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Sofosbuvir–velpatasvir–voxilaprevir for treating chronic hepatitis C

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Ms. Neelam Kalita, critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Ms. Petra Harris, critically appraised

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LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
AE	Adverse events
ALT	Alanine aminotransferase
APRI	AST:platelet ratio index
AST	Aspartate transaminase
BLAST	Basic Local Alignment Search Tool
BNF	British National Formulary
CC	Cirrhotic
CEAC	Cost effectiveness acceptability curve
CHC	Chronic hepatitis C
CI	Confidence interval
CS	Company submission
CSR	Clinical study report
DAA	Direct-acting antivirals
DCV	Daclatasvir
DDW	Digestive Disease Week
EASL	European Association for the Study of Liver
EBR	Elbasvir
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence review group
EudraCT	European Clinical Trials Database
FAS	Full analysis set
GFR	Glomerular filtration rate
GT	Genotype
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
LLOQ	Lower limit of quantification
NC	Non-cirrhotic
NI	Nucleoside inhibitor
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NS	Non-structural protein
OBV	Ombitasvir
Peg-IFN	Pegylated interferon
PHE	Public Health England
PPSRU	Personal Social Services Research Unit
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM	Patient reported outcome measures
PSA	Probabilistic sensitivity analyses
PSS	Personal social services
PTV	Paritaprevir
PWID	People who inject drugs

QALY(s)	Quality-adjusted life year(s)
RAV	Resistance-associated variant
RBV	Ribavirin
RCT	Randomised controlled trial
RNA	Ribonucleic acid
RTV	Ritonavir
RVR	Rapid viral response
SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SF-36	Short form 36
SHTAC	Southampton Health Technology Assessments Centre
SmPC	Summary of product characteristics
SMV	Simeprevir
SOF	Sofosbuvir
SOF/VEL	Sofosbuvir in combination with velpatasvir
STR	Single tablet regimen
SVR	Sustained virologic response
TE	Treatment-experienced
TN	Treatment-naïve
UKCTG	UK Clinical Trials Gateway
ULN	Upper limit of normal
VEL	Velpatasvir
VOX	Voxilaprevir
WHO ICTRP	World Health Organization International Clinical Trials Registry Platform
WTP	Willingness to pay

SUMMARY

Scope of the company submission

The company's submission (CS) broadly reflects the scope of the appraisal issued by the National Institute for Health and Care Excellence (NICE), but is more restricted in terms of the population groups that are included. The submission assesses the clinical effectiveness and cost effectiveness of sofosbuvir (SOF), velpatasvir (VEL) and voxilaprevir (VOX) (SOF/VEL/VOX) in two groups of patients: (i) those who have had previous treatment with direct-acting antiviral (DAA) agents for chronic hepatitis C (CHC) (DAA-experienced) and (ii) those who have had no previous treatment with DAA agents for CHC (DAA-naïve) who have hepatitis C virus (HCV) of genotype 3 (GT3). The three drugs, SOF, VEL and VOX target different elements of HCV. SOF is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication, VEL is a HCV inhibitor targeting the HCV NS5A protein, which is required for viral replication and VOX is an inhibitor of the HCV NS3/4A protease. All three component drugs are active against every genotype (GT) of HCV. Comparators include best supportive care and seven active treatments currently recommended by NICE (some of which are recommended for people with specific HCV genotypes).

Summary of submitted clinical effectiveness evidence

Overall, the searches conducted by the company were considered by the Evidence Review Group (ERG) to be appropriate and sufficiently comprehensive to have identified all the relevant evidence. The company's methods of systematic review were also considered appropriate.

The primary outcome for each of the included trials was sustained virological response (SVR) 12 weeks after cessation of treatment (SVR12).

The CS includes four relevant clinical trials of SOF/VEL/VOX:

DAA treatment-experienced patients

- POLARIS-1: Two trial arms of SOF/VEL/VOX or placebo were tested individually against a predefined performance SVR12 goal of 85% (i.e. the primary efficacy hypothesis was that the rate of SVR12 among patients receiving SOF/VEL/VOX would be superior to the pre-specified SVR12 of 85%). Enrolled DAA treatment-experienced participants, those with HCV genotype 1 (GT1) were randomised to study arms, but patients with other genotypes could only enter the SOF/VEL/VOX arm.

- POLARIS-4: Two trial arms of SOF/VEL/VOX or SOF/VEL were tested individually against a predefined performance SVR12 goal of 85%. Enrolled DAA treatment-experienced participants, those with HCV genotypes 1, 2 and 3 were randomised to study arms, but patients with other genotypes could only enter the SOF/VEL/VOX arm.

DAA treatment-naïve patients

- POLARIS-2: A non-inferiority trial of SOF/VEL/VOX versus SOF/VEL. Enrolled DAA treatment-naïve participants without cirrhosis who had any HCV genotype. Participants with HCV genotypes 1, 2, 3 and 4 were randomised to study arms, but those with other genotypes could only enter the SOF/VEL/VOX arm. However, only the subgroup of participants with HCV GT3 (19% of the total trial population) meets the company's decision problem criteria.
- POLARIS-3: Two trial arms of SOF/VEL/VOX or SOF/VEL were individually tested against a predefined performance SVR12 goal of 83%. Enrolled DAA treatment-naïve participants with cirrhosis and HCV GT3 were randomised to the study arms.

Thus there are two trials that provide evidence for SOF/VEL/VOX in DAA treatment-experienced patients of all genotypes (POLARIS-1 and POLARIS-4) and two trials that provide evidence SOF/VEL/VOX in DAA treatment-naïve patients with HCV GT3 (a subgroup of POLARIS-2 and the full trial population of POLARIS-3) (Table 1).

Table 1: Summary of the trials providing evidence for each of the HCV patient populations described in the NICE scope

NICE scope population	CS decision problem population	Evidence sources	Trial arms	Comparison made
Those who have had previous treatment for CHC (treatment-experienced)	Those who have had previous treatment with DAA agents for CHC (DAA-experienced)	POLARIS-1 (participants with and without cirrhosis)	SOF/VEL/VOX 12-weeks ▪ GT1 randomised ▪ Other genotypes (not randomised)	Trial arms not compared with each other. Instead arms were tested individually for superiority against a predefined
			Placebo 12-weeks	

			▪ GT1 randomised	performance goal of SVR12 85%.[a]
		POLARIS-4 (participants with and without cirrhosis)	SOF/VEL/VOX 12-weeks ▪ GT1,2 & 3 randomised ▪ Other genotypes (not randomised)	Trial arms not compared with each other. Instead arms were tested individually for superiority against a predefined performance goal of SVR12 85%.[a]
			SOF/VEL 12-weeks ▪ GT1, 2 & 3 randomised	
Those who have not had treatment for CHC before (treatment-naïve)	Those who have had no previous treatment with DAA agents for CHC (DAA-naïve) who have HCV of genotype 3 (GT3)	POLARIS-2 (participants without cirrhosis)	SOF/VEL/VOX 8-weeks ▪ GT3 randomised ▪ Other genotypes (not randomised)	Non-inferiority trial. Only the subgroup of participants with HCV GT3 (19% of the total trial population) meets the company's decision problem criteria.
			SOF/VEL 12-weeks ▪ GT1, 2, 3 & 4 randomised	
		POLARIS-3 (participants with cirrhosis)	SOF/VEL/VOX 8-weeks ▪ GT3 randomised	Trial arms were not compared with each other. Instead each arm was compared individually for superiority against a predefined
			SOF/VEL 12-weeks ▪ GT3 randomised	

				performance goal of SVR12 83%.[b]

[a] The performance goal of an SVR12 of 85% (i.e. 85% of the trial population achieving SVR12) was defined as a benchmark against which to test the efficacy of SOF/VEL/VOX. The basis for the 85% benchmark included the trend towards increasing SVR rates in recent years and the appeal of using a fixed clinically relevant threshold as a measure of treatment benefit of SOF/VEL/VOX in this population. The study protocol states that it is difficult to characterise a historical control rate for all the HCV genotypes because of the lack of a standard of care.

[b] The performance goal of 83% (i.e. 83% of the trial population achieving SVR12) was based on the prior results of SOF/VEL in this patient population in the ASTRAL-3 trial [SVR, 91%; 95% confidence interval (CI), 83–96].[1]

The trials that inform the effectiveness review for SOF/VEL/VOX were considered to be of reasonable quality, however it is important to note that not all participants enrolled into POLARIS-1, POLARIS-4 and POLARIS-2 were eligible for randomisation. Participants with GT2-6 or unknown in POLARIS-1, GT4-6 or unknown in POLARIS-4 and GT5-6 or unknown in POLARIS-2 were not eligible for randomisation and could only enter the SOF/VEL/VOX arm of the trial. Hence only POLARIS-3 employed conventional randomisation with all participants randomised to treatment arms. The absence of randomisation for the participants with certain genotypes did not have an impact on the primary outcome, SVR12, because as noted above in POLARIS-1 and POLARIS-4 the trial arms were not compared against each other but were compared to a predefined performance SVR12 goal of 85%, and in POLARIS-3 the participants who meet the decision problem, those with GT3, were eligible for randomisation. It is also important to note that POLARIS-4, POLARIS-2 and POLARIS-3 were open label trials, so there is scope for bias in these trials. However, the key outcome measure for these trials, SVR12, is an objective measure and thus not likely to be affected by performance or detection bias.

The CS does not include a meta-analysis or a network meta-analysis (NMA). For the DAA-experienced patient group, although not explicitly stated in the CS, the ERG believes that the POLARIS-1 trial is the only available source of evidence for the SOF/VEL/VOX versus no treatment comparison that is included in the economic analysis. For the DAA-naïve patients with HCV GT3 the company explored the feasibility of conducting a NMA, but ultimately the company decided it would be inappropriate to use outcomes from this NMA in the economic

analysis and the ERG agrees that a NMA for the DAA-naïve HCV GT3 population would not be robust.

The CS reports the effects of SOF/VEL/VOX treatment across a range of outcomes relevant to the NICE scope and company decision problem, which are summarised below.

DAA-experienced population, all HCV genotypes

SOF/VEL/VOX treatment resulted in a statistically significantly higher SVR12 rate (POLARIS-1: 96.2%, p<0.001; POLARIS-4 97.8, p<0.001) in comparison to a performance SVR12 goal of 85%. No participants in the placebo group (POLARIS-1) achieved SVR12 and in POLARIS-4, the SVR12 rate in the SOF/VEL arm (90.1%, p=0.092) was not statistically significantly greater than the 85% performance goal. SVR4 outcomes provided an early indication of SVR12 outcomes, and all participants who achieved SVR12 and who attended the SVR24 visit also achieved SVR24 (four participants with SVR12 did not attend the SVR24 visit).

During treatment with SOF/VEL/VOX HCV ribonucleic acid (RNA) levels were observed to fall rapidly, with more than half the participants receiving active treatment (i.e. SOF/VEL/VOX or SOF/VEL) at 'Week 2' having HCV RNA less than the lower limit of quantitation (LLOQ, 15 IU/mL).

On-treatment virologic failure in patients receiving SOF/VEL/VOX was very rare in the DAA-experienced population, occurring in only one participant (0.4%) of the SOF/VEL/VOX arm of POLARIS-1. Relapse after the end of SOF/VEL/VOX treatment was uncommon (2.3% POLARIS-1; 0.5% POLARIS-4).

Development of resistance

Resistance-associated variants (RAVs) in the HCV NS3 and/or NS5A genes were common at baseline in both POLARIS-1 and POLARIS-4 participants (78.8% and 49% respectively) but their presence did not impact on participant's SVR12 rates. During treatment across the two trials newly emergent RAVs in participants with on-treatment virologic failure were identified in one participant in the SOF/VEL/VOX group of POLARIS-1 and in one participant in the SOF/VEL group of POLARIS-4. After completion of treatment newly emergent RAVs occurred in one of the six who relapsed in the SOF/VEL/VOX arm of POLARIS-1 and there were no new

RAVs among those in the SOF/VEL/VOX arm who relapsed in POLARIS-4 (whereas 10 of the 14 in the SOF/VEL arm who relapsed had newly emergent NS5A RAVs).

Alanine aminotransferase (ALT) normalisation

Decreases in median ALT values were coincident with decreases in HCV RNA (i.e. suppression of viral replication) in the active treatment arms of both POLARIS-1 and POLARIS-4. There was no change in the placebo group of POLARIS-1.

DAA-naïve population, HCV GT3 only

The duration of SOF/VEL/VOX treatment was shorter (8 weeks of treatment) for the DAA-naïve HCV-GT3 participants in POLARIS-2 and POLARIS-3 than for the DAA-experienced participants of all genotypes in POLARIS-1 and POLARIS-4 (12 weeks of treatment). The SVR12 rate in the subgroup of participants in POLARIS-2 with HCV GT3 and who do not have cirrhosis was 98.9% for the SOF/VEL/VOX 8-week arm in comparison to 96.6% in the SOF/VEL 12-week arm. Overall (all HCV genotypes) in the POLARIS-2 trial, the SOF/VEL/VOX 8-week arm did not demonstrate non-inferiority in comparison to the SOF/VEL 12-week arm. In POLARIS-3 (DAA-naïve HCV GT3 participants with cirrhosis), SOF/VEL/VOX 8-week treatment resulted in a statistically significantly higher SVR12 rate (96.4%, $p<0.001$) in comparison to a performance SVR12 goal of 83% and this was also the case for the SOF/VEL 12-week group (96.3%, $p<0.001$). Similarly to studies in the DAA-experienced population, the SVR4 outcomes in the DAA-naïve population provided an early indication of SVR12 outcomes. SVR24 data were not reported for the subgroup of DAA-naïve HCV-GT3 participants without cirrhosis in POLARIS-2, but in POLARIS-3 (DAA-naïve HCV-GT3 participants with cirrhosis) all participants who achieved SVR12 also achieved SVR24.

During treatment with SOF/VEL/VOX HCV RNA levels were observed to fall rapidly, with at least half the participants in the whole POLARIS-2 (all HCV genotypes) and POLARIS-3 trials receiving active treatment (i.e. SOF/VEL/VOX or SOF/VEL) at 'Week 2' having HCV RNA less than the LLOQ (15 IU/mL). Data for this outcome in the subgroup of DAA-naïve HCV-GT3 participants in POLARIS-2 were not provided.

No DAA-naïve, non-cirrhotic or cirrhotic HCV GT3 participants experienced on-treatment virologic failure with SOF/VEL/VOX. There were no relapses after the end of SOF/VEL/VOX treatment or after SOF/VEL treatment among the DAA-naïve, non-cirrhotic HCV GT3 subgroup

of POLARIS-2. Only two participants in the SOF/VEL/VOX arm of POLARIS-3 relapsed (1.9%). In the SOF/VEL arm of POLARIS-3 one participant had on-treatment virologic failure (0.9%) and there was one relapse after the end of SOF/VEL treatment (0.9%).

Development of resistance

RAVs in the HCV NS3 or NS5A genes were present at baseline in both the POLARIS-2 and POLARIS-4 trial participants (POLARIS-2: SOF/VEL/VOX (8 weeks) 50.3%; [redacted]. POLARIS-3 [redacted]) but their presence did not impact on participant's SVR12 rates. During treatment across the two trials a newly emergent RAVs was identified in the sole participant (from the SOF/VEL group of POLARIS-3) who experienced on-treatment virologic failure. After completion of treatment newly emergent RAVs were absent from the majority of participants with relapse in POLARIS-2 and POLARIS-3.

ALT normalisation

Decreases in median ALT values were coincident with decreases in HCV RNA in both the arms of POLARIS-2 and of POLARIS-3 with no notable differences between the groups.

Health-related quality of life (HRQoL)

HRQoL typically improved during treatment and continued to improve from the end of treatment to post-treatment weeks 4 and 12. Outcomes were obtained from four HRQoL questionnaires.

Subgroup analyses

Results from 17 pre-planned subgroup analyses of SVR12 rates for all four of the POLARIS trials were presented in CS Appendix E. Notably the HCV GT3 subgroup from POLARIS-2 is of particular relevance to the decision problem and results from this group are reported in the main results section of the ERG report. High SVR12 rates were achieved in all subgroups of each trial, however for some subgroups numbers were small which limits the inferences that can be drawn.

Adverse events

Adverse events (AEs) were reported by the company for all participants regardless of HCV genotype because HCV genotype does not influence AEs. The majority of all patients in each

trial experienced at least one AE regardless of treatment arm but the majority of reported AEs were mild or moderate in severity (Grade 1 or Grade 2). Across all four POLARIS trials headache and fatigue were the most commonly reported AEs. AEs of Grade 3 (severe) or Grade 4 (life-threatening) occurred in small proportions of participants (DAA-experienced: POLARIS-1 SOF/VEL/VOX [redacted]; placebo 2.6%; POLARIS-4 SOF/VEL/VOX [redacted]; SOF/VEL 1.3%. DAA-naïve: POLARIS-2 SOF/VEL/VOX [redacted]; SOF/VEL 1.4%; POLARIS-3 SOF/VEL/VOX [redacted]; SOF/VEL 3.7%). The majority of Grade 3 and Grade 4 AEs were considered to be unrelated to study drug.

Treatment related AEs occurred in [redacted] of the patients receiving SOF/VEL/VOX in all the trials (DAA-experienced: POLARIS-1 SOF/VEL/VOX [redacted]; placebo 41.4%; POLARIS-4 (SOF/VEL/VOX [redacted]; SOF/VEL 51.0%. DAA-naïve: POLARIS-2 SOF/VEL/VOX [redacted]; SOF/VEL 41.4%; POLARIS-3 SOF/VEL/VOX [redacted]; SOF/VEL 46.8%). These were most commonly headache and fatigue.

Serious AEs (SAEs) were reported for a small proportion of participants and in all cases were considered to be unrelated to study drug (DAA-experienced: POLARIS-1 SOF/VEL/VOX [redacted], placebo 4.6%; POLARIS-4 SOF/VEL/VOX [redacted], SOF/VEL 2.6%. DAA-naïve: POLARIS-2 SOF/VEL/VOX [redacted], SOF/VEL 1.6%; POLARIS-3 SOF/VEL/VOX [redacted], SOF/VEL 2.8%). Few participants discontinued treatment due to AEs in any of the trials and neither of the two deaths ([redacted] in the SOF/VEL/VOX arm of POLARIS-4 and [redacted] in the SOF/VEL/VOX arm of POLARIS-3) was considered related to study drug.

In all four trials most laboratory abnormalities (haematological and chemistry abnormalities) were of Grade 1 or 2 in severity. There were no notable changes from baseline in vital sign measurements and there was only one ECG outcome that was considered clinically significant (POLARIS-2 SOF/VEL group one patient with atrial flutter).

In summary, there appear to be no major safety concerns about treatment with SOF/VEL/VOX in either CHC DAA-experienced patients or cirrhotic and non-cirrhotic DAA-naïve patients.

Summary of submitted cost effectiveness evidence

The CS includes:

- A review of published cost-effectiveness studies that presented economic data in hepatitis C
- An economic evaluation undertaken for the NICE STA process to assess the cost-effectiveness of SOF/VEL/VOX treatment in patients with hepatitis C for DAA-experienced patients and DAA-naïve patients with genotype 3.

The company conducted a systematic search of the literature to identify published economic evaluations in hepatitis C between 2007 and 2017. They searched Ovid SP®: MEDLINE and MEDLINE In-Process, Embase, NHS Economic Evaluations Database (NHS-EED) and EconLit. They identified 119 studies but focussed on the 13 studies that used UK based economic and resource inputs and used a UK economic perspective. None of these studies included either SOF/VEL/VOX or SOF/VEL as comparators.

The company constructed a Markov state-transition model that reflects the clinical progression of hepatitis C over patients' lifetime. The model structure has been widely used in previous NICE technology appraisals. The model compared SOF/VEL/VOX with i) no treatment for DAA-experienced patients; ii) SOF/VEL, SOF/daclatasvir (DCV)/ribavirin (RBV) (SOF/DCV/RBV), peginterferon alfa (Peg-IFN2a)/RBV (Peg-IFN2a/RBV), SOF/Peg-IFN2a/RBV and no treatment for cirrhotic DAA-naïve patients with genotype 3; and iii) SOF/VEL, SOF/DCV, Peg-IFN2a/RBV, SOF/Peg-IFN2a/RBV and no treatment in non-cirrhotic DAA-naïve patients with genotype 3.

The model had a lifetime horizon of 30 years, with discounting at 3.5% per annum for costs and benefits, a cycle length of two weeks for the first 18 months, followed by a 6-month cycle and annual transitions thereafter. The perspective of the analysis is the National Health Service and Personal Social Services. The model consists of nine health states: Non-cirrhotic, SVR-non cirrhotic, compensated cirrhosis, SVR-compensated cirrhosis, decompensated cirrhosis, hepatocellular cirrhosis, liver transplant, post-liver transplant and background mortality.

The model uses clinical effectiveness data on SVR rates form head-to-head trials (POLARIS-1 to -4) comparing SOF/VEL/VOX with SOF/VEL with no treatment in different sub-populations. SVR rates for other treatment comparisons are taken from relevant study arms for these treatments. Patients are treated according to the specified duration in the marketing licensing of the treatments. Transition probabilities used in the model were based upon those used in previous technology appraisals.

Health state utility values were derived from a study published by Wright 2006 et al. Furthermore, treatment-specific utility increments and decrements were included to take into account the differential impact of treatments on quality of life. Utility increments for SVR were

based on the study by Younossi et al. (2016) and applied to the non-cirrhotic, cirrhotic health states when patients had achieved a SVR.

SOF/VEL/VOX is taken orally as a single tablet, once daily. The list price for a pack of SOF/VEL/VOX is £14,942.33 which corresponds to a total cost of £29,884.68 for 8 weeks of treatment and £44,826.99 for 12 weeks of treatment. SOF/VEL/VOX is available with a confidential patient access scheme. The costs of comparator treatments are taken from the British National Formulary (August 2017). Besides drug acquisition costs, costs for monitoring and follow-up, costs associated with AEs, and costs related to health states were included in the cost effectiveness analysis. These were all based on previous studies.

The results of the economic model are presented as incremental cost effectiveness ratios (ICERs), measured as the incremental cost per quality-adjusted life-year (QALY). The results are shown in Table 2 - Table 4.

SOF/VEL/VOX 12 week has an ICER of under £10,000 per QALY compared to no treatment for DAA-experienced patients. In non-cirrhotic DAA-naïve GT3 patients SOF/VEL/VOX 8 week dominates treatment with SOF/VEL, SOF + Peg-IFN2a + RBV and SOF + DCV, and produces ICERs under £20,000/QALY compared to Peg-IFN2a + RBV and no treatment respectively. In DAA-naïve GT3 patients with compensated cirrhosis SOF/VEL/VOX 8 week dominates treatment with SOF + Peg-IFN2a + RBV, SOF + DCV + RBV and SOF+ RBV, and produces small ICERs versus Peg-IFN2a + RBV and no treatment. Against SOF/VEL, SOF/VEL/VOX is equivalent in efficacy and cost-saving.

