First Received: October 4, 2011
Start Date: September 2011
Completion Date: July 2023
Last Updated: August 11, 2014
Last Verified: August 2014
Acronym: null
Results First Received: No Study Results Posted
Primary Completion Date: July 2023
Outcome Measures: Viral Activity|Clinical progression of liver disease|Development of hepatocellular carcinoma (HCC)
URL: http://ClinicalTrials.gov/show/NCT01457768

Study 35:
NCT Number: NCT02064049
Title: Surveillance and Treatment of Prisoners With Hepatitis C
Recruitment: Not yet recruiting
Study Results: No Results Available
Conditions: Hepatitis C
Interventions: Drug: Sofosbuvir and ribavirin
Sponsor/Collaborators: Kirby Institute
Gender: Male
Age Groups: Adult|Senior
Phases: Phase 4
Enrollment: 650
Funded Bys: Other
Study Types: Interventional
Study Designs: Allocation: Non-Randomized|Endpoint Classification: Safety/Efficacy Study|Intervention Model: Parallel Assignment|Primary Purpose: Treatment|Masking: Open Label
Other IDs: VHCRP1302
First Received: February 12, 2014
Start Date: September 2014
Completion Date: December 2017
Last Updated: May 1, 2014
Last Verified: May 2014
Acronym: SToP-C
Results First Received: No Study Results Posted
Primary Completion Date: December 2017

Outcome Measures: Hepatitis C virus (HCV) incidence|Hepatitis C virus prevalence|SVR12|ETR|Rapid Virological Response (RVR)|Very rapid virological response (vRVR)|Treatment adherence|Number of patients with adverse events|Treatment uptake|On-treatment change in illicit drug use|HCV reinfection rate
URL: http://ClinicalTrials.gov/show/NCT02064049

Appendix 2: Description of ERG exploratory analysis

ERG analysis 1: ERG-preferred base case using "unblended" EMA-recommended treatment durations for LDV/SOF

The ERG performed "unblended" analyses using the company's model based on EMA recommended treatment durations for LDV/SOF+/-RBV; this analysis forms the ERG's preferred base case. This involved using the SVR rates for LDV/SOF corresponding to the treatment duration recommended by EMA based on the population genotype and cirrhotic status. This was achieved by changing the cells in sheets 'Treatment duration' and 'Treatment efficacy' (see below).

SVR rates and treatment duration used within the ERG base case analysis (EMA-recommended unblended LDV/SOF treatment)

Subgroup	Duration	SVR	Cells changed in the company's model
GT1/4 treatment-naïve			
non-cirrhotic	12 weeks	97.7%	N52 to 0% in sheet 'Treatment duration' N54 to 100% in sheet 'Treatment duration' H151 to 97.7% in sheet 'Treatment efficacy'
cirrhotic	24 weeks	97.0%	N100 to 0% in sheet 'Treatment duration' N102 to 100% in sheet 'Treatment duration' H190 to 97.0% in sheet 'Treatment efficacy'
GT1/4 treatment-experienced			
non-cirrhotic	12 weeks	93.6%	N145 to 100% in sheet 'Treatment duration' N147 to 0% in sheet 'Treatment duration' H229 to 93.6% in sheet 'Treatment efficacy' K30 to 0% in sheet 'Patient characteristics'
cirrhotic	24 weeks	97.4%	N145 to 0% in sheet 'Treatment duration' N147 to 100% in sheet 'Treatment duration' H265 to 97.4% in sheet 'Treatment efficacy' K30 to 100% in sheet 'Patient characteristics'
GT3 treatment-naïve			
non-cirrhotic	24 weeks	100%	N17 to 0% in sheet 'Treatment duration' N19 to 100% in sheet 'Treatment duration' K16 to 0% in sheet 'Patient characteristics'
cirrhotic	24 weeks	100%	N17 to 0% in sheet 'Treatment duration' N19 to 100% in sheet 'Treatment duration' K16 to 100% in sheet 'Patient characteristics'
GT3 treatment-experienced			
non-cirrhotic	24 weeks	89.3%	K18 to 0% in sheet 'Patient characteristics'
cirrhotic	24 weeks	77.3%	K18 to 100% in sheet 'Patient characteristics'

