Errata

Ledipasvir-sofosbuvir for treating chronic hepatitis C

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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. [TEXT DELETED]

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 included

only patients with GT1 infection, more patients of African/American origin and fewer patients of Asian origin. 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.

[TEXT DELETED]

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

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 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).

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 treatment naïve patients with cirrhosis and HCV GT3 treatment-experienced patients with or 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.

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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 [TEXT DELETED]
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.

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. [TEXT DELETED] 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).

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. Additionally, interim data were provided for the treatment arm with GT4 patients.

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

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] For the other two treatment groups, mean age was 56 (see table 22). 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]

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; additionally, interim data were provided for the treatment arm with GT4 patients.

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

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 SIRIUS 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.

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] Interim data available at time of submission - GT4 treatment-naïve or treatment experienced.	LDV/SOF for 12 weeks Other arms not included in CS that had unlicensed anti-viral agents [redacted] GT4 in CS (or n=20 in clarification response Figure 8)	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=[redacted]) PBO 12 weeks then LDV/SOF +RBV for 12 weeks (n=[redacted])	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

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	ION1[17]					141/144	97.9 94.0–99.6	143/148	96.6 92.3–98.9	144/146	98.6 95.1–99.8	141/143	98.6 95.0–99.8
GT1b Non-cirrhotic and compensated cirrhosis	ION1[17]					66/66	100 94.6-100	67/68	98.5 92.1-100	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						

Population	Study	LDV/SOF 8wks		LDV/SOF +RBV 8wks (not licensed)		LDV/SOF +RBV 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] [redacted]	159/171	93.0 88.1-96.3	159/172	92.4 87.4-95.9	[redacted]	[redacted]						
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]							LDV/SOF+RBV 25/25	LDV/SOF+RBV 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					20/20	100						

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

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 98.6% 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).

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, [TEXT DELETED] the addition of RBV [TEXT DELETED] did not significantly enhance the observed SVR12 rates (*p*-values not reported) (see CS[1] page 91). Similarly for ION-3, the addition of RBV did not significantly enhance the observed SVR12 rates, for LDV/SOF+RBV 8 weeks compared with[TEXT DELETED] LDV/SOF 8 weeks treatment (treatment difference 0.9%; 95% confidence interval: -3.9% to 5.7%). [TEXT DELETED]

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 98.9% 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).

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	98.9 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*

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."*

[redacted]

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 865 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 nine patients out of 431 patients (2.1%), 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-

For subgroups of GT1 treatment-naïve patients, SVR12 rates ranged from 92.4% to 98.6% 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 98.9%, 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.

It should be noted that the option of no treatment is not considered within the company's base case 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

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+RBV	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+RBV	89.3%	77.3%	ELECTRON-2[24]
SOF+RBV (24 wks)	87.0%	60.0%	VALENCE [40;32]

SVR – sustained virologic response

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 mentioned within the treatment indication 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

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 1/4 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.

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

Background mortality rates were applied to all health states based on age-specific general population mortality rates obtained from ONS.[80] These were not adjusted to remove deaths associated with the consequences of HCV. Increased mortality risks were associated with advanced liver disease health states (decompensated cirrhosis, HCC, liver transplant and post-liver transplant). (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.

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.

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	-	-	ext dom
SMV+PEG-IFN2a+RBV	15.02	£38,730.64	-	-	ext dom
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	-	-	ext dom
SMV+PEG-IFN2a+RBV	15.02	£38,730.64	-	-	ext dom
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

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 or extended 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 £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 or extended 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.

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 PEG-IFN2a+RBV versus no treatment is estimated to be £4,137/QALY. The ICER for SMV+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £13,213/QALY. The ICER for LDV/SOF versus SMV+PEG-IFN2a+RBV is estimated to be £17,390/QALY.

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 the proportion of patient receiving 24 weeks of treatment was increased in each patient population, as detailed below:

- The GT1 TN analysis tested an assumption of 85% of compensated cirrhosis patients receiving 12 weeks of treatment and the remaining 15% receiving 24 weeks.
- Similarly, the GT4 TN analysis tested an assumption of 85% of compensated cirrhosis patients receiving 12 weeks of treatment and the remaining 15% receiving 24 weeks.
- The GT1/4 TE analysis tested an assumption of 50% of compensated cirrhosis patients receiving 12 weeks of treatment and the remaining 50% receiving 24 weeks.

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	[TEXT DELETED] No treatment not included as comparator within the company's base case 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.

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%.

The company's health economic analysis has been implemented partly in line with NICE's Reference Case[63] (see Table 45). Two deviations from the final NICE scope[5] should be noted. Firstly,[TEXT DELETED] TVR and BOC are evaluated in the GT1/4

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. Secondly, 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).

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. All ERG analyses report total costs and QALYs for LDV/SOF and each comparator to two decimal places. This may produce some rounding error in the calculation of ICERs. 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

(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 at a higher cost than no treatment and is therefore dominated. The ICER for LDV/SOF versus no treatment 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.

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.[TEXT DELETED]

- 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.
- [TEXT DELETED]

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