Table 2: Base-case results: DAA-experienced (pan-GT and all non-cirrhotic/compensated cirrhosis) (list price) (CS Table 64)

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER Incremental (£)
No treatment	£23,262	10.01	-	-	-
SOF/VEL/VOX (12 wks)	£53,922	13.77	£30,660	3.76	£8,153

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

Table 3: Base-case results: DAA-naïve, GT3 infection, with compensated cirrhosis (list price) (CS Table 65)

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER Incremental (£)
No treatment	£36,262	4.98	-	-	-
Peg-IFN2a + RBV (24 wks)	£37,510	6.61	£1,248	1.63	£765
SOF/VEL/VOX (8 wks)	£51,289	9.98	£13,779	3.37	£4,088
SOF + Peg-IFN2a + RBV (12 wks)	£59,961	9.72	£8,672	-0.26	**Dominated** by SOF/VEL/VOX (8 wks)
SOF/VEL (12 wks)	£60,449	9.99	£9,160	0.01	£863,724
SOF + DCV + RBV (12 wks)	£83,447	9.31	£32,158	-0.67	**Dominated** by SOF/VEL/VOX (8 wks)
SOF+ RBV (24 wks)	£98,661	8.49	£47,372	-1.49	**Dominated** by SOF/VEL/VOX (8 wks)

DCV, daclatasvir; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN2a, pegylated-interferon alfa-2a; QALYs, quality-adjusted life years; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

[a] SOF/VEL (12 wks) has a smaller efficacy level than SOF/VEL/VOX. The model assumes that patients cannot die whilst on treatment; SOF/VEL has a longer treatment time than SOF/VEL/VOX. The difference in health outcomes can be attributed to modelling limitations.

Table 4: Base-case results: DAA-naïve, GT3 infection, non-cirrhotic (list price) (based on CS Table 66)

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER Incremental (£)
Peg-IFN2a + RBV (24 wks)	£12,256	16.03	-	-	-

No treatment	£18,938	12.83	£6,682	-3.20	**Dominated** by Peg-IFN2a + RBV (24 wks)
SOF/VEL/VOX (8 wks)	£32,917	17.27	£20,661	1.24	16,654
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	£41,303	17.13	£8,386	-0.14	**Dominated** by SOF/VEL/VOX (8 wks)
SOF/VEL (12 wks)	£42,519	17.17	£9,602	-0.10	**Dominated** by SOF/VEL/VOX (8 wks)
SOF + DCV (12 wks)	£62,698	17.20	£29,781	-0.07	**Dominated** by SOF/VEL/VOX (8 wks)

DCV, daclatasvir; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN2a, pegylated-interferon alfa-2a; QALYs, quality-adjusted life years; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

In probabilistic sensitivity analyses, the probability of SOF/VEL/VOX being cost-effective in DAA-experienced patients 100% at a willingness to pay threshold of £20,000 per QALY. For cirrhotic DAA-naïve patients SOF/VEL/VOX is cost-effective in 49% and 44% at willingness to pay thresholds of £20,000 and £30.000 per QALY respectively. For non-cirrhotic DAA-naïve patients SOF/VEL/VOX is cost-effective in 36% and 35% at willingness to pay thresholds of £20,000 and £30.000 per QALY respectively.

The company conducted sensitivity analyses and scenario analyses and concluded that the key drivers to the cost-effectiveness results were the treatment transition probabilities from non-cirrhotic with SVR to non-cirrhotic (re-infection), the discount rate applied for costs and outcomes and treatment costs.

Commentary on the robustness of submitted evidence

Strengths

Despite some concerns about the processes used by the company to identify relevant clinical evidence, the ERG does not believe that any key studies of SOF/VEL/VOX or of potential

comparators are missing from the CS. Two trials provide evidence for SOF/VEL/VOX 12-week treatment in DAA treatment-experienced patients of all genotypes (POLARIS-1 and POLARIS-4) and two trials provide evidence SOF/VEL/VOX 8-week treatment in DAA treatment-naïve patients with HCV GT3 (a subgroup of POLARIS-2 and the full trial population of POLARIS-3).

The model structure is representative of the clinical pathway for patients with hepatitis C and consistent with previous NICE technology appraisals. The company used methods for the economic evaluation that are consistent with NICE technological guidelines. The transition probabilities, costs and HRQoL are consistent with the previous NICE technology appraisal for SOF/VEL (TA430).

Weaknesses and Areas of uncertainty

The transition probabilities and utility values used in the model are based upon a previous model published several years ago. Some of these data may now be out of date and more relevant recent studies may be available. A full review and update of the transition probabilities and utility values would be preferred.

There is some uncertainty around the treatment duration that would be used for DAA-naïve cirrhotic patients with HCV GT3 who are treated with SOF/VEL/VOX. Whilst the treatment duration used in the POLARIS-3 is for 8 weeks, the SmPC for SOF/VEL/VOX recommends 12 weeks treatment (for all genotypes) with an option of considering 8 weeks treatment for patients infected with HCV GT3.

Summary of additional work undertaken by the ERG

The ERG conducted scenarios that consisted of changes to the follow-up costs for non-cirrhotic patients with SVR, the SVR rates for SOF/Peg-IFN2a/RBV, the mortality rates after liver transplant, the proportion of mild and moderate patients for non-cirrhotic patients, the source of the transition probabilities and the duration of treatment for SOF/VEL/VOX for cirrhotic patients. Of the scenarios conducted by the ERG, only the scenario which investigated the duration of treatment for SOF/VEL/VOX for DAA-naïve cirrhotic patients had significant effect on the model results.

The ERG base case consisted of changes to the follow-up costs for non-cirrhotic patients with SVR, the SVR rates for SOF/Peg-IFN2a/RBV, the mortality rates after liver transplant, the

proportion of mild and moderate patients for non-cirrhotic patients. The ERG base case was only slightly different to the company base case with no differences in the relative cost-effectiveness of the treatments.

1 Introduction to ERG Report

This report is a critique of the company's submission (CS) to the National Institute for Health and Care Excellence (NICE) from Gilead on the clinical effectiveness and cost effectiveness of sofosbuvir–velpatasvir–voxilaprevir (SOF/VEL/VOX) for treating chronic hepatitis C (CHC). It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the evidence review group (ERG) and to help inform this review.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on 20th September 2017. A response from the company via NICE was received by the ERG on 4th October 2017 and this can be seen in the NICE committee papers for this appraisal.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The ERG believes that the CS provides a clear and accurate overview of the cause of hepatitis C and disease progression (CS section B.1.3.1), including the impact of the disease on individual patients, their carers and society as a whole (CS section B.1.3.2). The CS highlights that although CHC is curable, a considerable burden of disease is still expected in the UK from advanced liver disease, cirrhosis, hepatocellular carcinoma (HCC) and liver-related mortality. This is due to a number of factors, including the slow progression of CHC, a patient population with CHC who were infected several decades ago, until more recent times a lack of efficacious therapies, poor adherence to previous treatment regimens (some of which had a treatment duration of 48 weeks) and patients being unwilling to receive the interferon (IFN)-based therapies.

2.2 Critique of company's overview of current service provision

The CS provides a clear overview of the management of CHC in UK clinical practice (CS section B.1.3.3). A NICE hepatitis C guideline is planned, albeit the development of this was paused in January 2014 and although some scoping work took place late in 2015, the pause in the guideline was continued in January 2016 and the latest update to the timeline for this guideline in September 2016 indicates that the pause is continuing. The reason for the pause is the number of new pharmacological therapies that are continuing to be evaluated through the

technology appraisals programme and changes to the cost to the National Health Service (NHS) of the drugs. In the absence of a NICE hepatitis C guideline, the CS states that the current clinical pathway of care takes into account European[2] and UK[3] guidelines and existing NICE technology appraisals on drugs for hepatitis C.[4-15]

Although the CS does mention the existence of NHS England (NHSE) Operational Delivery Networks (ODNs), their role in current service provision is not covered in detail. The consultee submissions for this appraisal however indicate that the regional ODNs are responsible for making decisions about prioritisation of patients for treatment, with the numbers of patients that can be treated each month limited by NHSE. Furthermore, NHSE is also responsible for indicating which of the NICE approved treatments for CHC has the lowest acquisition cost and thus should be used as first line therapy for patients (with treatment populations stratified by genotype (GT), prior DAA-experience, and presence of cirrhosis).

2.3 Critique of company's definition of decision problem

Population

The population defined in the decision problem is more restricted than that described in the NICE scope. The NICE scope encompasses all CHC patients, including any hepatitis C virus (HCV) genotype, those who are treatment naïve and those who are treatment experienced, and with no restriction on level of damage to the liver (i.e. with no cirrhosis or with compensated or decompensated cirrhosis). In contrast, the CS restricts treatment-experienced patients to those who had had previous treatment with direct-acting antiviral (DAA) agents for CHC (DAA-experienced) and restricts the treatment naïve group to those with CHC of genotype 3 (GT3), who have had no previous treatment with DAA agents for CHC (DAA-naïve). The term DAA is not explicitly defined in the CS, however CS Table 1 states that DAAs are considered first line of therapy in CHC in UK current practice and indicates that the term DAA excludes the early generation protease inhibitors such as telaprevir and boceprevir, both of which were administered in combination with peginterferon alfa (Peg-IFN2a) and ribavirin (RBV). Therefore patients who have received boceprevir or telaprevir would be classed as DAA-naïve and grouped with "true" treatment-naïve patients, and would be eligible for SOF/VEL/VOX or other DAAs. Further rationale for dividing the population into DAA-naïve or DAA-experienced is provided in the company's answer to clarification question A3 and details presented in CS Appendix D.1.1.6, which explain that the recent European Association for the Study of Liver

(EASL) guidelines[2] now include recommendations for treatment-naïve patients and treatment-experienced patients who are DAA-naïve as well as DAA-experienced patients.

Therefore the decision problem does not encompass all the patients who would be eligible for treatment with SOF/VEL/VOX (as per the licence for SOF/VEL/VOX). The groups omitted are:
- treatment-naïve patients (completely treatment naïve and DAA-naïve) with GT1, GT2, GT4, GT5 and GT6
Additionally, SOF/VEL/VOX is not licenced for patients with decompensated cirrhosis, so this group is not included in the decision problem.

The ERG and NICE posed a clarification question to the company (Clarification question B7) regarding the restriction by the company of the treatment naïve population to a DAA-naïve population with GT3 in the company's decision problem. The company responded that they were aware that limiting the DAA-naïve population to GT3 patients presents a group that is narrower than both the pan-genotypic marketing authorisation for SOF/VEL/VOX and the NICE scope. The company state that the focus of the submission is on the GT3 DAA-naïve population because this is where SOV/VEL/VOX can provide the most clinical benefit. The ERG agrees that approximately 44% of the total CHC population in England have HCV GT3. The company state that GT3 infection is regarded as difficult to treat, people with HCV GT3 are at the highest risk of progressing from the non-cirrhotic to cirrhotic state and there is high unmet need in this sub-population. The response to clarification question B7 also states that the option of 8 weeks of treatment (which is not available to DAA-experienced patients with HCV GT3 both with and without compensated cirrhosis) is likely to be beneficial in terms of treatment efficacy, adherence and tolerability due to the shorter treatment duration.

Intervention

The intervention described in the decision problem reflects the intended use of SOF/VEL/VOX in the UK and it is appropriate for the NHS.

The dose of SOF/VEL/VOX is not stated in the decision problem (CS Table 1) but details are provided in the 'Description of the technology being appraised' (CS Table 2). The intervention is taken as one film coated tablet (containing 400mg sofosbuvir, 100mg velpatasvir and 100mg voxilaprevir) daily and, although not stated in either CS B.1.1. Table 1 (The decision problem) or

B.1.2. Table 2 (Technology being appraised), the Summary of Product Characteristics (SmPC) indicates that the daily SOF/VEL/VOX tablet should be swallowed whole with food.

The duration of treatment is given in the decision problem for the two populations:
12- weeks of SOF/VEL/VOX for DAA-experienced patients
8 - weeks of SOF/VEL/VOX for DAA-naïve patients with HCV GT3 (both non-cirrhotic and cirrhotic).
These are in line with the durations of treatment stated in the Summary of Product Characteristics (SmPC), although the ERG notes that for DAA-naïve patients with GT3 and compensated cirrhosis the SmPC states that 8 weeks of treatment can be considered instead of 12 weeks of treatment (Table 5). The factors that should cause a clinician to consider 8 weeks of treatment instead of 12 weeks for GT3 patients with compensated cirrhosis are not stated. Clinical advice to the ERG suggested a higher risk of treatment failure (which can be judged by established criteria) would cause clinicians to prescribe a 12-week course of treatment, but this would apply to a minority of patients (<10%). The CS does indicate in a footnote to Table 1 that the 8-week treatment duration is based on the 8-weeks of therapy in the POLARIS-2 and POLARIS-3 trials and that a 12-week treatment period was not studied in these trials.

Table 5: SmPC recommended treatment durations for SOF/VEL/VOX

Patient population (all HCV genotypes)	Treatment duration
DAA-naïve patients without cirrhosis	8 weeks
DAA-naïve patients with compensated cirrhosis	12 weeks 8 weeks may be considered in HCV GT3 infected patients
DAA-experienced patients without cirrhosis or with compensated cirrhosis	12 weeks

DAA, direct-acting antiviral agent; GT3, genotype 3.

Comparators

The comparators described in the decision problem align with the two population groups that the company has included in their submission.

For the DAA-treatment-experienced patients (GT1-6) who have had previous treatment DAAs for CHC, the comparator in the decision problem is best supportive care (defined as no active

pharmacological treatment). This reflects current practice in the NHS for the majority of patients who have not been cured after receipt of a DAA-containing regimen for whom there is no other treatment option. A very recent exception to this is that in September 2017 an NHS England policy statement recommended the off-label use of 24 weeks treatment with sofosbuvir and velpatasvir (SOF/VEL) for retreatment of CHC infection of all genotypes in patients whose first course of DAA treatment failed to achieve cure and who have advanced or decompensated cirrhosis (who are at risk of death within 12 months).[16] If judged necessary based on clinical assessment of the patient's clinical condition RBV can be added to the SOF/VEL to strengthen the regimen.

For the DAA treatment-naïve group with HCV GT3 the comparator depends on whether the patient is non-cirrhotic or cirrhotic. For DAA treatment-naïve GT3 patients without cirrhosis the decision problem lists the following four comparators:

- Peg-IFN2a + RBV (24 weeks)
- Sofosbuvir (SOF) + Peg-IFN2a + RBV (12 weeks)
- SOF/velpatasvir (VEL) (12 weeks)
- SOF + daclatasvir (DCV) (12 weeks) if cannot have interferon (IFN) (ineligible or intolerant) and the person has significant fibrosis.

When aligning the DAA treatment-naïve group with NICE guidance, the ERG was mindful that NICE guidance, especially guidance that predates the introduction of DAAs, may split patients into 'treatment- naïve' and 'treatment-experienced', but that the 'treatment-experienced' grouping can include patients who are DAA treatment-naïve. Taking that into consideration, the ERG agrees that Peg-IFN2a+RBV (24 weeks), SOF + Peg-IFN2a + RBV (12 weeks), SOF/VEL (12 weeks) and SOF + DCV (12 weeks) are relevant comparators. However, in the case of SOF+DCV as stated above, NICE guidance recommends this only if the patient is ineligible for or intolerant of interferon and they have significant fibrosis.

For treatment-naïve GT3 patients with cirrhosis the decision problem lists five comparators:

- SOF/VEL (12 weeks)
- SOF + DCV + RBV (12 weeks)
- SOF + RBV (24 weeks)
- Peg-IFN2a + RBV (24 weeks)
- SOF + Peg-IFN2a + RBV (12 weeks)

The ERG agrees that these are relevant comparators, however for SOF+DCV+RBV the treatment duration recommended in NICE guidance TA364 is 24 weeks (not 12 weeks as stated in the CS) and the recommendation is only for people who are interferon-ineligible or interferon-intolerant. The SOF+RBV (24 weeks) is also only for those who cannot have interferon.

Outcomes

The decision problem states that the outcomes are as listed in the final NICE scope:

- sustained virological response (SVR)
- development of resistance to treatment
- mortality
- adverse effects of treatment
- health-related quality of life (HRQoL)

The CS states that the development of resistance to SOF/VEL/VOX is discussed only in CS section 2.10 - this appears to be an incorrect cross reference and the ERG believes this should read section 2.6 (which is the clinical effectiveness results section where development of resistance mutations is discussed for each trial).

Economic analysis

The CS states that the economic analysis specified in the decision problem is the same as the final scope issued by NICE (CS Table 1) and the ERG agrees; consequently it is appropriate for the NHS. The company have conducted a cost-utility analysis with a lifetime time horizon (until patients reach 100 years of age). Costs are considered from the NHS and Personal Social Services (PSS) perspective.

The company presents NHS list prices in the CS, but a confidential discount has been proposed for SOF/VEL/VOX and is in place for SOF/VEL (the confidential discount prices for SOF/VEL/VOX and SOF/VEL are provided as commercial in confidence (CIC) information in CS Table 53). Some of the other comparators are also subject to a confidential discount.

Other relevant factors

The decision problem states that evidence has allowed subgroup analyses for three of the seven subgroups listed in the final NICE scope. Evidence allowed consideration of the following three subgroups:

- genotype

- patients with and without cirrhosis
- previous treatment received (with or without DAA-containing regimens).

No equity or equality issues were specified in the final scope or identified by the company. The ERG is not aware of any issues related to equity or equality in the use of SOF/VEL/VOX in patients with CHC.

3 CLINICAL EFFECTIVENESS

3.1 Critique of company's approach to systematic review

3.1.1 Description of company's search strategy

The CS reports three systematic searches spanning the period 1 January 2007 to 17 March 2017:

- Clinical Efficacy Evidence (Appendix D)
- Cost Effectiveness (Appendix G)
- Health Related Quality of Life (Appendix H)

The ERG considers that the searches are fit for purpose and have an adequate design. The strategies all used a mix of controlled vocabulary terms (e.g. MESH) and free text terms, with search sets correctly combined. An acceptable range of databases has been searched (Medline, Embase and Cochrane: last 10 years). It is assumed from analysis of the descriptors in the search string, that these databases have been searched concurrently with pooling of results. The documentation of the searches was transparent and would enable the searches to be reproduced. Appropriate conferences were searched by the company [American Association for the Study of Liver Diseases (AASLD), Digestive Disease Week (DDW) and EASL]. The ERG searched abstracts from the April 2017 AASLD conference, as the CS searches were conducted a month prior to this conference. The results were checked by a researcher and nothing additional was detected.

Some inconsistencies were noted by the ERG in the searches, however these were not deemed significant enough to omit pertinent results. For example Taribavarin appeared in the interventions/comparators list but was not included in the search string, however being a prodrug of ribavirin (which is listed), it should have been captured by the search. Some drug trade names are listed and not others. All could have been included for the sake of consistency.

The ERG checked for any additional references on Medline and Embase, searching with the abbreviated form of SOF/VEL/VOX in all fields, but nothing extra was identified. The CS reported searching clinicaltrials.gov for ongoing trials. The ERG undertook further checks on the UK Clinical Trials Gateway (UKCTG), World Health Organization International Clinical Trials

Registry Platform (WHO ICTRP) and European Clinical Trials Database (EudraCT), with nothing extra of significance found.

Full search filters were not applied to the cost and HRQoL searches, however the truncated filters are considered by the ERG to be appropriately tailored. The QoL search filter included the use of some specific and appropriate patient reported outcome measures (PROM) questionnaires and rating scale instruments. The cost search contains filters to additionally find resource use papers instead of undertaking two separate searches. The clinical search used a limit command to restrict to a variety of trial types presumably for specificity rather than sensitivity of a fuller standard randomised controlled trial (RCT) filter. The ERG sought clarification from the company as to why certain drugs (including a comparator drug daclatasvir) were eliminated by the NOT command from the clinical search string. The company's response to clarification question A17 indicated that this was an inadvertent exclusion (and daclatasvir was still included as a comparator in the submission).

The company performed a retrospective search that did not identify any additional new studies on daclatasvir published since the SOF/VEL submission that would have provided additional evidence. The ERG also searched for daclatasvir on Medline and Embase, with no useful additional material being found. There is inconsistent truncation in the cost searches, although in mitigation the host computer may have been set to pick up automatic truncation. The company was asked to explain the discrepancy in the search results for HRQoL (table 24: n=726) and in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (CS Appendix H.1.8, Figure 7 n=932) (clarification question B13). The company explained this was a typographical error in accounting for the number of items identified by the grey literature search and provided an amended PRISMA diagram. The search results and PRISMA tables match in both the clinical and cost effectiveness searches. There was no separate adverse drug reaction search as the data were obtained from the four POLARIS trials.

In summary, it is considered that the searches conducted by the company to support the systematic reviews in the submission are generally comprehensive and are reported transparently.

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

The inclusion criteria and exclusion criteria for the company's systematic review of the literature are provided in Appendix D of the CS (Appendix D.1.1.6, Table 2). This table contained an error (inclusion criteria for study design were not presented, the detail on included outcomes was duplicated into the study design row, presumably in error, from the row above) so the ERG and NICE requested clarification (Clarification question A18) and details were supplied (given below). The inclusion criteria for the population were broader that the decision problem, more closely reflecting the original NICE scope. The company's inclusion criteria included limits that restricted the searches to human studies published in the English Language.

Population

The population included in the systematic review was adults (≥18 years of age) with any genotype of HCV, with or without compensated cirrhosis. It was not clear from the reported inclusion and exclusion criteria whether studies on patients with decompensated cirrhosis were specifically excluded from the systematic review so a clarification question was asked about this (Clarification question A19) and the company explained that as the license for SOF/VEL/VOX does not include patients with decompensated cirrhosis studies including patients with decompensated cirrhosis were excluded. Treatment-naïve and treatment-experienced patients were included. In the case of treatment-experienced patients, this was defined as either DAA-experienced or as IFN-experienced. This likely reflects, as described in CS Appendix D.1.1.6, the fact that the EASL definition of DAA-naïve and DAA-experienced patients came into effect in 2016 and thus prior to this published literature would use the earlier classifications of treatment-experienced and treatment-naïve patients.

Exclusion criteria were applied to populations to exclude specific subgroups of participants:
- studies only including Asian patients with HCV because they respond differently to treatment
- studies on acute hepatitis
- studies on HCV/hepatitis B virus (HBV) co-infected patients
- studies on small populations (<10)
- studies on patients with renal dysfunction or depression
- studies focusing on homeless populations and intravenous drug users

Intervention and comparators

The interventions/comparators listed in Appendix D.1.1.6 Table 2 included all the component drugs of the active comparators listed in the NICE scope, but it was not clear whether combinations of the individual drugs were included so clarification was sought (Clarification question A20). The company responded to affirm that combination therapies were included in the systematic review. Best supportive care (no pharmacological treatment) which appears in the NICE scope was not listed as an intervention/comparator. In contrast, there were five drugs (taibavirin, telaprevir, boceprevir, simeprevir and asunaprevir) that were listed as comparators in the systematic review, but which were not included as comparators in the NICE scope. It was not explicitly stated in CS Appendix D but from the description of company's exploration of the feasibility of conducting a network meta-analysis (NMA) (CS B.2.8), it appears likely that the additional interventions were included to help identify evidence for an NMA.