GT – genotype; SVR – sustained virologic response

None of the SVR rates or treatment durations for the comparators were changed. For GT1/4 treatment-naïve subgroup, the results for cirrhotic and non-cirrhotic patients were produced by selecting the appropriate group in the dropdown box in Cell L17 in sheet 'Results BC'. For GT1/4 treatment-experienced subgroup, the results for cirrhotic and non-cirrhotic patients were produced by amending cell K30 in sheet 'Patient characteristics' to 100% and 0%, respectively. For GT3 treatment-naïve subgroup, the results for cirrhotic and non-cirrhotic patients were produced by amending cell K16 in sheet 'Patient characteristics' to 100% and 0%, respectively. For GT3 treatment-experienced subgroup, the results for cirrhotic and non-cirrhotic patients were produced by amending cell K18 in sheet 'Patient characteristics' to 100% and 0%, respectively.

ERG analysis 2: ERG-scenario analysis using alternative "unblended" EMA-recommended treatment durations for LDV/SOF

The ERG performed "unblended" analyses using the company's model using alternative EMA recommended treatment durations for LDV/SOF+/-RBV. This involved using the SVR rates for LDV/SOF corresponding to the treatment duration recommended by EMA based on the population genotype and cirrhotic status. This was achieved by changing the cells in sheets 'Treatment duration' and 'Treatment efficacy' (see below).

SVR rates and treatment duration used within the ERG base case analysis (EMA-recommended unblended LDV/SOF treatment)

Subgroup	Duration	SVR	Cells changed in the company's model
GT1/4 treatment-naïve			
non-cirrhotic	8 weeks	94.0%	N52 to 100% in sheet 'Treatment duration' N54 to 0% in sheet 'Treatment duration' H151 to 94.0% in sheet 'Treatment efficacy'
cirrhotic	12 weeks	94.1%	N100 to 0% in sheet 'Treatment duration' N102 to 100% in sheet 'Treatment duration' H190 to 94.1% in sheet 'Treatment efficacy'
GT1/4 treatment-experienced			
non-cirrhotic	24 weeks	99.1%	N145 to 100% in sheet 'Treatment duration' N147 to 0% in sheet 'Treatment duration' H229 to 99.1% in sheet 'Treatment efficacy' K30 to 0% in sheet 'Patient characteristics'

For the comparators, the results for cirrhotic and non-cirrhotic patients were produced using the same methods described in ERG base case analyses. No further amendments were made to the model for producing the results for the comparators.

5.5.1.3 ERG analysis 3: Use of alternative transition probabilities based on the sofosbuvir STA model

This additional analysis uses the ERG-preferred base case analysis as a starting point i.e. all the amendments in the ERG-preferred base case analysis are performed again for the respective subgroups. Furthermore, transition probabilities used with the ERG base case analysis were replaced with those taken from the previous sofosbuvir model. This involved amending the cells in sheet *TPs* as follows: M29 to 0.039, M31 and M37 to 0.014.

5.5.1.4 ERG analysis 4: Use of UK valued utility increment derived by Wright et al

This additional analysis uses the ERG-preferred base case analysis as a starting point i.e. all the amendments in the ERG-preferred base case analysis are performed again for the respective subgroups. Furthermore, the utility increment gain associated with achieving SVR with the ERG base case analysis was replaced with an estimate of 0.05 based on a UK analysis of the UK HCV mild trial reported by Wright *et al.* This involved amending the cell J173 in sheet *Utilities* to 0.05.

5.5.1.5 ERG analysis 5: Use of shorter time horizons (5-years and 10-years) to dampen assumptions regarding no re-infection

This additional analysis uses the ERG-preferred base case analysis as a starting point i.e. all the amendments in the ERG-preferred base case analysis are performed again for the respective subgroups. Furthermore, shorter time horizons of 5-years and 10-years were used. This involved amending the cells "W16:W18" in *Results BC* sheet to 45, 50 and 55 respectively and choosing the appropriate time horizon in the dropdown box in Cell L19 in sheet 'Results BC'.

5.5.1.6 ERG analysis 6: Threshold analysis for SVR rates of comparators

The ERG undertook threshold analyses to identify the magnitude of change in SVR rate for the comparator (the next best intervention to LDV/SOF on the efficiency frontier) required in order for LDV/SOF to achieve an ICER of £30,000 per QALY gained against that comparator. This was conducted manually (i.e trial and error) by amending the SVR rates of the comparator until the ICER of LDV/SOF is £30,000 per QALY gained against that comparator.