Outcomes

Five outcomes were included in the inclusion criteria:

- SVR 12 weeks after the end of treatment (SVR12) or SVR 24 weeks after the end of treatment (SVR24)
- Rates of Grade 3, 4 and 5 adverse events (AE)
- Treatment discontinuations due to AEs
- Treatment discontinuations due to other reasons
- Mean treatment duration for patients who discontinued due to AEs

No outcomes are listed in the criteria for excluding studies.

Not included among the inclusion criteria for the systematic review were some outcomes that are included in the scope for this appraisal: development of resistance to treatment, mortality and HRQoL.

Design

As noted above, CS Appendix D.1.1.6 Table 2 contained an error and in response to clarification question A18, the company stated that the study designs eligible for inclusion were:

- Phase II, III or IV RCTs
- Systematic literature reviews
- Meta-analyses

No limits were used to restrict inclusion of studies in the systematic review on the basis of study quality and setting was not used as an inclusion criterion.

Appendix D.1.1.9 Figure 1 shows the PRISMA flow diagram for the selection of clinical effectiveness evidence. This diagram indicates that 108 studies were available to include in the qualitative synthesis. However, the overview on the number of studies identified by HCV GT and previous treatment experience Appendix D 1.1.10 Table 3 shows only a total of 92 studies. Furthermore the CS and appendices only present results from the four POLARIS trials.

It was not clear how the company selected the four POLARIS trials that form the evidence base reported in CS sections B.2.2 to B.2.11 from the 108 studies identified for inclusion in the systematic review, although all four trials supported the application for European Medicines Agency (EMA) marketing authorisation. The ERG and NICE therefore asked a clarification question (A1) so that the company could explain how studies were selected for detailed examination from the 108 studies identified for inclusion by searching and screening. The company responded that, as the published papers for the POLARIS trials were not available at the time the searches were undertaken and that evidence from the POLARIS studies was taken from the clinical study reports (CSRs). The POLARIS CSRs were therefore the only source of evidence for the efficacy and safety of SOF/VEL/VOX for the treatment of CHC in the CS. The ERG notes that, of the 108 studies identified for inclusion, reference number 13 in Appendix D.1.1.11 appears to be a conference abstract for the POLARIS-3 study. Furthermore, among the list of 337 excluded articles the ERG notes that excluded study 27 is a reference for the POLARIS-1 study (exclusion reason ‘Study Type’) and excluded study 32 is a reference for the POLARIS-4 study (exclusion reason ‘Intervention’). The ERG therefore has concerns about the processes used by the company to identify relevant clinical evidence.

3.1.3 Identified studies

Four trials of relevance to the decision problem were identified in the CS: POLARIS-1 and POLARIS-4 provide evidence for the DAA treatment-experienced population and POLARIS-2 and POLARIS-3 provide evidence for the DAA treatment-naïve population. It is important to note however that only the subgroup of participants with GT3 in POLARIS-2 (19% of the total trial population) match the population specified in the company’s decision problem as DAA treatment-naïve with CHC of genotype 3 (GT3).

Summary details of the four trials are presented in CS Tables 8-18:
- Summary of PICO elements of the four trials (CS Table 8)
- Comparative summary of trial methodology (CS Table 9), including details of pre-planned subgroups.
- Summary of and detailed eligibility criteria (CS Tables 10 and 11)
- Summary of outcomes investigated in the trials (CS Table 12)
- Comparative summary and detailed individual trial patient baseline characteristics (CS Tables 13-17)
- Summary of statistical analyses (CS Table 18), including power/sample size calculations and treatment of missing data. Intention-to-treat (ITT) analyses were not performed, instead a modified ITT analysis included all patients who underwent randomisation and received at least one dose of the study drug. The proportion of patients that did not get the study drug was small (POLARIS-1, -2 and -3 n=1, 2 and 1 respectively). Definitions of full analysis set (FAS) and safety analysis set (SAS) were provided in the CS text.

The source of information for the four trials was not referenced in the CS. In response to Clarification question A2 the company explained that data were taken from the relevant CSRs (using the CSRs updated to contain SVR24 data if available). CSRs for each trial were provided by the company and an accepted manuscript for the Jacobson 2017 publication[17] was provided but not cited in the CS. The ERG notes that both publications for POLARIS-1 and -4[18] and POLARIS-2 and -3[17] were published after the date of the literature searches conducted by the company.

All the included studies were designed and conducted by the company in collaboration with the principal investigators and no non-randomised studies were included in the CS.

<u>Equivalence of trial arms at baseline</u>

The CS describes the demographics and baseline characteristics for each of the trials as "*generally balanced across both treatment groups*". The CS does not comment on whether there are any exceptions to this. The ERG has brought together the data reported in CS Table 13, Table 14 and Table 15 for POLARIS-1 and POLARIS-4 (Table 6) and the data reported in CS Table 13, Table 16 and Table 17 for POLARIS-2 and POLARIS-3 (Table 7) and highlights differences between the trial arms of the studies below.

In POLARIS-1 (Table 6), because patients with GT1 were randomised to study arms but patients with other genotypes could only enter the SOF/VEL/VOX arm, there is inevitably an imbalance in HCV genotypes between the arms of this trial. Consequently the SOF/VEL/VOX arm is comprised of 57% HCV GT1 patients, 29.7% GT3 patients and smaller proportions of the GT2, GT4, GT5 and GT6 patients. In contrast, the placebo arm is 98.7% GT1 patients. As only patients with GT1 (determined by Abbott RealTime HCV genotype II assay at screening) were randomised to the placebo arm in POLARIS-1, it would appear from the CS table of baseline characteristics (CS Table 14) that two patients (1.3%) were later found to have HCV GT6 instead [CS states that genotype and subtype were subsequently determined by basic local alignment search tool (BLAST) analysis of NS3, NS5A, and NS5B sequences from deep sequencing]. The proportion with cirrhosis is higher in the SOF/VEL/VOX arm (46.0%) than the placebo arm (33.6%) and the proportion with in the baseline ALT category of >1.5x upper limit of normal (ULN) is higher in the SOF/VEL/VOX arm (54.4%) than the placebo arm (38.8%). The mean baseline ALT is higher in the SOF/VEL/VOX arm (89 U/L) than the placebo arm (74 U/L) and the estimated mean glomerular filtration rate (GFR) is higher in the SOF/VEL/VOX arm (119.2 mL/min) than the placebo arm (113.1 mL/min). Clinical advice to the ERG was that the differences observed between the SOF/VEL/VOX and placebo arms were not likely to be clinically significant. The types of prior DAA treatments received are broadly similar although with a slight difference in the relative proportions who had received treatment with a combination of non-structural protein (NS) 5A and NS5B DAA or a combination of NS5A+NS3 +/- NS5B DAAs (SOF/VEL/VOX arm NS5A and NS5B 61.2%, NS5A+NS3 +/- NS5B 31.6% versus placebo arm NS5A and NS5B 53.3%, NS5A+NS3 +/- NS5B 40.1%).

In POLARIS-4 (Table 6), because patients with HCV genotypes 1, 2 and 3 were randomised to study arms but patients with other genotypes could only enter the SOF/VEL/VOX arm, there is inevitably an imbalance in HCV genotypes between the arms of this trial. Consequently the SOF/VEL/VOX arm contains all 19 patients with GT4 (10.4% of the treatment arm); there were no patients with GT5 or GT6). Other characteristics were balanced between the study arms.

Table 6: Comparative summary of patient demographics and baseline characteristics in the POLARIS-1 and POLARIS-4 trials

	POLARIS-1		POLARIS-4	
Characteristic	**SOF/VEL/VOX**	**Placebo**	**SOF/VEL/VOX**	**SOF/VEL**
Number of patients (N)	263	152	182	151
Mean age (range), years	58 (27-84)	59 (29-80)	57 (24-85)	57 (24-80)
Male, n (%)	200 (76.0)	121 (79.6)	143 (78.6)	114 (75.5)
Mean BMI (range), kg/m^2	28.8 (18.4-66.7)	28.5 (18.0-61.2)	28.7 (18.0-45.4)	28.5 (17.8-53.3)
Race, n (%)[a]				
White	211 (80.2)	124 (81.6)	160 (87.9)	131 (86.8)
Black	38 (14.4)	22 (14.5)	16 (8.8)	13 (8.6)
Asian	8 (3.0)	6 (3.9)	2 (1.1)	4 (2.6)
Native Hawaiian or Pacific Islander	3 (1.1)	0	0	2 (1.3)
Not disclosed	1 (0.4)	0	NR	NR
American Indian or Alaska Native	1 (0.4)	0	2 (1.1)	0
Other	1 (0.4)	0	2 (1.1)	4 (2.6)
HCV GT/subtype by sequencing				
GT1, n (%)	150 (57.0)	150 (98.7)	78 (42.9)	66 (43.7)
1a	101 (38.4)	117 (77.0)	54 (29.7)	44 (29.1)
1b	45 (17.1)	31 (20.4)	24 (13.2)	22 (14.6)
1 Other	4 (1.5)	2 (1.3)	0	0
GT2	5 (1.9)	0	31 (17.0)	33 (21.9)
GT3	78 (29.7)	0	54 (29.7)	52 (34.4)
GT4	22 (8.4)	0	19 (10.4)	0
GT5	1 (0.4)	0	0	0
GT6	6 (2.3)	2 (1.3)	0	0
Unknown	1 (0.4)	0	0	0
Cirrhosis, n (%)				
Yes	121 (46.0)	51 (33.6)	84 (46.2)	69 (45.7)
No	142 (54.0)	101 (66.4)	98 (53.8)	82 (54.3)
IL28B genotype, n (%)				
CC	47 (17.9)	27 (17.8)	33 (18.1)	29 (19.2)
Non-CC	216 (82.1)	125 (82.2)	149 (81.9)	122 (80.8)
CT	165 (62.7)	93 (61.2)	107 (58.8)	95 (62.9)
TT	51 (19.4)	32 (21.1)	42 (23.1)	27 (17.9)
Baseline HCV RNA, log10 IU/mL, mean (SD)	6.3 (0.68)	6.3 (0.63)	6.3 (0.56)	6.3 (0.66)
Baseline HCV RNA category				
<800,000 IU/mL, n (%)	73 (27.8)	36 (23.7)	46 (25.3)	38 (25.2)
≥800,000 IU/mL, n (%)	190 (72.2)	116 (76.3)	136 (74.7)	113 (74.8)

	POLARIS-1		POLARIS-4	
Characteristic	**SOF/VEL/VOX**	**Placebo**	**SOF/VEL/VOX**	**SOF/VEL**
Baseline ALT (U/L), mean (SD)	89 (72.0)	74 (84.3)	84 (65.0)	85 (67.7)
Baseline ALT category				
≤1.5 x ULN, n (%)	120 (45.6)	93 (61.2)	88 (48.4)	72 (47.7)
>1.5 x ULN, n (%)	143 (54.4)	59 (38.8)	94 (51.6)	79 (52.3)
Previous HCV treatment experience, n (%)				
Treatment-experienced	263 (100)	152 (100)	182 (100)	151 (100)
DAA-naïve	0	0	0	1 (0.7)
DAA-experienced	263 (100)	152 (100)	182 (100)	150 (99.3)
NS5A +/- DAA(s)	262 (99.6)	151 (99.3)	NA	NA
NS5A + NS5B	161 (61.2)	81 (53.3)	NA	NA
NS5A + NS3 +/- NS5B	83 (31.6)	61 (40.1)	NA	NA
NS5A +/- Other(s)	18 (6.8)	9 (5.9)	NA	NA
Non-NS5A +/- DAA(s)	NA	NA	182 (100)	150 (99.3)
NS5B only	NA	NA	134 (73.6)	109 (72.2)
NS5B + NS3	NA	NA	46 (25.3)	38 (25.2)
Other(s)	1 (0.4)	1 (0.7)	2 (1.1)	3 (2.0)
Number of Patients Receiving at Least One Concomitant Medication, n (%)	239 (90.9)	138 (90.8)	153 (84.14)	132 (87.4)
Estimated GFR (mL/min), mean (SD)	119.2 (35.7)	113.1 (33.6)	123.3 (37.90)	123.7 (36.31)

ALT, alanine aminotransferase; BMI, body mass index (= weight (kg) / (height (m)2); DAA, direct-acting antiviral; EGFR, estimated glomerular filtration rate; GT, genotype; HCV, hepatitis C virus; IL28B, IL28B gene; NS (3/4A/5A/5B), NA, not applicable; nonstructural protein (3/4A/5A/5B); RNA, ribonucleic acid; SOF, sofosbuvir; SD, standard deviation; ULN, upper limit of normal; VEL, velpatasvir; VOX, voxilaprevir.

[a] In the SOF/VEL arm of POLARIS-4 the numbers of participants reported by race sum to 154 although the overall group size should be 151.

The CS reported the patient demographics and baseline characteristics for the total population of the POLARIS-2 trial (all genotypes). In response to a clarification request by the ERG and NICE (Clarification A3) these details were provided (as AIC data) for the GT3 subgroup of this trial. [redacted]. Across the total POLARIS-2 population (CS Tables

13 and 16) there was a slightly lower percentage of White participants (78.0%) and a higher percentage of Asian participants (10.2%) in the SOF/VEL/VOX arm than in the SOF/VEL arm (White 83.0%, Asian 5.0%). The proportion with HCV GT1 was also lower in the SOF/VEL/VOX arm (46.5%) whilst the proportion with GT6 was higher (6%) in comparison to the SOF/VEL arm (GT1 52.7%, GT6 2.0%). While low in proportion (3.6%), only the SOF/VEL/VOX arm included patients with GT5. Other characteristics seem balanced between the study arms.

Finally, in POLARIS-3 (Table 7) there were fewer male participants in the SOF/VEL/VOX arm (67.3%) than in the SOF/VEL arm (76.1%) and differences in the proportions with the CC and CT IL28B genotypes (SOF/VEL/VOX CC 37.3% and CT 51.7% versus SOF/VEL CC 47.7% and CT 40.4%) There were also differences in the proportions in the two baseline HCV RNA categories (reflecting viral load) and in mean baseline ALT (SOF/VEL/VOX HCV RNA <800,000 IU/ml 36.4%, baseline ALT 111 U/L; SOF/VEL HCV RNA <800,000 IU/ml 25.7%, baseline ALT 132 U/L) A lower proportion of participants in the SOF/VEL/VOX arm had received prior Peg-IFN+RBV (88.6%) than the SOF/VEL arm (93.8%) and finally the estimated mean GFR was higher for the SOF/VEL/VOX arm (126.4 mL/min) than the SOF/VEL arm (120.5 mL/min). Clinical advice to the ERG was that these differences would not be of any clinical significance.

Table 7: Comparative summary of patient demographics and baseline characteristics in the POLARIS-2 and POLARIS-3 trials

	POLARIS-2 GT3 Subgroup[a]		POLARIS-3	
Characteristic	**SOF/VEL/VOX**	**SOF/VEL**	**SOF/VEL/VOX**	**SOF/VEL**
Number of patients (N)	92	89	110	109
Mean age (range), years	[redacted]	[redacted]	54 (25-75)	55 (31-69)
Male, n (%)	[redacted]	[redacted]	74 (67.3)	83 (76.1)
Mean BMI (range), kg/m^2	[redacted]	[redacted]	28.3 (19.6-50.4)	27.8 (17.8-50.4)
Race, n (%)[b]				
White	[redacted]	[redacted]	100 (90.9)	97 (89.0)
Black	[redacted]	[redacted]	0	1 (0.9)
Asian	[redacted]	[redacted]	8 (7.3)	9 (8.3)
Other	[redacted]	[redacted]	1 (0.9)	0
American Indian or Alaska Native	[redacted]	[redacted]	1 (0.9)	1 (0.9)
Native Hawaiian or Pacific Islander	NR for subgroup	NR for subgroup	0	1 (0.9)
Black or African American	NR	NR	0	1 (0.9)

	POLARIS-2 GT3 Subgroup[a]		POLARIS-3	
Characteristic	**SOF/VEL/VOX**	**SOF/VEL**	**SOF/VEL/VOX**	**SOF/VEL**
HCV GT/subtype by sequencing				
GT3, n (%) [a]	92 (100)	89 (100)	110 (100.0)	109 (100.0)
Cirrhosis, n (%)				
Yes	[redacted]	[redacted]	110 (100)	109 (100)
No	[redacted]	[redacted]	0	0
IL28B genotype, n (%)				
CC	[redacted]	[redacted]	41 (37.3)	52 (47.7)
Non-CC	[redacted]	[redacted]	69 (62.7)	57 (52.3)
CT	[redacted]	[redacted]	57 (51.7)	44 (40.4)
TT	[redacted]	[redacted]	12 (10.9)	13 (11.9)
Baseline HCV RNA, log10 IU/mL, mean (SD)	[redacted]	[redacted]	6.0 (0.80)	6.3 (0.63)
Baseline HCV RNA category				
<800,000 IU/mL, n (%)	[redacted]	[redacted]	40 (36.4)	28 (25.7)
≥800,000 IU/mL, n (%)	[redacted]	[redacted]	70 (63.6)	81 (74.3)
Baseline ALT (U/L), mean (SD)	[redacted]	[redacted]	111 (62.2)	132 (74.6)
Baseline ALT category				
≤1.5 x ULN, n (%)	[redacted]	[redacted]	20 (18.2)	20 (18.3)
>1.5 x ULN, n (%)	[redacted]	[redacted]	90 (81.8)	89 (81.7)
Previous HCV treatment experience, n (%)				
Treatment-naïve	[redacted]	[redacted]	75/110 (68.2)	77/109 (70.6)
Treatment-experienced	[redacted]	[redacted]	35/110 (31.8)	32/109 (29.4)
DAA-naïve	[redacted]	[redacted]		
Peg-IFN+RBV	[redacted]	[redacted]	31/35 (88.6)	30/32 (93.8)
Other	[redacted]	[redacted]	4/35 (11.4)	2/32 (6.3)
Number of Patients Receiving at Least One Concomitant Medication, n (%)	NR for subgroup	NR for subgroup	153 (84.1)	132 (87.4)
Estimated GFR (mL/min), mean (SD)	[redacted]	[redacted]	126.4 (43.1)	120.5 (37.8)

ALT, alanine aminotransferase; BMI, body mass index (= weight (kg) / (height (m)2); EGFR, estimated glomerular filtration rate; GT, genotype; HCV, hepatitis C virus; IL28B, IL28B gene; NR, not reported; Peg-IFN, pegylated interferon; ribonucleic acid; RNA, ribonucleic acid; SOF, sofosbuvir; SD, standard deviation; ULN, upper limit of normal; VEL, velpatasvir; VOX, voxilaprevir.

[a] The GT3 subgroup of the POLARIS-2 trial represents approximately 19% of the total trial population. In the full trial population the represented HCV genotypes were approximately 49% GT1; 12% GT2; 19% GT3; 13% GT4; 2% GT5; 4% GT6 and 0.2% unknown.

[b] In the SOF/VEL arm of POLARIS-3 the numbers of participants reported by race sum to 110 although the overall group size should be 109.

Differences between trials in patient characteristics

In addition to looking at differences between the trial arms of each study, the ERG has also looked at the differences between POLARIS-1 and POLARIS-4, which provide evidence on the DAA-experienced patient population, and between POLARIS-2 and POLARIS-3, which provide evidence on the DAA-naïve population.

POLARIS-1 & POLARIS-4 (DAA treatment-experienced patients) differed in the proportions of the different HCV genotypes within the patient populations as shown in Table 8. Furthermore, because of the inclusion criteria in POLARIS-1, all the participants with GT2-GT6 or indeterminate HCV genotypes were assigned to the SOF/VEL/VOX arm, whereas in POLARIS-4 all the GT4, 5, or indeterminate (including GT6) participants were assigned to the SOF/VEL/VOX arm.

Table 8: Proportions of HCV genotypes in the POLARIS-1 and POLARIS-4 trials

HCV genotype	POLARIS-1	POLARIS-4
GT1	72%	43%
GT2	1%	19%
GT3	19%	32%
GT4	5%	6%
GT5	<1%	0
GT6	2%	0

Due to the difference in the inclusion criterion regarding prior treatment experience (in POLARIS-1 that participants had previously received a non-structural protein 5A (NS5A) inhibitor and in POLARIS-4 that they should have received a DAA-containing regimen but not a NS5A inhibitor) there were inevitably differences in the types of DAAs that participants in the two trials had previously received.

In both trials the majority of participants were White, but the proportion was slightly higher in POLARIS-4 (87% compared to 81% in POLARIS-1) whilst the proportion of Black participants was lower (9% compared to 14% in POLARIS-1).

Finally, the estimated mean GFR was slightly higher in POLARIS-4 (around 123 mL/min) than in POLARIS-1 (119 mL/min and 113 mL/min in each of the two trial arms) but clinical advice to the ERG was that this would not be clinically significant.

In the trials enrolling DAA treatment-naïve participants, POLARIS-3 enrolled a higher proportion of males than POLARIS-2 (72% versus 52%) and a higher proportion of the participants were White (90% versus 80% in POLARIS-2). There was only one Black participant (0.5%) in POLARIS-3 compared with 10% of participants being Black in POLARIS-2.

Due to the differences in trial inclusion criteria all the participants in POLARIS-3 had HCV GT3 and cirrhosis, whereas in POLARIS-2 almost half the participants (49%) had HCV GT1, 12% GT2, 19% GT3, 13% GT4 and around 6% with either GT5, GT6 or an unknown HCV genotype. Only the 19% of participants with HCV GT3 in POLARIS-2 meet the company's decision problem population criteria, whereas the whole of the POLARIS-3 study population are included.

Differences between the POLARIS-2 and POLARIS-3 trials in baseline ALT and the proportions in the two baseline ALT categories [higher baseline ALT and a greater proportion in the >1.5 x ULN ALT category in POLARIS-3 (82% versus 43% in POLARIS-2)] could be a consequence of all participants in POLARIS-3 having cirrhosis and would not be expected to affect SOF/VEL/VOX treatment effectiveness.

Another difference, that may also be a consequence of the requirement for participants in POLARIS-3 to have cirrhosis, was that fewer participants in POLARIS-3 were completely treatment-naïve (69% versus 77% in POLARIS-2). Of the participants that were not completely treatment naïve but who were DAA-naïve, 91% had received Peg-IFN+RBV in POLARIS-3 in comparison to 80% in POLARIS-2.

Although all four of the trials meet the inclusion criteria of the company's systematic review, the ERG has already highlighted that the process that resulted in four studies being selected for detailed examination from the 108 studies identified for inclusion by searching and screening was unclear. Furthermore the POLARIS-1 and POLARIS-4 studies, whilst allowing randomisation for some participants (those with HCV GT1 in POLARIS-1 and those with HCV GT1-3 in POLARIS-4), those participants who did not match the HCV genotype criteria for randomisation were assigned only to the SOF/VEL/VOX group of each of the trials. It is also

important to reiterate that for POLARIS-2 only the subgroup of participants with GT3 (19% of the total trial population) match the population specified in the company's decision problem as DAA treatment-naïve with CHC of genotype 3 (GT3).

The ERG believes that all the relevant trials have been identified and the ERG agrees with CS section B.2.12 which states that there are currently no ongoing studies involving SOF/VEL/VOX. The combined population from the POLARIS trials included 83 patients from the UK, but as recruitment occurred across a number European countries the CS suggests that the population is representative of the UK hepatitis C population. Clinical advice to the ERG agreed that the trial results would be expected to be applicable to the UK hepatitis C population.

3.1.4 Description and critique of the approach to validity assessment

The CS reported a quality assessment for each of the four trials (CS Table 19), using standard criteria as recommended by NICE.[19] Additional details are contained in the appendices (D.1.3 Tables 8-11).

The ERG's critique of the company's quality assessment for the four POLARIS trials is shown in Table 9. As has been described in ERG report section 2.3, the CS restricts the treatment naïve group to those with HCV GT3, who are DAA-naïve. This means that only a subgroup of the POLARIS-2 trial matches the decision problem but the CS quality assessment is provided for the POLARIS-2 trial population as a whole.

Table 9: Company and ERG assessment of trial quality

Trial name **Quality assessment question**		**POLARIS-1**	**POLARIS-4**	**POLARIS-2**	**POLARIS-3**
1. Was the method used to generate random allocations adequate?	CS:	Yes	Yes	Yes	Yes
	ERG:	Yes for GT1. N/A for other GTs	Yes for GT1-3. N/A for other GTs	Yes for GT1-4. N/A for other GTs	Yes
ERG comments: While methods to generate random allocation were adequate not all participants enrolled into the trials were eligible for randomisation. POLARIS-1, POLARIS-4 and POLARIS-2 enrolled participants with certain genotypes (GT2-6 or unknown in POLARIS-1; GT4-6 or unknown in POLARIS-					

4; GT5-6 or unknown in POLARIS-3) into the SOF/VEL/VOX treatment arm only. Thus, not all participants in these trials were randomly allocated to their treatment arm.					
2. Was the allocation adequately concealed?	CS:	Yes	Yes	Yes	Yes
	ERG:	Yes for GT1.	Yes for GT1-3.	Yes for GT1-4.	Yes
ERG comments: Some participants with genotypes not eligible for randomisation were allocated to the SOF/VEL/VOX treatment arm in POLARIS-1, POLARIS-4 and POLARIS-2.					
3. Were the groups similar at outset in terms of prognostic factors?	CS:	Yes	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes	Yes
ERG comments: This question resulted in a clarification request by the ERG and NICE to the company, as baseline characteristics for the trials were presented for all genotypes combined and no separate baseline characteristics for the population specified in the CS are presented (DAA-naïve, GT3 non-cirrhotic patients). The company subsequently provided details for the POLARIS-2 subgroup as part of their clarification responses (clarification request A3). Although there were some baseline differences between treatment groups in the trials (as described in section 3.1.3) clinical advice to the ERG was that these were unlikely to have had an effect on outcomes.					
4. Were the care providers, participants and outcome assessors blind to treatment allocation?	CS:	Yes	No	No	No
	ERG:	Yes for GT1 to post-treatment week 4. Unclear for other genotypes.	No	No	No
ERG comments: POLARIS-4, POLARIS-2 and POLARIS-3 were open-label trials.					
5. Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	CS:	No	No	No	No
	ERG:	No	No	No	No
ERG comments: Although there was a difference in dropouts between the treatment groups in all four trials, the number of dropouts in all four trials was very small (Appendix D.1.2.1.1: POLARIS-1: SOF/VEL/VOX n=0 vs SOF/VEL n=2; POLARIS-2: SOF/VEL/VOX n=1 vs SOF/VEL n=3; POLARIS-3 SOF/VEL/VOX n=0 vs SOF/VEL n=2). Due to the small numbers involved, no adjustment in analysis was needed in the trials. Reasons for discontinuations were provided for each of the trials.					

6. Is there any evidence that authors measured more outcomes than they reported?	CS:	No	No	No	No
	ERG:	No	No	No	No
ERG comments: none					
7**. Did the trial include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?**	CS:	Yes	Yes	Yes	Yes
	ERG:	No	Yes	No	No
ERG comments: The CS reports a modified ITT analysis for all trials, labelled a full analysis set in the CS, defined as all patients who underwent randomisation and received at least one dose of the study drug. This type of analysis is common in pharmaceutical trials. In POLARIS-4, all the randomised patients received study drug and hence the analysis is in effect an ITT analysis. In POLARIS-1, -2 and -3 there were only 1, 2 and 1 participants respectively who were randomised, but who did not receive study drug so there is unlikely to be any impact on outcomes Missing data appears to have been dealt with appropriately in all four of the trials.					

There were some disagreements between the company's assessments of the trial quality and the ERG's. Not all participants in POLARIS-1, POLARIS-4 and POLARIS-2 were randomised to a treatment arm. Participants with certain genotypes could only be enrolled into the SOF/VEL/VOX treatment arm. The allocation of participants of certain genotypes to only one arm of POLARIS-1, -4 and -2 led to differences between the treatment groups in these trials. Clinical advice to the ERG was that, randomisation for the rarer HCV genotypes would have been difficult, but the inclusion of the rarer genotypes in the trials has provided valuable clinical information about response to treatment in patients with these rarer HCV genotypes. Although there were differences in baseline characteristics between treatment arms in some of the trials (for details see section 3.1.3) these are not expected to have affected treatment effectiveness. There were also differences in dropouts between the treatment groups in the four trials, although numbers were low in all four trials reducing the impact that this might have had.

3.1.5 Description and critique of company's outcome selection

The outcomes in the CS match those listed in the NICE scope and the decision problem (see Table 10), with some additional outcomes also present in the submission.

Table 10: Comparison of outcomes listed in the NICE scope and the CS

Outcome	NICE scope	CS	Notes
SVR	✓	✓	Reported as SVR at 12 weeks, which is the primary outcome and as a secondary outcome at 4 and 24 weeks.
Development of resistance to treatment to SOF/VEL/VOX	✓	✓	States that development of resistance to SOF/VEL/VOX is discussed only in section 2.10 (appears to be an error, presumed to be section 2.6)
Mortality	✓	✓	
Adverse effects of treatment	✓	✓	
HRQoL	✓	✓	Validated measures were • 36-Item Short-Form Survey (SF-36) • Chronic Liver Disease Questionnaire-Hepatitis C Version (CLDQ-HCV) • Fatigue Index (FACIT-F) • Work productivity and Activity Impairment: Hepatitis C (WPAI: Hep C)

CS, company submission; HCV, hepatitis-c virus; HRQoL, health related quality of life; SOF/VEL/VOX, Sofosbuvir/Velpatasvir/ Voxilaprevir; SVR - sustained virological response.

The primary outcome in the submission is SVR reported at 12 weeks (SVR12), defined as HCV RNA less than the lower limit of quantitation (LLOQ) 12 weeks after cessation of treatment. This endpoint was accepted by the EMA and FDA in the evidence submitted by the company for regulatory approval. It is also a secondary outcome reported at week 4 (SVR4) and 24 weeks (SVR24). These endpoints were also included in the evidence submitted to the EMA. The CS states that SVR12 has been shown to have high concordance with SVR24 rates based on clinical trial data of various treatment regimens and durations, and that this is supported by evidence.[20 21]

HRQoL is presented in the form of outcomes obtained from four validated questionnaires: 36-Item Short-Form Survey (SF-36), Chronic Liver Disease Questionnaire-Hepatitis C Version (CLDQ-HCV), Fatigue Index (FACIT-F) and Work productivity and Activity Impairment: Hepatitis C (WPAI: Hep C). While the SF-36 questionnaire is a well-recognised generic HRQoL instrument, the CLDQ-HCV questionnaire is a disease-specific instrument developed for patients with CHC.[22] The FACIT-F on the other hand is a compilation of questions that measure HRQoL in patients with cancer[23] and other chronic diseases.[24] The WPAI questionnaire is long-established,[25] and the hepatitis C version has been used in previous sofosbuvir studies.[26]

Other secondary outcomes provided in the CS that were not included in the NICE scope are: HCV RNA change from baseline to end of treatment (EOT), HCV RNA<LLOQ on treatment and virologic failure. ALT normalisation is listed with HRQoL under 'Other outcomes of interest' (CS Table 12). The CS provides justification for the inclusion of each of these additional outcomes. The company proposes that outcomes such as the kinetics of circulating HCV RNA during treatment (used to monitor and, for some HCV drugs, to guide treatment) and ALT normalisation (important laboratory test marker for monitoring HCV disease activity) are clinically relevant, while virologic failure provides a measure of treatment failure either on-treatment (by way of viral breakthrough, rebound, or non-response) or in the post-treatment phase (relapse). Advice to the ERG suggests that clinicians will rely almost entirely on SVR12, HCV RNA monitoring is unlikely to come into routine use.

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

The CS reports the results for all the outcomes listed in the company's decision problem (CS Table 1) for all four of the POLARIS trials included in the submission. No interim of analyses are presented.

The CS presents a summary of the statistical analyses in CS Table 18 for each trial. This table reports the trial hypothesis, statistical analysis methods for the primary and secondary endpoints, details about the sample size and power calculations and methods for managing missing data. POLARIS-1, -4, and -3 were each designed such that the individual trial arms were tested against a predefined performance SVR12 goal. The trial arms were not compared with each other. For POLARIS-1 and POLARIS-4 the predefined SVR12 goal was 85% (i.e. the primary efficacy hypothesis was that the rate of SVR12 among patients receiving

SOF/VEL/VOX would be superior to the pre-specified SVR12 of 85%), for POLARIS-3 the SVR12 goal was 83%. The basis for the SVR12 85% goal for the DAA-experienced trials included the trend towards increasing SVR rates in recent years, the appeal of using a fixed clinically relevant threshold as a measure of treatment benefit of SOF/VEL/VOX and the fact that it is difficult to characterise a historical control rate for all the HCV genotypes because of the lack of a standard of care. The basis for the 83% SVR12 performance goal for the DAA-naïve trials was the prior results of SOF/VEL in this patient population in the ASTRAL-3 trial[1] [SVR, 91%; 95% confidence interval (CI), 83–96]. Neither POLARIS-1 nor POLARIS-4 recruited sufficient participants to achieve the sample size determined by the power calculations. For POLARIS-1 the calculated sample size for the SOF/VEL/VOX arm was 280 patients, but 263 were actually enrolled and treated in the SOF/VEL/VOX arm. In POLARIS-4, the calculated sample sizes were 205 for the SOF/VEL/VOX arm (182 actually enrolled and treated) and 175 for the SOF/VEL arm (151 actually enrolled and treated). POLARIS-4 was not powered for a comparison between SOF/VEL/VOX and SOF/VEL (as stated each arm was compared to the SVR 85% performance goal). The CS does not indicate why neither of these studies met the required sample size or what the impact could have been (if any) on the primary outcome. Although POLARIS-2 (a non-inferiority trial) achieved the required sample size for the study as a whole, the submission focuses on the HCV GT3 subgroup of this trial and therefore the primary outcome for this GT3 subgroup (which represents approximately 19% of the total enrolment for the trial) will not be sufficiently powered.

Efficacy results are presented in the CS predominantly in terms of percentages with 95% CIs and p-values. The number of participants included in these analyses is clearly identified. Some outcomes (e.g. HCV RNA levels and HRQoL) are presented as mean values with standard deviation. The number of participants contributing data to these outcomes is not clearly stated.

Analysis sets

The CS describes two analysis sets for the four POLARIS trials, which are summarised in CS B.2.4. The FAS includes all patients who were randomised or enrolled (in the case of patients with HCV genotypes that were not eligible for randomisation) into the study and who received at least one dose of study drug. The CS states that patients were grouped within the FAS by the treatment group to which they were randomised or enrolled, which would be similar to an ITT analysis, but has excluded a small proportion of participants that did not receive the study drug.

The second analysis set was the safety analysis set (SAS). The CS states that this set included patients who were randomised into the study, but from the patient numbers given the ERG believes patients enrolled (who were not eligible for randomisation) were also included. Patients had to have received at least one does of study drug (including placebo) and were grouped by the treatment to which they were randomised or enrolled.

Subgroups

The CS summarises the 17 characteristics in B.2.7 (randomisation stratification factors and prognostic baseline characteristics) that were included in the pre-planned subgroup analyses of SVR12 rates across all four of the POLARIS trials. Results were not presented in the main report document but in CS Appendix E.

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

The submission provides a narrative summary of the four included trials based all of the genotypes included in the treatment arms. For POLARIS-2 this means that instead of focussing on the DAA-naïve, HCV GT3 non-cirrhotic patients specified in the decision problem data are included for participants of other genotypes who are not relevant to the company's decision problem. Where possible the ERG has checked key data presented in the CS against those in the publications and aside from a few minor discrepancies, the data reported in the CS appears to be accurate.

The CS does not include a meta-analysis. For the DAA-experienced patient group the justification is that the economic analysis compares SOF/VEL/VOX with no treatment and POLARIS-1 provides data for this head-to-head comparison. Although not explicitly stated by the CS, the ERG believes that the POLARIS-1 trial is the only available source of evidence for this comparison (i.e. there are no other trials to combine in a meta-analysis). Results from POLARIS-4 are used in a scenario analysis in the economic analysis.

For the second patient group defined in the decision problem, DAA-naïve patients with HCV GT3, the company did provide a figure for an exploratory NMA based on their clinical systematic literature review. This built on work done by the company for an earlier systematic literature review for the SOF/VEL submission to NICE (NICE TA 430).[14] The only new SVR data to add

to the network for DAA-naïve patients with HCV GT3 came from the POLARIS-3 (cirrhotic patients) and the POLARIS-2 trial (non-cirrhotic patients), albeit for the latter patients with GT3 were a subgroup. To be consistent with the SOF/VEL submission, the reference treatment was defined as Peg-IFN2a+RBV (selected because it represents a historical standard of care), but the network could only be created if both non-cirrhotic and cirrhotic patients were included. To complete the network, the small phase II ELECTRON trial[27] was included (CS Figure 1), but there was a 100% SVR12 for both arms treatment arms (SOF+RBV and SOF+Peg-IFN+RBV).[27] As this SVR12 rate has not been replicated in other studies, the company suggests that the trial lacks clinical credibility.

For those trials which provided data for the DAA-naïve patients with a HCV GT3 population, the CS states that the proportion of patients with cirrhosis varied significantly (16-38%). The ERG has checked and found this to be the case based on the publications of the included trials. Taking all of the above into account, the company deemed it to be inappropriate to use the NMA in the economic analysis (CS B.2.8). The CS states that this is consistent with the conclusions drawn for the SOF/VEL submission. The ERG agrees that this is the case for the SOF/VEL submission to NICE. Considering all these factors, the ERG agrees that a NMA for the DAA-naïve, HCV GT3 population stipulated in the CS would not be robust. It should be noted that the NICE committee considering the SOF/VEL submission judged the use of SVR rates from individual trials instead of a NMA appropriate for the model comparisons.[14]

The ERG has not reproduced the proposed network diagram for DAA-naïve patients with HCV GT3 infection (cirrhotic and non-cirrhotic) provided in the CS (CS section B.2.8, Figure 2), as the colour keys for the diagram would not be easily distinguishable in the black and white format of the ERG report.

3.2 Summary statement of company's approach

Table 11 provides the ERG's quality assessment of the company's systematic review of clinical effectiveness.

Information concerning the processes of the literature review were contained in CS Appendix D. The table presenting the inclusion criteria and exclusion criteria for the company's systematic review of the literature contained an error omitting the study design (see Table 11), which was

rectified by the company's response to following a clarification request (A18). It was not clear from the exclusions criteria, whether studies on patients with decompensated cirrhosis were specifically excluded, which again was rectified by the company's response to clarification request A19, in that the license for SOF/VEL/VOX does not include these patients, hence they were excluded.

Methods for inclusion and exclusion of trials followed standard systematic review procedures. Title/ abstract (screened against pre-determined eligibility criteria) and full papers and ongoing trials were screened independently by two researchers, with disagreements resolved by a third researcher (CS Appendix D.1.1.6). Data extractions, on the other hand, were performed by one researcher and checked by a second. This is an acceptable method in conducting systematic reviews. It is unclear if the quality assessments of the trials were conducted by a single reviewer and checked by a second, or if this was carried out independently by two reviewers. Either would be an acceptable method.

The searches in the CS covered a wide range of electronic databases, but as stated earlier it was not clear how the company selected the four POLARIS trials from the 108 identified studies for inclusion in the systematic review (CS sections B.2.2 to B.2.11). In response to clarification request A1, the company states that at the time of the searches for the systematic literature review the four trials were unpublished and hence not identified in this manner. Evidence for the POLARIS trials came from the Company Study Reports (CSRs). The ERG has found that the searches did identify three references to POLARIS trials, one (for POLARIS-3) in the included studies list and two (for POLARIS-1 and -4) in the excluded studies list. Therefore, despite appropriate methods in place to identify relevant literature, two relevant references appear to have been excluded.

The validity of all four of the included trials is adequately assessed in the CS, using standard CRD criteria (CS Table 19).[19] The population described in the CS decision problem is more restricted than that described in the NICE scope. However, the evidence submitted generally reflects the company's decision problem, which is informed by the NICE scope. Presentation of data from the POLARIS-2 is the exception, as the main body of the CS did not focus on the subgroup of participants from this trial who met the more restricted population defined in the CS decision problem (GT3 DAA-naïve). Instead, data for the whole POLARIS-2 trial population were reported. The ERG and NICE asked the company to supply data for the GT3 subgroup

from POLARIS-2 and in response to a clarification request (A3), the company provided baseline characteristics, as well as results for SVR12 and virological outcomes for this subgroup.

The CS presents sufficient detail in of the individual studies, although each trial is reported separately.

In summary, the ERG is confident that the systematic search identified all the relevant evidence but, due to shortcomings in the execution of the inclusion and exclusion screening processes relevant references were excluded. However, since this systematic review was conducted by the company who had access to and included the CSRs for all the POLARIS trials, the ERG does not believe that any relevant evidence has been omitted from the CS.

Table 11: Quality assessment (CRD criteria) of CS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes. Inclusion and exclusion criteria are clearly tabulated but placed in an appendix (Appendix D.1.1.6, Table 2). The table did however contain an error as previously stated (inclusion criteria for study design were not presented - instead details were duplicated on included outcomes. Inclusion criteria on study design were supplied as response to a clarification request (A18) which indicated phase II, III or IV RCTs, systematic literature reviews and meta-analyses were eligible for inclusion. In addition, it was unclear whether studies including patients with decompensated cirrhosis were specifically excluded. In response to a clarification request by the ERG and NICE (A19), the company stated they were excluded because patients with decompensated cirrhosis were not included under the license for SOF/VEL/VOX.
2. Is there evidence of a substantial effort to search for all relevant research? i.e. all studies identified	Yes (please see section 3.1.1 for our critique of the company's searches). A wide range of electronic databases and other sources were searched. However, it was unclear how the company selected the four POLARIS trials from the 108 identified studies for inclusion in the systematic review (CS appendix D.1.1.6 to D.1.1.11). In response to a clarification request A1 by the ERG and NICE, the company stated that the four POLARIS trials were not identified through the systematic literature review, instead the presented clinical evidence was based on the POLARIS trials CSRs. The ERG however identified one reference

	to POLARIS-3 among the included studies list, and found references to POLARIS-1 and POLARIS-4 among the excluded studies list. The ERG has concerns about the processes used to identify relevant clinical evidence from among the literature search results.
3. Is the validity of included studies adequately assessed?	Yes. Standard CRD[19] criteria as recommended by NICE are used to quality assess the four included trials (CS section B.2.5, Table 19).
4. Is sufficient detail of the individual studies presented?	Yes. Methodology, patient characteristics and outcomes of the four included trials are presented in sufficient detail. However, sufficient details were not provided for the GT3, DAA treatment-naïve patient subgroup of POLARIS-2 The ERG and NICE requested further details which were provided in response to clarification request A3. Outcomes for the four included trials are presented in a separate sections of the CS (CS sections B.2.6.1 to B.2.6.4).
5. Are the primary studies summarised appropriately?	Yes. However, as stated previously, only the subgroup of participants with GT3 in POLARIS-2 (19% of the total trial population) match the population specified in the company's decision problem (GT3, DAA treatment-naïve) whereas the summaries in the CS are for the total trial population of POLARIS-2 (SVR12 data were provided in Appendix E.1.3 and also presented together with virological outcomes by genotype for GT3 patients for POLARIS-2 in response to clarification request A3).

3.3 Summary of submitted evidence

Results are presented separately, firstly for the DAA-experienced population (section 3.3.1) and then for the DAA-naïve population (section 3.3.2).

Data have been reproduced here chiefly from the CS, but supplemented by the ERG with data from the trial journal publications and CSRs where necessary.

3.3.1 Adults with CHC who have had previous treatment with DAA agents for CHC (DAA-experienced)

3.3.1.1 Summary of SVR12 results for the DAA-experienced population (Primary outcome)

The POLARIS-1 and POLARIS-4 trials provide evidence on the efficacy of SOF/VEL/VOX but the two trial arms in each study were not compared with each other. Instead, each arm was tested individually for superiority against a predefined performance SVR12 goal of 85% (i.e. 85% of the trial population achieving SVR12 was defined as a benchmark against which to test the efficacy of SOF/VEL/VOX). In both trials, the proportion of participants in the SOF/VEL/VOX arm achieving SVR12 was statistically significantly greater than the pre-specified 85% performance goal (Table 12). In POLARIS-1 no participants in receipt of placebo achieved SVR12 and in POLARIS-4, although just over 90% of participants in the SOF/VEL arm achieved SVR12, this was not statistically significantly greater than the 85% performance goal. POLARIS-4 was not powered for a comparison between SOF/VEL/VOX and SOF/VEL.

Table 12: Proportion of DAA-experienced patients who achieve SVR12 (Final analysis set)

Trial name	POLARIS-1		POLARIS-4	
Parameter	SOF/VEL/VOX (n=263)	Placebo (n=152)	SOF/VEL/VOX (n=182)	SOF/VEL (n=151)
SVR12, n/N (%) [a]	253/263 (96.2)	0/152	178/182 (97.8)	136/151 (90.1)
SVR12 95% CI	93.1 to 98.2		94.5 to 99.4	84.1 to 94.3
p-value (compared with 85% performance goal) [b]	<0.001		<0.001	0.092

CI, confidence interval; LLOQ, lower limit of quantitation; SOF, sofosbuvir; SVR, sustained virological response; TND, target not detected; VEL, velpatasvir; VOX, voxilaprevir.

[a] SVR12 was defined as HCV RNA less than the lower limit of quantitation (LLOQ) 12 weeks after discontinuation of the study drug. A missing SVR12 value was imputed as a success if it was bracketed by values that were termed successes (i.e. '<LLOQ TND' or '<LLOQ detected'), otherwise, the missing SVR12 value was imputed as a failure.

[b] The exact 95% CI for the proportion within treatment group is based on the Clopper-Pearson method. The p-value was obtained from the 2-sided exact 1-sample binomial test for the superiority over the performance goal of 85%

Data based on CS Table 20 and CS Table 25

3.3.1.2 Summary of SVR4 and SVR24 results for the DAA-experienced population (Secondary outcomes)

The SVR4 outcomes provided an early indication of SRV12 outcomes. In POLARIS-1 four participants in the SOF/VEL/VOX arm who attained SVR4 were not represented in the SVR12 data (three relapsed and one withdrew consent), whilst there was one relapse in the SOF/VEL/VOX arm of POLARIS-4 and two among the SOF/VEL participants. Not all the POLARIS-1 participants who achieved SVR12 attended the post-treatment 24 week visit, however of the 249/253 (98%) who did attend, all achieved SVR24. All participants in POLARIS-4 who achieved SVR12 also achieved SVR24.

Table 13: Proportion of DAA-experienced patients who achieve SVR4 and SVR24 (Final analysis set)

Trial name	**POLARIS-1**		**POLARIS-4**	
Parameter	**SOF/VEL/VOX (n=263)**	**Placebo n=152**	**SOF/VEL/VOX (n=182)**	**SOF/VEL (n=151)**
SVR4, n/N (%) [a]	257/263 (97.7)	0/152	179/182 (98.4)	138/151 (91.4)
SVR4 95% CI	95.1 to 99.2	0.0 to 2.4	95.3 to 99.7	85.7 to 95.3
SVR24, n/N (%) [a]	249/249 [b]	-	178/182 (97.8)	136/151 (90.1)
SVR24 95% CI	NR	-	94.5 to 99.4	84.1 to 94.3

CI, confidence interval; NR, not reported; SOF, sofosbuvir; SVR, sustained virological response; VEL, velpatasvir; VOX, voxilaprevir.

[a] SVR4 and SVR24 were defined as HCV RNA less than the lower limit of quantitation (LLOQ) 4 weeks or 24 weeks respectively after discontinuation of the study drug. A missing SVR4 or SVR24 value was imputed as a success if it was bracketed by values that were termed successes (i.e. '<LLOQ TND' or '<LLOQ detected'), otherwise, the missing SVR value was imputed as a failure. The exact 95% CI for the proportion within treatment group is based on the Clopper-Pearson method.

[b] SVR24 data for POLARIS-1 comes from the published paper and was confirmed by the company's response to Clarification question A8. In total 253 participants achieved SVR12 but SVR24 data are missing for four of these participants, the missing data will be reconciled in the final CSR due in 2018.

Data based on CS Table 21 and CS Table 26

3.3.1.3 Proportion of DAA-experienced patients with HCV RNA < LLOQ (15 IU/mL) while on treatment

The data on HCV RNA levels less than the lower limit of quantitation (LLOQ) during treatment show the rapid response to treatment with the 'Week 2' data already showing more than half of participants receiving active treatment with SOF/VEL/VOX or SOF/VEL having HCV RNA <LLOQ (Table 14).

Table 14: Proportion of DAA-experienced patients with HCV RNA < LLOQ (15 IU/mL) while on treatment by visit (Final analysis set)

Trial name	POLARIS-1		POLARIS-4	
Parameter, n/N (%)	SOF/VEL/VOX 12 weeks N=263	Placebo 12 weeks N=152	SOF/VEL/VOX 12 weeks N=182	SOF/VEL 12 weeks N=151
Baseline				
<LLOQ [a]	0/263	0/152	0/182	0/151
Week 1				
<LLOQ	41/263 (15.6)	0/152	29/182 (15.9)	26/151 (17.2)
95% CI	11.4 to 20.5	0.0 to 2.4	10.9 to 22.1	11.6 to 24.2
<LLOQ detected	38/263 (14.4)	0/152	25/182 (13.7)	22/151 (14.6)
<LLOQ TND	3/263 (1.1)	0/152	4/182 (2.2)	4/151 (2.6)
Week 2				
<LLOQ	149/263 (56.7)	0/150	114/182 (62.6)	85/151 (56.3)
95% CI	50.4 to 62.7	0.0 to 2.4	55.2 to 69.7	48.0 to 64.3
<LLOQ detected	93/263 (35.4)	0/150	83/182 (45.6)	61/151 (40.4)
<LLOQ TND	56/263 (21.3)	0/150	31/182 (17.0)	24/151 (15.9)
Week 4				
<LLOQ	243/262 (92.7)	0/150	161/182 (88.5)	137/151 (90.7)
95% CI	88.9 to 95.6	0.0 to 2.4	82.9 to 92.7	84.9 to 94.8
<LLOQ detected	76/262 (29.0)	0/150	46/182 (25.3)	47/151 (31.1)
<LLOQ TND	167/262 (63.7)	0/150	115/182 (63.2)	90/151 (59.6)

Week 8				
<LLOQ	262/262 (100.0)	0/150	182/182 (100.0)	149/151 (98.7)
95% CI	98.6 to 100.0	0.0 to 2.4	98.0 to 100.0	95.3 to 99.8
<LLOQ detected	5/262 (1.9)	0/150	6/182 (3.3)	4/151 (2.6)
<LLOQ TND	257/262 (98.1)	0/150	176/182 (96.7)	145/151 (96.0)
Week 12				
<LLOQ	260/261 (99.6)	0/149	180/182 (98.9)	149/150 (99.3)
95% CI	97.9 to 100.0	0.0 to 2.4	96.1 to 99.9	96.3 to 100.0
<LLOQ detected	0/261	0/149	0/182	1/150 (0.7)
<LLOQ TND	260/261 (99.6)	0/149	180/182 (98.9)	148/150 (98.7)

CI, confidence interval; LLOQ, lower limit of quantitation; SOF, sofosbuvir; TND, target not detected; VEL, velpatasvir; VOX, voxilaprevir.

[a] LLOQ=15 IU/mL. Missing values for on-treatment visits were imputed up to the time of last dose (if the study day associated with the last dose date was greater than or equal to the lower bound of a visit window, the missing value at the visit was imputed, otherwise, the value was excluded); Missing values bracketed by values of '<LLOQ TND' were set to '<LLOQ TND'; bracketed by '<LLOQ detected', or '<LLOQ TND' and '<LLOQ detected' were set to '<LLOQ detected'; otherwise, the missing values were set as '≥LLOQ'. The exact 95% CI for the proportion within treatment group and genotype is based on the Clopper-Pearson method.

Data based on CS Table 22 and CS Table 27

3.3.1.4 HCV RNA level change from baseline in the DAA-experienced population

Participants receiving active treatment with SOF/VEL/VOX or SOF/VEL exhibited a rapid fall in HCV RNA level that was observed from Week 1 and was maintained throughout the 12 week treatment period. No change in HCV RNA level was observed in the placebo group of POLARIS-1 (Table 15).

Table 15: Summary of HCV RNA levels at baseline and at Weeks 1 and 12 of treatment for DAA-experienced patients

Trial name	POLARIS-1				POLARIS-4			
HCV RNA level (Log10 IU/mL)	SOF/VEL/VOX 12 weeks N=263		Placebo 12 weeks N=152		SOF/VEL/VOX 12 weeks N=182		SOF/VEL 12 weeks N=151	
Baseline	n=263	6.25 (0.678)	n=152	6.27 (0.635)	n=182	6.31 (0.562)	n=151	6.25 (0.659)
Week 1, mean (SD)	n=258	2.06 (0.674)	n=150	6.29 (0.569)	n=181	2.02 (0.662)	n=148	2.09 (0.697)
Change from baseline		-4.20 (0.733)		0.02 (0.300)		-4.29 (0.627)		-4.17 (0.651)
Week 12, mean (SD)	n=261	1.15 (0.119)	n=138	6.28 (0.565)	n=180	1.15 (0.000)	n=150	1.17 (0.239)
Change from baseline		-5.10 (0.690)		0.03 (0.430)		-5.17 (0.559)		-5.09 (0.727)

SD, standard deviation; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

Data based on CS text and Tables S3 and S4 in the Supplementary Appendix to the published paper[18]

3.3.1.5 Virologic failure in the DAA-experienced population

Among participants receiving SOF/VEL/VOX, on-treatment virologic failure only occurred once (one participant in POLARIS-1), with relapse after cessation of treatment occurring in six participants in POLARIS-1 and one participant in POLARIS-4. A further three POLARIS-1 and three POLARIS-4 participants did not achieve SVR12, but did not meet the criteria for virologic failure and were therefore categorised as 'Other' (Table 16).

Of the seven participants across the two trials who received SOF/VEL/VOX and relapsed after treatment, relapse was identified at post-treatment week 4 in four participants (three POLARIS-1 and one POLARIS-4) and at the post-treatment week 12 visit in the remaining three participants (all POLARIS-1).

The proportion of participants with overall virologic failure in the SOF/VEL arm of POLARIS-4 was numerically greater than the overall virologic failure in the SOF/VEL/VOX arm. One SOF/VEL participant experienced on-treatment virologic failure and 14 participants relapsed.

Table 16: Virologic outcomes among DAA-experienced patients (Final analysis set)

Trial name / Parameter	POLARIS-1[a]	POLARIS-4	
	SOF/VEL/VOX 12 weeks N=263	SOF/VEL/VOX 12 weeks N=182	SOF/VEL 12 weeks N=151
SVR12, n/N (%)	253/263 (96.2)	178/182 (97.8)	136/151 (90.1)
Overall virologic failure	7/263 (2.7)	1/182 (0.5)	15/151 (9.9)
Relapse [b]	6/261 (2.3)	1/182 (0.5)	14/150 (9.3)
Completed study treatment	6/260 (2.3)	1/182 (0.5)	13/149 (8.7)
Discontinued study treatment	0/1	0/0	1/1 (100.0)
On-treatment virologic failure [c]	1/263 (0.4)	0/182	1/151 (0.7)
Other [d]	3/263 (1.1)	3/182 (1.6)	0/151

SOF, sofosbuvir; SVR, sustained virological response; VEL, velpatasvir; VOX, voxilaprevir.

[a] No participants achieved SVR12 in the placebo arm of the POLARIS-1 study so as there had not been any virological successes, there could not be any virological failures.

[b] Relapse = confirmed HCV RNA ≥LLOQ during the post-treatment period having achieved HCV RNA<LLOQ at last on-treatment visit.

[c] On-Treatment Virologic Failure = Breakthrough (confirmed HCV RNA ≥LLOQ after having previously had HCV RNA<LLOQ while on treatment), Rebound (confirmed >1 log10IU/mL increase in HCV RNA from nadir while on treatment), or Nonresponse (HCV RNA persistently ≥LLOQ through 8 weeks of treatment).

[d] Other = participants who did not achieve SVR12 and did not meet virologic failure criteria. In POLARIS-1, 2 withdrew consent and 1 was lost to follow-up. In POLARIS-4 1 died and 2 were lost to follow-up.

Data based on CS Table23 and CS Table 28

3.3.1.6 Development of resistance in the DAA-experienced population

The CS presents virologic resistance analysis for patients in the SOF/VEL/VOX group in POLARIS-1 and the SOF/VEL/VOX and SOF/VEL groups in POLARIS-4. The resistance

analysis population is defined as all subjects in the safety analysis set with a confirmed virologic outcome. The resistance analysis focuses on the three genes that encoding the proteins that are the targets for SOF, VEL and VOX, the NS5B, NS5A, and NS3/4A genes respectively.

In POLARIS-1 at baseline, 78.8% patients in the SOF/VEL/VOX group had NS3 and/or NS5A resistance-associated variants (RAVs). The most common RAVs across all genotypes were NS5A RAVs (75.4%). In POLARIS-4 at baseline 49% of patients had NS3 or NS5A RAVs.[18] The presence of baseline RAVs did not impact on patient's SVR12 rates (POLARIS-1: RAVs 97.1%, no RAVs 97.7%; POLARIS-4 SOF/VEL/VOX: RAVs 100.0%, no RAVs 98.8%; SOF/VEL: RAVs 90.0%, no RAVs 89.3%).

The single participant with on-treatment virologic failure in the POLARIS-1 SOF/VEL/VOX group had two additional NS5A RAVs emerge (in addition to an existing NS5A RAV present at baseline) but there was evidence to suggest nonadherence to study medication in this participant.[18] In POLARIS-4 the only on-treatment virologic failure was in the SOF/VEL group in a participant with a treatment-emergent NS5A RAV and a NS5B RAV.

Relapse after completion of study treatment occurred in six participants in the SOF/VEL/VOX group of POLARIS-1, a newly emergent NS5A RAV is reported in one participant (who already had a different NS5A RAV at baseline). Among the remaining five in POLARIS-1 with relapse, one had no RAVs, two had the same RAVs at baseline and at relapse and two had enrichment for a NS5A RAV present at baseline.[18] In POLARIS-4 one participant in the SOF/VEL/VOX arm relapsed but no NS3, NS5A, or NS5B nucleoside inhibitor (NI) RAVs were detected at baseline or at time of relapse. Among the 14 participants in the SOF/VEL arm of POLARIS-4 who relapsed after completion of study treatment 10 had newly emergent NS5A RAVs. No newly emergent NS5B NI RAVs were observed in any of the relapsed patients in POLARIS-4.

3.3.1.7 ALT normalisation in the DAA-experienced population

The CS does not present detailed outcome data on change in ALT normalisation (observed in all active treatment groups). Decreases in median ALT values were coincident with decreases in HCV RNA (i.e. suppression of viral replication). In the SOF/VEL/VOX arm of POLARIS-1 there was a median decrease of -40U/L for the duration of the treatment period and at the post-treatment week 4 visit (with no relevant changes in the placebo group). In POLARIS-4 the

median changes from baseline to post-treatment week 4 ranged from −40 to −38 U/L across both treatment groups.

3.3.2 Adults with CHC of genotype 3 (GT3) who have not received any previous treatment with DAA agents for CHC (the DAA-naïve population)

Although the NICE scope encompasses treatment naïve CHC patients with any genotype of CHC, the CS restricts the treatment naïve group to those with CHC of GT3 who have had no previous treatment with DAA agents for CHC (DAA-naïve). Evidence is presented in the CS from the POLARIS-2 and POLARIS-3 trials, however patients with HCV GT3 who do not have cirrhosis form a subgroup of the POLARIS-2 trial and no outcome data are presented for this subgroup in the main body of the CS (limited data are presented in Appendix E.1.3). All the participants in the POLARIS-3 trial had HCV GT3 and cirrhosis. In response to clarification question A3 the company reiterated the data presented in the CS Appendix but did not provide any other results (e.g. SVR4, SVR24, HRQoL) for this subgroup.

3.3.2.1 Summary of SVR12 results for the DAA-naïve HCV GT3 population (Primary outcome)

In the case of the overall POLARIS-2 trial population (all HCV genotypes), the SVR12 rate for the SOF/VEL/VOX 8-week arm did not demonstrate non-inferiority in comparison to the SOF/VEL 12-week arm (data not shown but available in CS Table 30). In the subgroup of participants in POLARIS-2 with HCV GT3 and who do not have cirrhosis (who are relevant to the decision problem), the SVR12 rate for the SOF/VEL/VOX 8-week arm was 98.9% in comparison to 96.6% in the SOF/VEL 12-week arm (Table 17).

In POLARIS-3, SVR12 was reported and tested against a performance SVR12 goal of 83%. The proportion of participants in the SOF/VEL/VOX 8-week arm and in the SOF/VEL 12-week arm achieving SVR12 was statistically significantly greater than the prespecified 83% performance goal (Table 17). The SVR12 rate was just above 96% in both arms of the POLARIS-3 trial.

Table 17: Proportion of DAA-naïve patients with HCV GT3 who achieve SVR12 (Final analysis set)

Trial name	POLARIS-2 DAA-naïve, non-cirrhotic HCV GT3 (subgroup)		POLARIS-3 DAA-naïve, cirrhotic HCV GT3 (whole study)	
Parameter	SOF/VEL/VOX 8 weeks (n=92)	SOF/VEL 12 weeks (n=89)	SOF/VEL/VOX 8 weeks (n=110)	SOF/VEL 12 weeks (n=109)
SVR12, n/N (%) [a]	91/92 (98.9)	86/89 (96.6)	106/110 (96.4)	105/109 (96.3)
SVR12 95% CI	[redacted]	[redacted]	91.0 to 99.0	90.9 to 99.0
SOF/VEL/VOX 8 weeks vs SOF/VEL 12 weeks Prop Diff (95% CI)	[redacted]		NR	NR
p-value (compared with 83% performance goal) [b]	NR	NR	<0.001	<0.001

CI, confidence interval; LLOQ, lower limit of quantitation; NR, not reported; SOF, sofosbuvir; SVR, sustained virological response; TND, target not detected; VEL, velpatasvir; VOX, voxilaprevir.

[a] SVR12 was defined as HCV RNA less than the lower limit of quantitation (LLOQ) 12 weeks after discontinuation of the study drug. A missing SVR12 value was imputed as a success if it was bracketed by values that were termed successes (i.e. '<LLOQ TND' or '<LLOQ detected'), otherwise the missing SVR12 value was imputed as a failure.

[b] The p-value was obtained from the 2-sided exact 1-sample binomial test for the superiority over the performance goal of 83%

Data based on CS Appendix E.1.3 Table 14 and CS Table 35.

3.3.2.2 Summary of SVR4 and SVR24 results for the DAA-naïve HCV GT3 population (Secondary outcomes)

In line with the studies in the DAA-experienced population (POLARIS-1 and POLARIS-4), the SVR4 outcomes in the DAA-naïve populations of POLARIS-2 and POLARIS-3 provided an early indication of SRV12 outcomes. For the relevant HCV GT3 subgroup of POLARIS-2 however, separate SVR4 and SVR24 data were not presented. In POLARIS-3 one participant in the SOF/VEL/VOX arm and one in the SOF/VEL arm who attained SVR4 were not represented in the SVR12 data (due to a death in the SOF/VEL/VOX arm and one participant failed to return

for the SVR12 visit in the SOF/VEL arm). All participants in POLARIS-3 who achieved SVR12 also achieved SVR24 (Table 18).

Table 18: Proportion of DAA-naïve patients with HCV GT3 who achieve SVR4 and SVR24 (Final analysis set)

Trial name	POLARIS-2 DAA-naïve, non-cirrhotic HCV GT3 (subgroup)		POLARIS-3 DAA-naïve, cirrhotic HCV GT3 (whole study)	
Parameter	SOF/VEL/VOX 8 weeks (n=92)	SOF/VEL 12 weeks (n=89)	SOF/VEL/VOX 8 weeks (n=110)	SOF/VEL 12 weeks (n=109)
SVR4, n/N (%) [a]	NR	NR	107/110 (97.3)	106/109 (97.2)
SVR4 95% CI	NR	NR	92.2 to 99.4	92.2 to 99.4
SVR24,n/N (%) [a]	NR	NR	106/110 (96.4)	105/109 (96.3)
SVR24 95% CI	NR	NR	91.0 to 99.0	90.9 to 99.0

CI, confidence interval; NR, not reported; SOF, sofosbuvir; SVR, sustained virological response; VEL, velpatasvir; VOX, voxilaprevir.

[a] SVR4 and SVR24 were defined as HCV RNA less than the lower limit of quantitation (LLOQ) 4 weeks or 24 weeks respectively after discontinuation of the study drug. A missing SVR4 or SVR24 value was imputed as a success if it was bracketed by values that were termed successes (i.e. '<LLOQ TND' or '<LLOQ detected'), otherwise the missing SVR value was imputed as a failure.

Data based on CS Table 36

3.3.2.3 Proportion of the DAA-naïve HCV GT3 population with HCV RNA < LLOQ while on treatment

The data from POLARIS-3 on HCV RNA levels less than the lower limit of quantitation (LLOQ) during treatment show the rapid response to treatment with the 'Week 2' data already showing at least half of participants receiving active treatment with SOF/VEL/VOX or SOF/VEL having HCV RNA <LLOQ and over 85% with HCV RNA <LLOQ at 'Week 4' (Table 19). Data were not presented for the DAA-naïve, non-cirrhotic HCV GT3 subgroup of POLARIS-2, but a rapid response to treatment was observed in the whole POLARIS-2 trial population (all genotypes) which can be seen in CS Table 32.

Table 19: Proportion of DAA-naïve patients with HCV GT3 with HCV RNA < LLOQ (15 IU/mL) while on treatment by visit (final analysis set)

Trial name	POLARIS-2 DAA-naïve, non-cirrhotic	HCV GT3 (subgroup)	POLARIS-3 DAA-naïve, cirrhotic	HCV GT3 (whole study)
Parameter	SOF/VEL/VOX 8 weeks (n=92)	SOF/VEL 12 weeks (n=89)	SOF/VEL/VOX 8 weeks (n=110)	SOF/VEL 12 weeks (n=109)
Baseline, n/N (%)				
<LLOQ [a]	NR	NR	0/110	0/109
95% CI	NR	NR	0.0 to 3.3	0.0 to 3.3
Week 1				
<LLOQ	NR	NR	19/110 (17.3)	11/109 (10.1)
95% CI	NR	NR	10.7 to 25.7	5.1 to 17.3
<LLOQ detected	NR	NR	15/110 (13.6)	10/109 (9.2)
<LLOQ TND	NR	NR	4/110 (3.6)	1/109 (0.9)
Week 2				
<LLOQ	NR	NR	62/100 (56.4)	55/108 (50.9)
95% CI	NR	NR	46.6 to 65.8	41.1 to 60.7
<LLOQ detected	NR	NR	49/110 (44.5)	46/108 (42.6)
<LLOQ TND	NR	NR	13/110 (11.8)	9/108 (8.3)
Week 4				
<LLOQ	NR	NR	96/110 (87.3)	92/108 (85.2)
95% CI	NR	NR	79.6 to 92.9	77.1 to 91.3
<LLOQ detected	NR	NR	32/110 (29.1)	45/108 (41.7)
<LLOQ TND	NR	NR	64/110 (58.2)	47/108 (43.5)
Week 8				
<LLOQ	NR	NR	107/110 (97.3)	107/108 (99.1)
95% CI	NR	NR	92.2 to 99.4	94.9 to 100.0
<LLOQ detected	NR	NR	6/110 (5.5)	10/108 (9.3)
<LLOQ TND	NR	NR	101/110 (91.8)	97/108 (89.8)
Week 12				
<LLOQ	NA	NR	N/A	107/107 (100.0)

95% CI	NA	NR	N/A	96.6 to 100.0
<LLOQ detected	NA	NR	N/A	0/107
<LLOQ TND	NA	NR	N/A	107/107 (100.0)

CI, confidence interval; LLOQ, lower limit of quantitation; not applicable; NR, not reported; SOF, sofosbuvir; TND, target not detected; VEL, velpatasvir; VOX, voxilaprevir.

[a] LLOQ = 15 IU/mL. Missing values for on-treatment visits were imputed up to the time of last dose (if the study day associated with the last dose date was greater than or equal to the lower bound of a visit window, the missing value at the visit was imputed, otherwise the value was excluded); Missing values bracketed by values of '<LLOQ TND' were set to '<LLOQ TND'; bracketed by '<LLOQ detected', or '<LLOQ TND' and '<LLOQ detected' were set to '<LLOQ detected'; otherwise the missing values were set as '≥LLOQ'. The exact 95% CI for the proportion within treatment group and genotype is based on the Clopper-Pearson method.

Data based on CS Table 37

3.3.2.4 HCV RNA level change from baseline in the DAA-naïve HCV GT3 population

Although change in HCV RNA level was not reported by genotype for POLARIS-2, the CS does report that HCV RNA levels declined rapidly and that similar decreased were observed in both treatment groups and across genotypes. In POLARIS-3, the overall mean (SD) change from baseline in HCV RNA levels after one week of treatment was −4.06 (0.716) log10 IU/mL in the SOF/VEL/VOX 8-week group and −4.09 (0.653) log10 IU/mL in the SOF/VEL 12-week group. The HCV RNA decreases were maintained throughout the 12-week treatment period.

3.3.2.5 Virologic failure in the DAA-naïve HCV GT3 population

As Table 20 shows, there were no virologic failures among the DAA-naïve, non-cirrhotic HCV GT3 subgroup of POLARIS-2 (although there were 21 failures across the POLARIS-2 trial population as a whole, CS Table 33). One DAA-naïve, non-cirrhotic HCV GT3 participant did not achieve SVR12, but did not meet virologic failure criteria (no further details provided). In POLARIS-3, two participants from each arm of the trial experienced virologic failure. In the SOF/VEL/VOX arm both were due to relapse, while in the SOF/VEL arm one was due to relapse and one due to on-treatment virologic failure. In addition to these virologic failures, there were also two participants in each arm classed as 'Other' who did not achieve SVR12 but who did not meet virologic failure criteria (no further details provided).

Table 20: Virologic outcomes among DAA-naïve patients with HCV GT3 (Final analysis set)

Trial name	POLARIS-2 DAA-naïve, non-cirrhotic HCV GT3 (subgroup)		POLARIS-3 DAA-naïve, cirrhotic HCV GT3 (whole study)	
Parameter	SOF/VEL/VOX 8 weeks (n=92)	SOF/VEL 12 weeks (n=89)	SOF/VEL/VOX 8 weeks (n=110)	SOF/VEL 12 weeks (n=109)
SVR12, n/N (%)	91/92 (98.9)	86/89 (96.6)	106/110 (96.4)	105/109 (96.3)
Overall virologic failure	0/92	0/89	2/110 (1.8)	2/109 (1.8)
Relapse [a]	0/92	0/88	2/108 (1.9)	1/107 (0.9)
Completed study treatment	0/92	0/87	2/108 (1.9)	1/107 (0.9)
Discontinued study treatment	0/92	0/1	0/0	0/0
On-treatment virologic failure [b]	0/92	0/89	0/110	1/109 (0.9)
Other [c]	1/92 (1.1)	3/89 (3.4)	2/110 (1.8)	2/109 (1.8)

SOF, sofosbuvir; SVR, sustained virological response; VEL, velpatasvir; VOX, voxilaprevir.

[a] Relapse = confirmed HCV RNA ≥LLOQ during the post-treatment period having achieved HCV RNA<LLOQ at last on-treatment visit.

[b] On-Treatment Virologic Failure = Breakthrough (confirmed HCV RNA ≥LLOQ after having previously had HCV RNA<LLOQ while on treatment), Rebound (confirmed >1 log10IU/mL increase in HCV RNA from nadir while on treatment), or Nonresponse (HCV RNA persistently ≥LLOQ through 8 weeks of treatment).

[c] Other = participants who did not achieve SVR12 and did not meet virologic failure criteria.

Data based on CS Appendix E.1.3. Table 16 and CS Table 38

3.3.2.6 Development of resistance in the DAA-naïve population

The CS presents virologic resistance analysis for both the SOF/VEL/VOX and SOF/VEL groups of the POLARIS-2 and POLARIS-3 trials. As for POLARIS-1 and -4 the resistance analysis focuses on the NS5B, NS5A, and NS3/4A genes because these encode the proteins that are the targets for SOF, VEL and VOX respectively. Data on development of resistance for the DAA-naïve GT3 subgroup of POLARIS-2 are not provided but there were no virologic failures in this subgroup.

At baseline, deep sequencing of the HCV NS3, NS5A, and NS5B genes Indicated that 50.3% of participants in the SOF/VEL/VOX (8 weeks) group [redacted][28] of POLARIS-2 (whole trial population), had NS3 and/or NS5A RAVs. The CS does not report on baseline RAVs for POLARIS-3 but the ERG found this information in the CSR[29] [redacted]. The CS states that the presence of baseline RAVs did not impact on patient's SVR12 rates (SVR12: POLARIS-2 - SOF/VEL/VOX RAVs 93.6%, no RAVs 97.8%; SOF/VEL RAVs 99.5%, no RAVs 99.0%. POLARIS-3 - all patients with baseline NS3 and/or NS5A RAVs in either group achieved SVR12).

Only one participant across the two trials experienced on-treatment virologic failure. In this participant in the SOF/VEL (12 week) group of POLARIS-3 a NS5A RAV had emerged.

Among the participants who relapsed after completion of study treatment in the SOF/VEL/VOX (8 weeks) group of POLARIS-2 90% (19/21) did not have detectable NS3, NS5A or NS5B treatment-emergent NI RAVs at relapse. Of the other two participants, one had treatment-emergent NS5A RAVs Q30R and L31M (no NS3 or NS5B NI RAVs) and the second participant did not have available sequencing data at relapse. . In the SOF/VEL (12 weeks) group of POLARIS-2 one of the three participants with relapse had a treatment-emergent NS5A RAV. In POLARIS-3, two patients who had received SOF/VEL/VOX and one participant who had received SOF/VEL experienced virologic failure. In the SOF/VEL/VOX participants, no NS3 or NS5A RAVs were detected at baseline or virologic failure. One patient with the NS5B NI RAV N142T at baseline relapsed; however, the RAV was not observed at virologic failure. The SOF/VEL participant had the NS5A RAV Y93H emerge, with no other RAVs detected at baseline or at virologic failure in this patient.

3.3.2.7 ALT normalisation

The CS does not present detailed outcome data on change in ALT normalisation (which was observed in all active treatment groups). Decreases from baseline in median ALT values were coincident with decreases in HCV RNA (i.e. suppression of viral replication) and were observed in both groups of the POLARIS-2 and POLARIS-3 trials for the duration of treatment and at the post-treatment week 4 visit. Median changes from baseline across both treatment groups ranged from −24 to −34 U/L in POLARIS-2 and from −41 to −106 U/L in POLARIS-3. The CS states that for both the trials there were no notable difference between the groups.

3.3.3 Summary of Health related quality of life

3.3.3.1 Adults with CHC who have had previous treatment with DAA agents for CHC (DAA-experienced) (Final analysis set)

Outcomes from four HRQoL questionnaires are presented in the CS for baseline, end of treatment and post-treatment weeks 4 and 12. The CS states that when participants completed the post-treatment questionnaires they were unaware of their virologic response status. These data have been reproduced in Table 21 below for both POLARIS-1 and POLARIS-4. As can be observed from the data, the mean scores for most scales improved during treatment and continued to improve from the end of treatment to post-treatment weeks 4 and 12.

Table 21: Summary of HRQL outcomes among DAA-experienced patients with CHC

Trial name	POLARIS-1[a]						POLARIS-4[a]					
	SOF/VEL/VOX 12 weeks			Placebo 12 weeks			SOF/VEL/VOX 12 weeks			SOF/VEL 12 weeks		
Instrument	**BL**	**EOT**	**PT wk 12**	**BL**	**EOT**	**PT wk 12**	**BL**	**EOT**	**PT wk 12**	**BL**	**EOT**	**PT wk 12**
SF-36, Physical component	49.6 (9.03)	50.0 (8.50)	50.7 (8.72)	48.0 (9.55)	48.6 (8.50)	N/A	48.4 (9.03)	49.0 (8.51)	49.8 (9.01)	48.4 (9.17)	49.1 (8.46)	49.9 (8.74)
SF-36, Mental component	49.2 (10.26)	49.4 (10.46)	51.2 (9.78)	49.9 (10.12)	48.8 (10.40)	N/A	47.8 (11.15)	48.9 (10.54)	50.6 (10.06)	48.3 (10.23)	47.9 (10.55)	50.1 (10.34)
CLDQ-HCV	5.3 (1.10)	5.5 (1.11)	5.7 (1.02)	5.2 (1.19)	5.2 (1.20)	N/A	5.1 (1.12)	5.4 (1.04)	5.6 (1.00)	5.1 (1.16)	5.3 (1.04)	5.6 (1.07)
FACIT-F Trial Outcome Index	82.6 (20.60)	82.6 (20.82)	86.5 (19.50)	80.0 (22.30)	79.6 (21.82)	N/A	77.9 (21.96)	79.8 (21.37)	84.5 (20.30)	78.9 (20.79)	80.2 (19.97)	84.8 (19.18)
FACIT-F Total score	121.4 (26.40)	122.4 (27.10)	127.8 (26.11)	118.7 (28.52)	117.9 (28.59)	N/A	116.2 (27.99)	119.9 (27.07)	124.7 (26.92)	117.7 (26.75)	119.7 (25.64)	125.3 (26.12)
WPAI, percentage of overall work impairment due to CHC	11.9 (21.35)	14.4 (23.55)	11.8 (22.15)	18.8 (27.54)	14.9 (24.61)	N/A	17.0 (24.61)	16.9 (24.27)	14.2 (25.94)	15.2 (21.83)	18.2 (22.54)	9.4 (17.21)
WPAI, percentage of activity	18.3 (26.29)	16.5 (24.22)	12.6 (22.55)	20.7 (28.25)	19.5 (25.65)	N/A	21.6 (25.01)	19.2 (25.22)	12.5 (22.74)	23.2 (27.12)	20.7 (25.04)	13.8 (22.13)

impairment due to CHC												

BL, baseline; CHC, chronic hepatitis C; CLDQ-HCV, Chronic Liver Disease Questionnaire-Hepatitis C Virus; EOT, end of treatment; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HRQL, health related quality of life; PT, post-treatment; SF-36, Short Form Health Survey; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir; WPAI, Work productivity and Activity Impairment.

[a] For both trials scores reported as mean (standard deviation). The ERG has omitted the p-values from this table because the CS states that multiple endpoints were tested and the study was not powered to test these endpoints so the results should be interpreted with caution (p-values are reported for the change from baseline to time point, the between treatment difference for change from baseline and the change from EOT to time point)

Data based on CS Table 24 and CS Table 29

3.3.3.2 Adults with CHC of genotype 3 (GT3) who have not received any previous treatment with DAA agents for CHC (the DAA-naïve population) (Final analysis set)

Outcomes from four HRQoL questionnaires are presented in the CS for baseline, end of treatment and post-treatment weeks 4 and 12. The CS states that when participants completed the post-treatment questionnaires they were unaware of their virologic response status. Separate data were not provided for the subgroup of DAA-naïve, non-cirrhotic HCV GT3 participants in POLARIS-2. Clinical advice to the ERG was that HRQoL would not be expected to differ between patients with different HCV genotypes. Therefore the ERG would expect that the HRQoL data for the non-cirrhotic HCV GT3 participants would be in line with that for the whole POLARIS-2 trial population. Data for the total POLARIS-2 trial and POLARIS-3 have been reproduced in Table 22 below. As can be observed from the data, the mean scores for most scales improved during treatment and continued to improve from the end of treatment to post-treatment weeks 4 and 12.

Table 22: Summary of HRQL outcomes among CHC DAA-naïve GT3 patients with CHC

Trial name	POLARIS-2 [a] DAA-naïve, non-cirrhotic Whole study (HCV GT3 subgroup is 19%)						POLARIS-3 [a] DAA-naïve, cirrhotic HCV GT3 (whole study)					
	SOF/VEL/VOX 8 weeks (n=501)			SOF/VEL 12 weeks (n=440)			SOF/VEL/VOX 8 weeks (n=110)			SOF/VEL 12 weeks (n=109)		
Instrument	**BL**	**EOT**	**PT wk 12**	**BL**	**EOT**	**PT wk 12**	**BL**	**EOT**	**PT wk 12**	**BL**	**EOT**	**PT wk 12**
SF-36, Physical component	48.7 (9.95)	50.2 (9.61)	50.8 (9.62)	49.8 (9.74)	51.5 (8.62)	52.6 (8.40)	43.9 (10.64)	45.6 (10.01)	46.7 (10.17)	47.1 (9.22)	48.8 (8.80)	49.5 (9.70)
SF-36, Mental component	47.2 (11.19)	49.4 (10.91)	50.1 (10.91)	47.7 (11.48)	50.3 (10.61)	52.0 (10.10)	45.2 (11.76)	48.3 (11.13)	48.7 (10.53)	46.2 (10.86)	47.9 (11.77)	49.5 (10.77)
CLDQ-HCV	5.0 (1.29)	5.6 (1.11)	5.7 (1.10)	5.2 (1.23)	5.7 (1.08)	5.9 (0.97)	4.5 (1.28)	5.2 (1.19)	5.3 (1.17)	4.8 (1.17)	5.4 (1.10)	5.5 (1.11)
FACIT-F Trial Outcome Index	77.2 (23.33)	82.6 (22.25)	85.4 (21.57)	80.0 (22.69)	85.8 (21.31)	89.8 (19.79)	66.1 (24.46)	75.7 (24.89)	77.5 (22.95)	73.9 (21.66)	79.5 (23.14)	83.4 (21.95)
FACIT-F Total score	115.8 (30.13)	124.2 (28.58)	127.2 (28.82)	119.0 (29.37)	127.7 (27.58)	132.8 (26.61)	101.1 (30.75)	114.6 (31.99)	116.6 (29.98)	110.8 (27.61)	119.7 (29.24)	124.0 (27.82)
WPAI, percentage of overall work impairment due to CHC	15.6 (25.29)	11.9 (21.91)	9.0 (20.31)	12.8 (21.62)	10.3 (21.42)	5.0 (13.88)	19.1 (27.95)	17.8 (25.92)	19.2 (29.38)	21.2 (26.21)	16.1 (25.97)	11.9 (20.18)
WPAI, percentage of activity impairment due to CHC	23.0 (29.03)	16.6 (24.44)	10.7 (21.03)	19.3 (27.22)	13.7 (26.67)	9.2 (19.44)	33.8 (32.61)	22.7 (29.09)	21.6 (29.22)	27.1 (27.95)	22.8 (26.52)	15.3 (23.72)

BL, baseline; CHC, chronic hepatitis C; CLDQ-HCV, Chronic Liver Disease Questionnaire-Hepatitis C Virus; EOT, end of treatment; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HRQL, health related quality of life; NR, not reported; PT, post-treatment; SF-36, Short Form Health Survey; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir; WPAI, Work productivity and Activity Impairment.

[a] Scores reported as mean (standard deviation). The ERG has omitted the p-values from this table because the CS states that multiple endpoints

were tested and the study was not powered to test these endpoints so the results should be interpreted with caution (p-values are reported for the change from baseline to time point, the between treatment difference for change from baseline and the change from EOT to time point)
Data based on CS Table 34 and CS Table 39.

3.3.4 Sub-group analyses results

The CS summarises results of 17 pre-planned subgroup analyses of SVR12 rates all of the POLARIS trials (randomisation stratification factors and prognostic baseline characteristics), with data located in CS Appendix E.

DAA-experienced population

In POLARIS-1 and POLARIS-4 high SVR12 rates were achieved in all subgroups, however, for some subgroups numbers were small which limits the inferences that can be drawn. In these two trials all participants were DAA treatment-experienced and SVR rates were high for the various subgroups of DAA-treatment class or DAA-treatment class combinations (SVR12 in treatment experience subgroups: POLARIS-1 over 93% in the SOF/VEL/VOX arm; POLARIS-4 97% or more in the SOF/VEL/VOX arm, 90% or more in the SOF/VEL arm for all except the NS5B+NS3 subgroup in which SVR12 was 86.8%). The two trials also enrolled participants with and without cirrhosis, the SVR12 rate was lower in participants with cirrhosis than in those without cirrhosis (POLARIS-1 SOF/VEL/VOX group SVR12 with cirrhosis 93.4%, without cirrhosis 98.6%; POLARIS-4 SOF/VEL/VOX group SVR12 with cirrhosis 96.4%, without cirrhosis 98%; POLARIS-4 SOF/VEL group SVR12 with cirrhosis 85.5%, without cirrhosis 93.4%). Full details of the subgroup analyses for the POLARIS-1 and POLARIS-4 trials are presented in CS Appendix E.1.1 and E.1.2.

DAA-naïve population

The CS decision problem already focuses on the GT3 group from POLARIS-2 and results for this subgroup have been presented earlier in this report. In POLARIS-2 (whole study population, not the HCV GT3 subgroup of relevance to the decision problem) and POLARIS-3 high SVR12 rates (≥90%) were achieved in almost all key subgroups, the exception being in the SOF/VEL/VOX arm of POLARIS-3 for participants with baseline ALT ≤1.5 x ULN where SVR12 was 85% (17/20 participants). Similarly to the DAA treatment-experienced trials, for some subgroups numbers were small which limits the inferences that can be drawn. Full details of the subgroup analyses for the POLARIS-2 and POLARIS-3 trials are presented in CS Appendix E.1.3 and E.1.4.

3.3.5 Summary of adverse events

3.3.5.1 Adults with CHC who have had previous treatment with DAA agents for CHC (DAA-experienced) (Safety analysis set)

The majority of DAA-experienced patients with CHC had at least one AE regardless of treatment arm in both POLARIS-1 (SOF/VEL/VOX [redacted]; placebo 70.4%) and POLARIS-4 (SOF/VEL/VOX [redacted]; SOF/VEL 73.5%). The top two most commonly reported AEs occurring in ≥5% of patients were headache and fatigue. Both of these occurred in a greater proportion of patients receiving SOF/VEL/VOX in POLARIS-1 compared to those receiving a placebo (see Table 23). In POLARIS-4, headache and fatigue occurred in a smaller proportion of the SOF/VEL/VOX group than in the SOF/VEL group (SOF/VEL/VOX [redacted] for headache and fatigue respectively; SOF/VEL 28.5% for both). The majority of reported AEs were mild or moderate in severity (Grade 1 or Grade 2). AEs graded as 3 (severe) or 4 (life-threatening) occurred in a smaller proportion of those receiving SOF/VEL/VOX in both trials (AEs ≥ Grade 3: POLARIS-1 SOF/VEL/VOX [redacted]; placebo 2.6%; POLARIS-4 SOF/VEL/VOX [redacted]; SOF/VEL 1.3%). In POLARIS-1 most Grade 3 or Grade 4 AEs were considered to be unrelated to study drug and in POLARIS-4 all were considered to be unrelated to study drug.

Treatment-related AEs

Over half of the participants experienced a treatment-related AE, which occurred in a greater proportion of patients receiving SOF/VEL/VOX in both POLARIS-1 (SOF/VEL/VOX [redacted]; placebo 41.4%) and POLARIS-4 (SOF/VEL/VOX [redacted]; SOF/VEL 51.0%). The two most commonly reported treatment-related AEs (occurring in ≥5% of patients) were headache and fatigue.

Serious AEs (SAE), discontinuations and death

A smaller proportion of SAEs were reported in patients receiving SOF/VEL/VOX in both POLARIS-1 (SOF/VEL/VOX [redacted]; placebo 4.6%) and POLARIS-4 (SOF/VEL/VOX [redacted]; SOF/VEL 2.6%). All SAEs in both trials were considered to be unrelated to study drug.

Few participants discontinued treatment due to AEs in either trial (POLARIS-1: SOF/VEL/VOX n=1; placebo n=3. POLARIS-4 SOF/VEL/VOX n=0; SOF/VEL n=1). AEs leading to interruption of the treatment occurred in one patient in the POLARIS-1 placebo group and in [redacted] in the SOF/VEL/VOX group of POLARIS-4.

No deaths were reported during POLARIS-1. In POLARIS-4 the [redacted] death that occurred in the SOF/VEL/VOX treatment group of POLARIS-4 was the result of an illicit drug overdose (this was considered a Grade 4 serious event but not related to study drug).

Other AEs

In both trials, most laboratory abnormalities were Grade 1 or 2 in severity. In POLARIS-1 the incidence of Grade 3 and 4 haematological laboratory abnormalities was stated to be similar for both treatment groups. In POLARIS-4 the most common Grade 3 haematological laboratory anomaly (decreased platelet count) was similar in the two treatment groups and there were no Grade 4 events. The CS states that none of the haematological abnormalities were clinically meaningful. A small proportion of participants in both trials had grade 3 or 4 chemistry abnormalities. Among the treatment groups of both trials, there were no notable changes from baseline in vital sign measurements. No patients in either trial had clinically significant ECG abnormalities.

Table 23: Adverse event summary in DAA-experienced patients

Trial name	POLARIS-1		POLARIS-4	
	SOF/VEL/VOX 12 weeks (n=263)	**Placebo 12 weeks (n=152)**	**SOF/VEL/VOX (n=182)**	**SOF/VEL (n=151)**
Number of participants experiencing any, n (%)				
AE	[redacted]	107 (70.4)	[redacted]	111 (73.5)
≥ Grade 3	[redacted]	4 (2.6)	[redacted]	2 (1.3)
Treatment related AE	[redacted]	63 (41.4)	[redacted]	77 (51.0)
≥ Grade 3 treatment related AE	[redacted]	0	[redacted]	0
Serious AE	[redacted]	7 (4.6)	[redacted]	4 (2.6)
Treatment related SAE	[redacted]	0	[redacted]	0
AE leading to premature discontinuation of the study drug	[redacted]	3 (2.0)	[redacted]	1 (0.7)
AE leading to interruption of the study drug	[redacted]	1 (0.7)	[redacted]	0
All Deaths	[redacted]	0	[redacted]	0
AE in ≥5% of participants, n (%)				

Headache	[redacted]	26 (17.1)	[redacted]	43 (28.5)
Fatigue	[redacted]	30 (19.7)	[redacted]	43 (28.5)
Diarrhoea	[redacted]	19 (12.5)	[redacted]	7 (4.6)
Nausea	[redacted]	12 (7.9)	[redacted]	12 (7.9)
Asthenia	[redacted]	9 (5.9)	[redacted]	9 (6.0)
Insomnia	[redacted]	8 (5.3)	[redacted]	3 (2.0)
Dizziness	[redacted]	14 (9.2)	-	-
Back pain	[redacted]	8 (5.3)	[redacted]	8 (5.3)
Arthralgia	[redacted]	8 (5.3)	-	-
Abdominal pain	[redacted]	-	[redacted]	9 (6.0)
Irritability	[redacted]	-	[redacted]	8 (5.3)
Treatment related AE in ≥5% of participants, n (%)				
Headache	[redacted]	21 (13.8)	[redacted]	34 (22.5)
Fatigue	[redacted]	23 (15.1)	[redacted]	34 (22.5)
Diarrhoea	[redacted]	14 (9.2)	[redacted]	4 (2.6)
Nausea	[redacted]	10 (6.6)	[redacted]	5 (3.3)
Asthenia	[redacted]	6 (3.9)	[redacted]	9 (6.0)
Insomnia	[redacted]	5 (3.3)	-	-
Irritability	[redacted]	-	[redacted]	8 (5.3)

AE, adverse event; SAE, serious adverse event.
Common AEs were those that occurred in ≥5% of participants in any treatment group.
Data come from CS Table 40 and CS Table 41

3.3.5.2 Adults with CHC of genotype 3 (GT3) who have not received any previous treatment with DAA agents for CHC (the DAA-naïve population) (Safety analysis set)

AEs for POLARIS-2 were reported for the total trial population with no separate reporting of AEs for the subgroup of participants with HCV GT3 who were the focus of the company's decision problem. In response to clarification request A3, the company states that AE data were not split by genotype, as genotype of HCV infection does not influence AEs.

The majority of DAA-naïve patients with CHC experienced at least one AE regardless of cirrhosis status or treatment arm in POLARIS-2 (SOF/VEL/VOX [redacted]; SOF/VEL 68.9%) and POLARIS-3 (SOF/VEL/VOX [redacted]; SOF/VEL 74.3%). The most commonly reported AEs occurring in >10% of patients and not related to treatment were headache, fatigue, nausea and

diarrhoea in both studies. Across the two trials a [redacted] proportion of patients being treated with SOF/VEL/VOX experienced nausea and diarrhoea compared to those treated with SOF/VEL (POLARIS-2: nausea [redacted] vs 9.1%; diarrhoea [redacted] vs 7.3%. POLARIS-3: nausea [redacted] vs 9.2%; diarrhoea [redacted] vs 4.6%). Most of the reported AEs in both studies were mild or moderate in severity (Grade 1 or Grade 2). AEs graded as 3 (severe) or 4 (life-threatening) occurred in a small proportion of participants (POLARIS-2 SOF/VEL/VOX [redacted]; SOF/VEL 1.4%; POLARIS-3 SOF/VEL/VOX [redacted]; SOF/VEL 3.7%). Only one Grade 4 AE was reported across the two trials, this was related to the attempted suicide of one patient in the SOF/VEL treatment arm of POLARIS-2.

Treatment-related AEs

[redacted] patients receiving SOF/VEL/VOX in both POLARIS-2 ([redacted]; SOF/VEL 41.4%) and POLARIS-3 ([redacted]; SOF/VEL 46.8%) experienced a treatment-related AE, this was a [redacted] percentage than patients receiving SOF/VEL only. The most commonly reported treatment-related AEs were headache, fatigue, diarrhoea, and nausea in both trials. There were some treatment-related AE ≥ Grade 3, [redacted] ([redacted]) in the SOF/VEL/VOX treatment arm of POLARIS-2 and two (2.8%) in the SOF/VEL treatment arm of POLARIS-3.

Serious AEs (SAE), discontinuations and death

The proportion of patients experiencing SAEs was [redacted] in both trials (POLARIS-2: SOF/VEL/VOX [redacted]; SOF/VEL 1.6%. POLARIS-3: SOF/VEL/VOX [redacted]; SOF/VEL 2.8%)(Table 24). There were no treatment-related SAEs in either trial. [redacted] patients in the SOF/VEL/VOX treatment arms discontinued early due to AEs but across the two trials three participants in the SOF/VEL arms (two in POLARIS-2 and one in POLARIS-2) discontinued due to AEs that were all considered to be unrelated to the study drug. There was [redacted] reported death in the SOF/VEL/VOX treatment group of POLARIS-3 due to hypertension and unrelated to treatment. [redacted] in the SOF/VEL/VOX group in POLARIS-2 became pregnant during the study.

Other AEs

In both trials, most laboratory abnormalities were Grade 1 or 2 in severity and across treatment groups, there were no notable changes from baseline in vital sign measurements. Although there were some changes in haematological laboratory parameters none were assessed as AEs. The most common grade 3 haematology laboratory abnormalities in POLARIS-2 were

decreased platelet count [redacted] in the SOF/VEL/VOX group and decreased lymphocytes, neutrophils and platelets (each 0.5%) in the SOF/VEL group. In POLARIS-3 they were decreased lymphocytes ([redacted]) in the SOF/VEL/VOX group with none reported for the SOF/VEL group. The only grade 4 haematology laboratory abnormalities in both trials were decreased lymphotypes (POLARIS-2 was one patient in the SOF/VEL arm; POLARIS-3 [redacted] in each treatment group). The most common grade 3 chemistry laboratory abnormality in both trials was increased serum glucose and all patients with this finding had a history of diabetes. Increased lipase (grade 3 or 4 in POLARIS-2, grade 3 in POLARIS-3) occurred in both arms of each trial but all cases were asymptomatic. In Polaris-3, [redacted] in the SOF/VEL/VOX group experienced a Grade 4 chemistry laboratory abnormality for creatinine kinase. The only clinically significant ECG outcome reported was for one patient in the SOF/VEL group in POLARIS-2 who had an ECG with atrial flutter, considered clinically significant at the week 12 visit.

Table 24: Adverse event summary in DAA-naïve patients

Trial name	**POLARIS-2 DAA-naïve, non-cirrhotic Whole trial population**		**POLARIS-3 DAA-naïve, cirrhotic HCV GT3 (whole study)**	
Adverse events, n (%)	**SOF/VEL/VOX 8 weeks (n=501)**	**SOF/VEL 12 weeks (n=440)**	**SOF/VEL/VOX 8 weeks (n=110)**	**SOF/VEL 12 weeks (n=109)**
Number of participants experiencing any, n (%)				
AE	[redacted]	303 (68.9)	[redacted]	81 (74.3)
Grade 3 or above AE	[redacted]	6 (1.4)	[redacted]	4 (3.7)
Treatment-related AE	[redacted]	182 (41.4)	[redacted]	51 (46.8)
Grade 3 or above treatment related AE	[redacted]	0	[redacted]	2 (1.8)
Serious AE	[redacted]	7 (1.6)	[redacted]	3 (2.8)
Treatment-related serious AE	[redacted]	0	[redacted]	0
AE leading to premature discontinuation of the study drug	[redacted]	2 (0.5)	[redacted]	1 (0.9)
AE leading to interruption of the study drug	[redacted]	2 (0.5)	[redacted]	0
All deaths	[redacted]	0	[redacted]	0
AE in ≥5% of participants, n (%)				

Fatigue	[redacted]	90 (20.5)	[redacted]	31 (28.4)
Headache	[redacted]	99 (22.5)	[redacted]	32 (29.4)
Nausea	[redacted]	40 (9.1)	[redacted]	10 (9.2)
Diarrhoea	[redacted]	32 (7.3)	[redacted]	5 (4.6)
Abdominal pain	[redacted]	-	[redacted]	5 (4.6)
Insomnia	[redacted]	21 (4.8)	[redacted]	5 (4.6)
Abdominal pain upper	[redacted]	-	[redacted]	7 (6.4)
Muscle spasms	[redacted]	-	[redacted]	2 (1.8)
Vomiting	[redacted]	-	[redacted]	1 (0.9)
Back pain	[redacted]	-	[redacted]	6 (5.5)
Myalgia	[redacted]	-	[redacted]	6 (5.5)
Asthenia	[redacted]	27 (6.1)	[redacted]	-
Arthralgia	[redacted]	24 (5.5)	[redacted]	-
Treatment related AE in ≥5% of participants, n (%)				
Headache	[redacted]	76 (17.3)	[redacted]	24 (22.0)
Fatigue	[redacted]	57 (13.0)	[redacted]	15 (13.8)
Diarrhoea	[redacted]	16 (3.6)	[redacted]	3 (2.8)
Nausea	[redacted]	32 (7.3)	[redacted]	7 (6.4)

AE, adverse event; SAE, serious adverse event.

Common AEs were those that occurred in ≥5% of participants in any treatment group.

Data come from CS Table 42 and CS Table 43

3.4 Summary

The CS includes four trials (the POLARIS trials) of SOF/VEL/VOX as a treatment for people with CHC.

- POLARIS-1: Two trial arms SOF/VEL/VOX or placebo
- POLARIS-4: Two trial arms SOF/VEL/VOX 12-weeks or SOF/VEL 12-weeks
- POLARIS-2: Two trial arms SOF/VEL/VOX 8-weeks or SOF/VEL 12-weeks.
- POLARIS-3: Two trial arms SOF/VEL/VOX 8-weeks or SOF/VEL 12-week

Two trials (POLARIS-1 and POLARIS-4) provide evidence for the DAA-experienced population with all HCV genotypes and two (POLARIS-2 and POLARIS-3) provide evidence for the DAA-naïve population with HCV GT3. However, for the latter DAA-naïve population only the subgroup of POLARIS-2 with HCV GT3 (19%) meets the company's decision problem criteria.

These trials were not identified by the company's systematic literature review. Evidence came from the trial CSRs.

The four trials were judged to be of reasonable methodological quality although only POLARIS-3 randomised all participants. In POLARIS-1, POLARIS-4 and POLARIS-2 not all participants were eligible for randomisation hence participants with HCV GT2-6 or unknown genotype in POLARIS-1, GT4-6 or unknown in POLARIS-4 and GT5-6 or unknown in POLARIS-2 could only enter the SOF/VEL/VOX arm of these trials. Another notable feature of the trial designs was that for three of the four trials (POLARIS-1, POLARIS-4 and POLARIS-3) the trial arms were not compared with each other. Instead each arm was compared individually against a predefined performance SVR12 goal (SVR12 of 85% for POLARIS-1 and POLARIS-4, SVR12 of 83% for POLARIS-3). POLARIS-2 was a non-inferiority trial comparing SOF/VEL/VOX 8 weeks with SOF/VEL 12 weeks but as noted, only the subgroup of participants with HCV GT3 met the company's decision problem criteria. Therefore, for the subgroup of interest, the POLARIS-2 trial will not be sufficiently powered. POLARIS-4, POLARIS-2 and POLARIS-3 were open label trials, so there is scope for bias in these trials. However, the key outcome measure for these trials, SVR12, is an objective measure and thus not likely to be affected by performance or detection bias.

The primary clinical efficacy outcome reported in the CS is SVR12 (SVR4 and SVR24 are reported as secondary outcomes). Other secondary outcomes are changes in HCV RNA level, virologic failure, development of resistance, normalisation of ALT and HRQoL. AE outcomes are also reported.

The CS provides a narrative summary of the outcomes from the four POLARIS trials. Results for the whole trial population of POLARIS-2 are presented, instead of results for the DAA-naïve, GT3 non-cirrhotic patient group specified in the decision problem. There is no meta-analysis or NMA. The company did explore the possibility of an NMA for the DAA-naïve HCV GT3 patient group but this was not feasible.

DAA-experienced population, all HCV genotypes

SOF/VEL/VOX treatment resulted in a statistically significantly higher SVR12 rate in comparison to the SVR12 performance goal of 85% in both POLARIS-1 and POLARIS-4 (POLARIS-1: 96.2%, $p<0.001$; POLARIS-4 97.8, $p<0.001$).

An early indication of SVR12 outcomes was obtained from SVR4 outcome. Of those who received SOF/VEL/VOX and who attained SVR4, four did not go on to achieve SVR12 in POLARIS-1 (three relapses, one consent withdrawal) and one did not achieve SVR12 in POLARIS-4.

All participants who achieved SVR12 and who attended the post-treatment 24 week visit (there were four missing participants) achieved SVR24.

HCV RNA levels fell rapidly to less than the LLOQ by Week-2 among more than half of the participants during receipt of active treatment. No change in HCV RNA level was observed in the placebo group of POLARIS-1.

Overall virologic failure occurred in 2.7% of participants in the SOF/VEL/VOX arm of POLARIS-1, 0.5% of the SOF/VEL/VOX arm of POLARIS-4 and 9.9% of the SOF/VEL arm of POLARIS-4.

The presence of RAVs was common at baseline in both trials but these did not impact on SVR12 rates. Across the two trials three newly emergent RAVs (among two participants) were identified in participants who received SOF/VEL/VOX and 12 RAVs newly emerged among 11 participants who received SOF/VEL. The majority of RAVs were in the NS5A gene.
ALT normalisation - decreases in median ALT values were coincident with decreases in HCV RNA.

The mean scores for most of the four HRQoL scales used during the trials improved during treatment and continued to improve after treatment to post-treatment week 12.

High SVR12 rates were achieved in all subgroups but in some sub-groups numbers were small limiting the inferences that can be drawn.

AEs and SAEs - The majority of reported AEs were mild or moderate in severity (Grade 1 or Grade 2). Small proportions of participants in the trial arms experienced SAEs but all were considered to be unrelated to study drug. Very few participants discontinued treatment due to AEs.

DAA-naïve HCV GT3 population

High SVR12 rates were obtained in the DAA-naïve HCV GT3 non-cirrhotic subgroup of POLARIS-2 (SOF/VEL/VOX 8 weeks 98.9%; SOF/VEL 12 weeks 96.6%) and in the DAA-naïve HCV GT3 cirrhotic whole study population of POLARIS-3 (SOF/VEL/VOX 8 weeks 96.4%; SOF/VEL 12 weeks 96.3%). POLARIS-2 was a non-inferiority trial and for the whole trial population (all genotypes) non-inferiority of SOF/VEL/VOX 8-weeks was not demonstrated in comparison to SOF/VEL 12-weeks but this comparison was not made (and would not be powered) for the HCV GT3 subgroup of this trial. In POLARIS-3 both trial arms were compared with an SVR12 performance goal of 83% and in both arms the SVR12 rate achieved (just over 96% for both arms) was statistically significantly greater than this benchmark value.

SVR4 data were not presented for the DAA-naïve HCV GT3 population without cirrhosis but in the total (all genotypes) non-cirrhotic population the SVR4 outcomes provided an early indication of SVR12 outcomes, and the same was apparent in the DAA-naïve HCV GT3 cirrhotic population of POLARIS-3. Two POLARIS-3 participants who achieved SVR4 did not contributed to SVR12 (one death in the SOF/VEL/VOX arm and one in the SOF/VEL arm failed to attend the SVR12 visit).

SVR24 - All participants in POLARIS-3 who achieved SVR12 also achieved SVR24 but SVR24 data were not presented for the GT3 subgroup of POLARIS-2.

HCV RNA levels fell rapidly to less than the LLOQ by Week-2 among at least half of the participants in POLARIS-3 during receipt of active treatment. Data were not presented for the DAA-naïve, non-cirrhotic HCV GT3 subgroup of POLARIS-2, but a rapid response to treatment was observed in the whole POLARIS-2 trial population (all genotypes).

Virologic failure did not occur among the DAA-naïve, non-cirrhotic HCV GT3 subgroup of POLARIS-2. There were four virologic failures in POLARIS-3 [two participants (1.8%) from each arm] due to relapse (two in the SOF/VEL/VOX arm and one in the SOF/VEL arm) and on-treatment virologic failure (one in the SOF/VEL arm).

Baseline RAVs were present in both trial arms of both trials but these did not impact on SVR12 rates. As noted above there were no virologic failures in the HCV GT3 subgroup of POLARIS-2.

In POLARIS-3 two newly emergent RAVs were identified in participants who received SOF/VEL (one on-treatment failure, one relapse) and both were in the NS5A gene.

Decreases in median ALT values were coincident with decreases in HCV RNA.

HRQoL is not expected to differ between patients with different HCV genotypes, consequently the HRQoL data for the DAA-naïve HCV GT3 non-cirrhotic participants in POLARIS-2 should mirror that of the whole trial population. The mean scores for most of four HRQoL scales improved during treatment and continued to improve from the end of treatment to post-treatment week 12.

In terms of subgroup analyses, for POLARIS-2 the focus has already been on the HCV GT3 subgroup of this trial. Across the whole POLARIS-2 (all genotypes) trial and the POLARIS-3 trial high SVR12 rates were achieved in all subgroups. However, in some sub-groups numbers were small limiting the inferences that can be drawn.

The genotype of HCV infection does not influence AEs, hence the company presented AE data for the whole POLARIS-2 trial population. The majority of reported AEs in POLARIS-2 and POLARIS-3 were mild or moderate in severity (Grade 1 or Grade 2). A [redacted] proportion of SOF/VEL/VOX treated patients in both trials experienced nausea and diarrhoea compared to those treated with SOF/VEL. Small proportions of participants in the trial arms experienced SAEs but all were considered to be unrelated to study drug. No participants in receipt of SOF/VEL/VOX discontinued treatment due to AEs.

The ERG agrees with the company's interpretation of the clinical and safety evidence. Very high SVR12 rates have been achieved following treatment with SOF/VEL/VOX for 12 weeks in the POLARIS studies in adult patients who are either DAA-experienced or DAA-naïve and either with or without compensated cirrhosis. In the case of DAA-naïve patients with HCV GT3 infection very high SVR12 rates can be achieved with 8 weeks of SOF/VEL/VOX treatment. Although the POLARIS-2 trial did not demonstrate non-inferiority of 8 weeks SOF/VEL/VOX in comparison to 12 weeks of SOF/VEL treatment for treatment naïve non-cirrhotic participants, in the subgroup of participants with HCV GT3 in this trial 8-weeks of SOF/VEL/VOX led to an SVR12 rate of 98.9% in comparison to the 96.6% SVR12 rate obtained after 12-weeks of SOF/VEL treatment.

4 COST EFFECTIVENESS

4.1 Overview of company's economic evaluation

The CS to NICE includes:

i) a review of published economic evaluations in patients with CHC

ii) a report of an economic evaluation undertaken for the NICE STA process. The cost effectiveness of SOF/VEL/VOX is compared with -

- no treatment in DAA-experienced patients;
- SOF/VEL, SOF+DCV+RBV,SOF+RBV, Peg-IFN2a +RBV, SOF + Peg-IFN2a +RBV and no treatment in cirrhotic patients within the DAA-naïve sub group; and
- SOF/VEL, SOF+DCV, Peg-IFN2a +RBV, SOF + Peg-IFN2a +RBV and no treatment in non-cirrhotic patients within the DAA-naïve sub group.

4.2 Company's review of published economic evaluations

A systematic search of the literature was conducted by the company to identify published economic evaluations in CHC across four databases via Ovid SP®: MEDLINE and MEDLINE In-Process, Embase, NHS Economic Evaluations Database (NHS-EED) and EconLit. The company limited their search strategy to include publications in the last 10 years (i.e. from 1st January 2007 to 17 March 2017). An additional search was conducted for abstracts reporting treatment-related AEs in HCV in three conferences viz: AASLD, DDW and EASL in annual conferences held from 1st January 2014 to 17 March 2017. Further details of our critique of the company's search strategy are presented in section 3.1.1.

The inclusion and exclusion criteria for the systematic review are listed in CS Appendix G Table 22. The company included studies of patients (aged ≥18 years) with any HCV genotype, with or without compensated cirrhosis who were treatment naïve or treatment-experienced (either DAA- or IFN-experienced) but excluded studies with only Asian HCV patients as they react differently to treatment. Further, studies were excluded if they were on patients with acute hepatitis or HCV/HBV co-infection, renal dysfunction or depression, homeless and intravenous drug users. The company included a list of drugs in their search strategy which returned studies on both monotherapy and combination therapies. Studies on combination therapies which included

drugs not in the list were excluded. The ERG considers eligibility criteria applied for outcomes, study designs and limits (as outlined in Appendices Table 22) are appropriate.

Three hundred and fifty-four studies were identified from screening 1368 titles and abstracts. Of these, 235 were excluded, mainly as the studies had inappropriate outcomes (n=136), followed by inappropriate- study type (n=63), comparator (n=17), intervention (n=8), population (n=5), and six duplicate studies. Of the remaining 119 studies included in data extraction, only 13 studies were included for full review as they used UK based economic and resource inputs and used a UK economic perspective. These studies are summarised in CS Table 44. The company presented a detailed checklist of the quality assessment of the included studies in CS Appendix G.1.11. However, the ERG notes that the company does not provide any discussion about the assessments, especially in context of their relevance to the current submission. Further, the ERG notes the studies included in the review reported patients as treatment-naïve (TN) / treatment–experienced (TE), and not as DAA- naïve / DAA- experienced as patients are grouped in the current submission.

Of the 13 studies included in the review, none included SOF/VEL/VOX or SOF/VEL as an intervention/comparator. Further, the characteristics of the patient population in the included studies differed across the studies. Most of the included studies grouped patients by treatment status (n=8) and genotype (n=5) and the level of stratification of these groups varied. To illustrate, two studies[30,31] included patients grouped by genotype and treatment-history, whilst another two studies[32,33] grouped patients by genotype alone. Only one study[34] targeted GT3 only patients. Six studies contained relevant comparators and population group for this appraisal, as shown in Table 25.

Table 25: Patient characteristics in the included CE studies

Study	Treatments	Patient population	ICER
Cure et al. 2015 [33]	Arm 1 (all): GT3: Peg-IFN-RBV 12 or 24 weeks or null or Peg-IFN-RBV 24 or 48 weeks GT4/5/6: SOF + Peg-IFN-RBV 12 weeks or Peg-IFN-RBV 48 weeks Arm 2 (cirrhotic): GT1: SOF + Peg-IFN-RBV 12 weeks or Peg-IFN-RBV 48 weeks or TVR + Peg-IFN-RBV	Divided by GT and treatment history	GT1: £11,836; £7,292; £14,930; (TN IE) GT1: £49,249 (TN UI); GT2: £46,324 (TN IE) £8154 (TN UI) £14,185; £10,126 (TE IE); £8,591 (TE UI) GT3: £20,613 (TN IE); £21,478 (TN UI); £8,557; £12,246 (TE IE); £28,569 (TE UI)

Study	Treatments	Patient population	ICER
	or BOC + Peg-IFN-RBV GT2: SOF + RBV 12 weeks or Peg-IFN-RBV or null GT3: Peg-IFN-RBV 12 or 24 weeks or null or Peg-IFN-RBV 24 or 48 weeks GT4/5/6: SOF + Peg-IFN-RBV 12w or Peg-IFN-RBV 48 weeks		GT4/5/6: £26,797 (TN)
McEwan et al. 2015 [32]	Arm 1: DCV+ SOF 12 or 24 weeks Arm 2: TVR + Peg-IFN-RBV 12 or 48 weeks Arm 3: Peg-IFN-RBV 24 or 48 weeks	Divided by GT	GT1 Arm 1 vs 2: £7,864 Arm 1 vs null: £4,277 GT3 Arm 1 vs 3: £30,871 Arm 1 vs null: £13,442 GT4 Arm 1 vs 3: £8,806 Arm 1 vs null: £3,491
Cure et al. [33]2015	Arm 1: SOF+ Peg-IFN-RBV 12 weeks or SOF/RBV 12/24 weeks Arm 2: Peg-IFN-RBV or TVR + Peg-IFN-RBV or BOC + Peg-IFN-RBV	Divided by GT	GT1: £15,533 GT2: £12,180 GT3: £18,450 GT4/5/6: £26,797 GT1: £15,533 All: £17,981
Humphreys et al. 2012[35]	Arm 1: BOC + Peg-IFN-RBV Arm 2: Peg-IFN-RBV	Divided by treatment history	TN: £11,601 TE: £2,909
Curtis et al. 2012 [36]	Arm 1: TVR + Peg-IFN-RBV Arm 2: Peg-IFN-RBV	Divided by treatment history, responders and IL28B type	TN: £13,553,TE: £8,688 relapse: £4,514, partial: £12,554, null: £23,981 TN: CC: £16,585 ,CT: £6,224, TT: £5,056 TE: CC: £19,037,CT: £7,516, TT: £8,428
McEwan et al. 2015 [34]	Arm 1: SOF + DCV Arm 2: SOF + RBV	GT3, with separate results for TN, TE and IFN-ineligible	DCV+SOF vs SOF+RBV TN: **Dominant** TE: **Dominant** IFN-ineligible - **Dominant** DCV+SOF vs no treatment IFN-ineligible: £7,736

CC - cirrhotic; GT, genotype; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; NR, not reported; Peg-IFN: pegylated-interferon; RBV, ribavirin; BOC, boceprevir, DCV daclatsavir, TVR, telaprevir, SOF, sofosbuvir; SVR, sustained virological response; TN, treatment-naïve; TE, treatment-experienced.

The ERG has the following observations on the cost-effectiveness review conducted by the company. First, we view that the eligibility criteria used to identify the cost-effectiveness studies

are reasonable. In their review, the company grouped HCV patients as TN /TE which aligns with the NICE scope. However, in the economic analyses, they grouped the patients as DAA-naïve and DAA-experienced. Whilst we acknowledge that TN patients could include DAA-naïve and that TE could include DAA- naïve and DAA-experienced patients this association is not discussed in the review. Secondly, it is unclear how relevant the findings of the review are as there is no explicit evidence of these findings informing the economic model which is discussed in the following sections of this report. Finally, the company presented an overview of the included studies but did not draw any conclusions from the review. Therefore, we are unable to comment on the conclusion of the cost-effectiveness review.

4.3 Critical appraisal of the company's submitted economic evaluation

4.3.1 NICE reference case

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

Table 26: NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Partly	The company included adults with HCV who were DAA–naïve or DAA treatment experienced whereas the NICE scope includes HCV patients who are TE/TN Further details are discussed in in section 2.3
Comparator: As listed in the scope developed by NICE	Partly	The comparators included in the company's economic analyses deviates slightly from the NICE scope. Further details are discussed in sections 2.3 and 4.3.4
Perspective on costs: NHS and Personal Social Services (PSS)	Yes	
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	Yes	Further details in section 4.3.7
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Yes	

Type of economic evaluation: Cost utility analysis with fully incremental analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	Yes	
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	
Measuring and valuing health effects: Health effect should be expressed in quality-adjusted life years (QALYs). The European Quality of Life-5 Dimensions (EQ-5D) is the preferred measure of HRQoL.	Yes	Further details in section 4.3.6
Source of data for measurement of HRQoL of life: Reported directly by patients and/or carers.	Yes	Further details in section 4.3.6
Source of preference data: Representative sample of the UK population	Yes	
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	
Discount rate: 3.5% per annum for costs and health effects	Yes	

As shown in Table 26, the company's analysis broadly conforms to NICE's reference case requirements, but deviates from the NICE scope with regard to the populations and comparators. A detailed critique of these deviations is discussed earlier in section 2.3 and reiterated in sections 4.3.3 and 4.3.4.

4.3.2 Model Structure

The company presented a Markov state-transition model to reflect the clinical progression of the disease over the lifetime horizon. A schematic of the model was presented in CS Figure 3 which is reproduced below in Figure 1. The company used the same model structure for all patients irrespective of HCV genotype or treatment experience. This model structure has been adapted from the model by Dusheiko and Roberts.[37] The company presented the following arguments in favour of the chosen model structure:

i. It has been widely used and adapted for HTA purposes and is in line with previous Gilead submissions to NICE (TA363,[6] TA330,[12] and TA430[14]),
ii. It reflects the natural history of CHC and UK clinical practice. The health states before compensated cirrhosis state are grouped together as one non-cirrhotic stage.
iii. It provided the best fit for the Gilead pivotal Phase III trials for SOF/VEL/VOX (POLARIS-1 to 4) wherein patients were split between being non-cirrhotic [defined by Fibroscan® (in countries where locally approved) with a result of ≤12.5 kPa within ≤6

months of baseline/day one or a Fibrotest® score of ≤0.48 and an Aspartate transaminase (AST):platelet ratio index (APRI) of ≤1 performed during screening for POLARIS clinical trials] or cirrhotic [defined by Fibroscan® (in countries where locally approved) with a result of >12.5 kPa or a Fibrotest® score of >0.75 and an APRI of >2 performed during screening for POLARIS clinical trials)

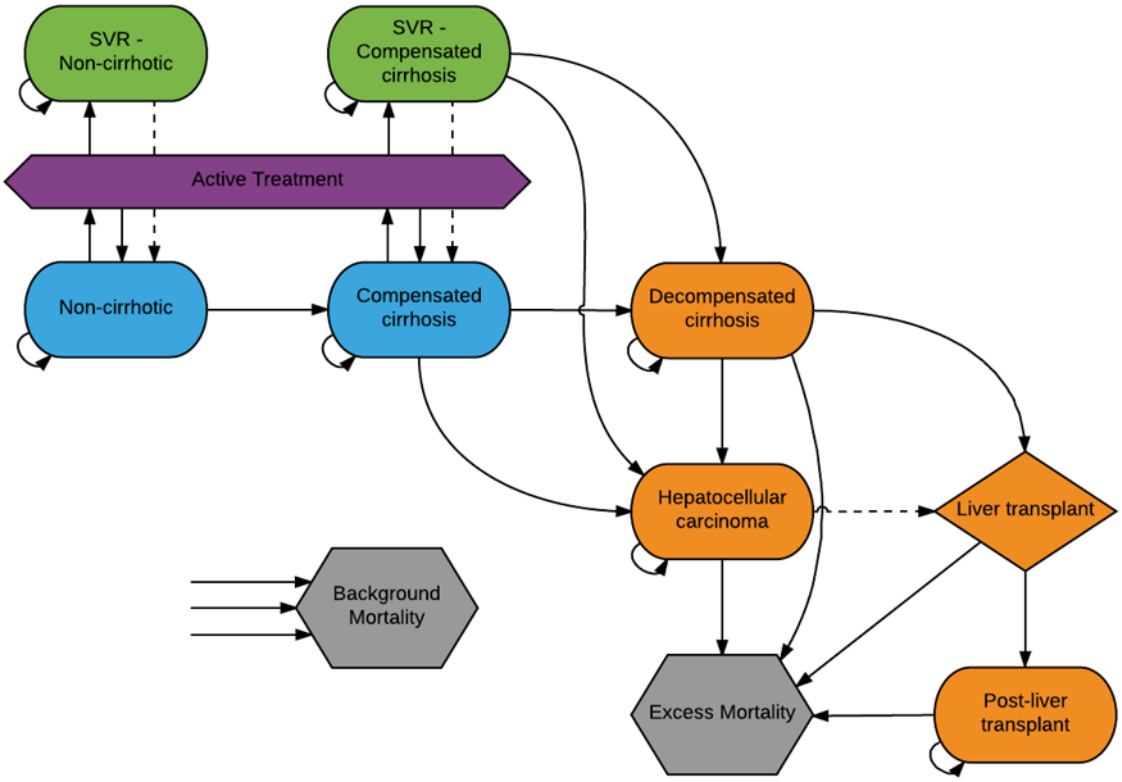


Figure 1: Model structure (CS Figure 3)

The company's model consisted of nine health states: non-cirrhotic, SVR-non cirrhotic, compensated cirrhosis, SVR-compensated cirrhosis, decompensated cirrhosis, hepatocellular cirrhosis, liver transplant, post-liver transplant and background mortality. These states capture two critical aspects:

- the on-treatment phase (consisting of either active therapy or best supportive care) where the patients are in the:
    - SVR non-cirrhotic or SVR cirrhosis states
    - Non-cirrhotic CHC or CHC with compensated cirrhosis
- the post-treatment phase.

Patients enter the model with non-cirrhotic CHC or compensated cirrhosis and may transition to the SVR health states after being cured following treatment. Some cirrhotic patients who achieve SVR may transition to the decompensated cirrhosis and HCC states. Those with compensated and decompensated cirrhosis subsequently progress to the HCC stage. From decompensated cirrhosis, patients may progress to a liver transplant and post liver transplant states. Mortality is accounted for from decompensated cirrhosis, HCC, liver-transplant and post liver-transplant stages.

The model has a cycle length of two weeks for the first 18 months, followed by one six month cycle and thereafter annual transitions. The company adopted shorter initial cycles to enable them to model different treatment strategies with patients transitioning to SVR in the same model at different time points.

The CS presented definitions of the health states in CS Table 45. Patients were classified as non-cirrhotic or compensated cirrhosis based on Fibroscan, Fibrotest and/or METAVIR scores. Further, they converted between the Fibrotest, Fibroscan and METAVIR scores wherein non-cirrhotic patients corresponded to F0-F3 and cirrhotic patients to F4 in the METAVIR scores.

To inform the clinical parameters of the SVR rates, AE rates and treatment duration within the economic model, the company used data from the SOF/VEL/VOX clinical trials, comparator trials, literature and expert opinion. The model included costs associated with treatments, health states, monitoring and AE costs. Quality-adjusted life years (QALYs) were incorporated by assigning utility values to the health states and accounting for adverse impact of treatments by applying utility decrements.

The ERG views that the strength of the company's model is that the structure is similar to previous NICE technology appraisals for CHC (LDV/SOF (TA363),[6] SOF/RBV (TA330)[12] and SOF/VEL (TA430)[14]) which have been through the process of rigorous discussion and validation in previous technology appraisals. Further, in the current appraisal, the company attempted to address the issue relating to re-treatment due to re-infection or treatment failure which was raised in the previous NICE submission of SOF/VEL (NICE TA430)[14] by conducting a scenario analysis incorporating a dynamic transmission model (further details are discussed in section 4.3.10).

The model structure reasonably represents the key clinical stages of patients' transition over the course of CHC. The company, however, did not address the following issues which were highlighted in the previous NICE submission of SOF/VEL (NICE TA430).[14]

- The model did not distinguish between mild and moderate cirrhosis but grouped all the health states prior to compensated-cirrhosis into the non-cirrhotic state.
- It did not account for mortality risk or disease progression while patients were in the active treatment phase.

The company states that the mortality assumption is aligned with the POLARIS studies and the approach in previous NICE submissions (SOF/VEL (TA430),[14] LDV/SOF(TA363)[6] and SOF(TA330)).[12] The effect of this assumption in the comparison between SOF/VEL/VOX and SOF/VEL for DAA-naïve patients is to produce counter-intuitive outcome results, whereby the QALYs for SOF/VEL are greater than SOF/VEL/VOX whilst the SVR rates are lower for SOF/VEL than SOF/VEL/VOX. This occurs because treatment-related and background mortality in the model starts earlier for SOF/VEL/VOX than SOF/VEL, as it is related to treatment duration. The company states that this is conservative for SOF/VEL/VOX, however the ERG considers that it would be more appropriate for mortality to start at the same time point in the model for all treatments.

4.3.3 Population

The economic evaluation includes two sub-populations defined by previous treatment status with DAA. The groups are:

- DAA-experienced (pan-genotypic GT1-6; cirrhotic and non-cirrhotic patients
- DAA-naïve, GT3 patients:
    - With cirrhosis
    - Without cirrhosis

With respect to the selection of the patient population, the company acknowledged that the two included patient sub-populations are a narrower patient group than that covered by the marketing authorisation for SOF/VEL/VOX. However, they asserted that these patients reflected the subset of patients receiving the most clinical benefit. Secondly, the company did not model co-infected HCV/HIV patients separately which is in line with the agreement with NICE at the

Decision Problem meeting for SOF/VEL/VOX. Finally, the company did not model the treatment of patients in a post-liver transplant health state separately due to lack of data. This approach is consistent with previous submissions.

The ERG presents a detailed critique of the selection of the patient population for this appraisal in section 2.3. In short, the population included in the model is more restricted than the NICE scope. Whilst the NICE scope encompasses all CHC patients, irrespective of HCV genotype, treatment status and no restriction on the level of liver damage, the company included only those patients who were DAA-experienced and restricted the DAA–naïve patients to those with HCV GT3. The company excluded treatment naïve patients with GT-1, 2, 4, 5 and 6 and patients with decompensated cirrhosis for whom SOF/VEL/VOX is not licensed.

4.3.4 Interventions and comparators

The intervention used in the economic analysis is SOF/VEL/VOX which is a fixed dose combination of 400 mg SOF, 100 mg VEL and 100 mg VOX taken orally as a single tablet, once daily. SOF/VEL/VOX is administered for 12 weeks in DAA-experienced patients as outlined in the NICE scope. In DAA-naïve patients with GT3 infection, the treatment regimen is administered for 8 weeks, irrespective of their cirrhosis state. Whilst this treatment duration is the same as used in the POLARIS-3 trial, it is a slight deviation from the marketing authorisation which recommends 12 weeks treatment for all genotypes with an option of treating patients with HCV GT3 for 8 weeks. On clarification with clinical experts, the ERG understands that clinicians may prefer to treat DAA treatment-naïve patients with HCV GT3 and compensated cirrhosis for 12 weeks duration as cirrhotic patients are at a high risk of failing to achieve SVR. The company conducted a scenario analysis in which the treatment duration for this patient group was changed to 12 weeks. Further details are presented in section 4.3.10

The comparators used in the analysis, differ by treatment status and cirrhosis state as shown in Table 27 (reproduced from CS Table 48).

Table 27: Comparators used in the economic model

DAA-naïve / DAA-experienced	GT	CC/NC	Comparators	Treatment duration (weeks)
DAA-experienced	All	All	No treatment	-
DAA-naïve	3	CC	SOF/VEL	12
			SOF + DCV + RBV	12
			SOF + RBV	24
			Peg-IFN2a + RBV	24
			SOF + Peg-IFN2a + RBV	12
			No treatment	-
		NC	SOF/VEL	12
			SOF + DCV	12
			Peg-IFN2a + RBV	24
			SOF + Peg-IFN2a + RBV	12
			No treatment	-

CC, cirrhotic; DAA, direct-acting antivirals; DCV, daclatasvir; GT, genotype; HCV, hepatitis C virus; NC, non-cirrhotic; Peg-IFN2a, pegylated-interferon alfa-2a; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

In their economic analyses, the company excluded elbasvir / grazoprevir, ledipasvir / sofosbuvir, ombitasvir / paritapravir / ritonavir + dasabuvir ± ribavirin as comparators for DAA-naïve GT3 patients as these treatments have not been recommended in this patient population. Furthermore, as previously stated in section 2.3, it is to be noted that SOF+DCV (12 weeks) is only recommended in DAA-naïve GT3 non-cirrhotic patients if they are either ineligible for or intolerant of interferon and have significant fibrosis. Similarly, for DAA-naïve GT3 cirrhotic patients, only those patients who cannot have interferon (either intolerant or ineligible) should receive treatment with SOF+DCV+RBV (12 weeks) or SOF+RBV (24 weeks).

A detailed critique of the comparators included in this appraisal is presented in section 2.3.

4.3.5 Treatment effectiveness and extrapolation

SVR

The key clinical event in the economic model is the proportion of patients achieving SVR within the relevant treatment period. Different SVR rates are used for DAA-naïve patients with HCV GT3 with and without cirrhosis and for DAA-experienced patients. The SVR rates used in the company's base case analysis are shown in Table 28. The SVR rates for SOF/VEL/VOX, SOF/VEL and no treatment are taken from the company's own POLARIS trials (described in section 3.1.3).

The CS does not provide a rationale for the choice of studies for the comparator treatments. In response to clarification question B2, the company provided a rationale for their choice of studies to inform the SVR rates for each of the treatments considered. For SOF/VEL/VOX, SOF/VEL and no treatment the company used the POLARIS studies as these provided head-to-head evidence. For the other treatments the company uses SVR rates from individual trials to inform the model rather than the results of a network meta-analysis (discussed in more detail in section 3.1.7), The ERG considers this an appropriate approach for CHC as it has been accepted by NICE in previous CHC technology appraisals. The company stated that the studies chosen were consistent with those used in previous NICE technology appraisals, including for SOF/VEL (TA430),[14] and that they had not identified any more appropriate data since the previous NICE appraisal for SOF/VEL. The ERG considers that the SVR rates chosen by the company are generally appropriate.

The ERG notes that CS Table 60 incorrectly reported the SVR rate for SOF/DCV as 96.3%, rather than 97.3%, although the correct SVR rate has been used in the company's economic model (Clarification question B5). The ERG noted that the SVR rates for SOF/RBV for cirrhotic patients from the ASTRAL 3[1] trial in this submission (66.3%) differed from used in the previous technology appraisal for SOF/VEL (73.3%). The company clarified (Clarification question B4) that the efficacy data was for treatment naïve and treatment experienced (DAA treatment naïve) patients. However the ERG note that in contrast, for SOF/Peg-IFN2a/RBV the SVR rates have been estimated only for treatment naïve patients and do not include treatment experienced (DAA-naïve) patients. The ERG therefore suggests that the SVR rates for SOF/Peg-IFN2a/RBV for DAA-naïve patients should be 95.1% for non-cirrhotic patients and 87.9% for cirrhotic patients. In general, the ERG considers that the studies chosen and the SVR estimates used for

the considered treatment are appropriate. The ERG has conducted a scenario analysis using these SVR rates for SOF/Peg-IFN2a/RBV in section 4.4.

Table 28: SVR rates for DAA-experienced (all GTs) and DAA-naïve patients with GT3 infection (with or without cirrhosis) (CS Table 60, section B.3.6.2)

Treatment experience	GT	CC/NC	Intervention/Comparator	Base-case SVR	Data source
DAA-experienced	All	All	SOF/VEL/VOX	96.2%	POLARIS-1 (DAA-experienced population)[18] POLARIS-4 (DAA-experienced population) (to be run as sensitivity analysis: 97.8%)
			No treatment	0%	POLARIS-1 (placebo arm) (DAA-experienced population)[18]
DAA-naïve	3	CC	SOF/VEL/VOX	96.4%	POLARIS-3 (DAA-naïve population)[17]
			SOF/VEL	96.3%	POLARIS-3 (DAA-naïve population)[17] ASTRAL 3 (to be run as sensitivity analysis)[1]
			SOF + DCV + RBV	83.3%	ALLY 3+ (DAA-naïve population)[38]
			SOF + RBV	66.3%	ASTRAL 3 (DAA-naïve population)[1]
			Peg-IFN2a + RBV	29.7%	Sovaldi SmPC [FISSION] (TN population)[39]
			SOF + Peg-IFN2a + RBV	91.3%[a]	BOSON (TN population)[40]

Treatment experience	GT	CC/NC	Intervention/Comparator	Base-case SVR	Data source
			No treatment	0%	POLARIS-1 (placebo arm)[18] (treatment-naïve population)
		NC	SOF/VEL/VOX	98.9%	POLARIS-2 (DAA-naïve population)[17]
			Peg-IFN2a + RBV	71.2%	Sovaldi SmPC [FISSION] (TN population)[39]
			SOF + Peg-IFN2a + RBV	95.8%[b]	BOSON (TN population)[40]
			SOF/VEL	96.6%	POLARIS-2 (DAA-naïve population)[17] ASTRAL 3 (TN population) (to be run as sensitivity analysis)[1]
			SOF + DCV	97.3%[c]	ALLY-3, DCV SmPC; TA364 limits this to F3 only[41]
			No treatment	0%	POLARIS-1 (placebo arm)[18] (treatment-naïve population)

[a] ERG suggests SVR values should be 87.9%
[b] ERG suggests SVR values should be 95.1%
[c] Corrected from original CS Table 60 (Clarification question B5).

Transition probabilities

Patients move between health states in the economic model according to the transition probabilities shown in Table 29. The transition probabilities used for the base case analysis are the same as used in the previous NICE technology appraisal for SOF/VEL (TA430).[14]

The model assumes the same transition probabilities between health states for all HCV genotypes with the exception of the transition from non-cirrhotic to compensated cirrhosis which differs between genotypes. The transition probabilities from non-cirrhotic to cirrhosis are from a study of the clinical progression of US armed forces veterans with CHC over 10 years from 2000 to 2009.[42] The company stated that this study was selected as the most appropriate source to inform these transitions, given its large size, recent publication, pan-genotypic coverage. and its previous use in the SOF/VEL NICE technology appraisal (TA430).[14]

The transition probabilities for patients progressing from compensated cirrhosis (with or without SVR) to decompensated cirrhosis and HCC and from decompensated cirrhosis to HCC were taken from Cardoso et al.[43] Cardoso et al. conducted a retrospective review of CHC patients with bridging fibrosis or cirrhosis to assess the incidence of HCC, liver-related complications and liver-related death. All other transition probabilities were similar to those used in previous NICE appraisals and were based upon those from Wright et al.[44]

The ERG reiterates concerns raised by previous ERG reports that the data used for transition probabilities are based on old sources and may need updating based on more recent sources. In particular, the ERG notes that the model uses transition probabilities for mortality after liver transplantation that were published 20 years ago and suggest that these data are out of date. For example, current mortality rates for liver transplant give a lower mortality of 16% in year 1 and 5.2% in subsequent years.[45] The ERG explores the effect of changing the transition probabilities for mortality after liver transplant in section 4.4.

The transition probabilities for compensated (with or without SVR) to decompensated cirrhosis and HCC are taken from Cardoso et al.[43] The ERG notes that the NICE committee for TA430[14] recommended that analyses were also provided using alternative transition probabilities from Fattovich et al[46] but the company has not included these analyses in their submission. The ERG completes these analyses in section 4.4. The ERG notes that the probability values calculated from Cardoso et al.[43] differ slightly from the original source.

The ERG were unclear how the values used for the probabilities from Cardoso et al. were calculated. The company provide clarification on the calculations used to derive the transition probabilities from the original data (Clarification question B10). The calculation process followed

a series of steps calculating the probability of the event and the number of years of follow-up per patient and then converting this to an annual probability. The ERG was unable to find the estimate for the transition probability for decompensated cirrhosis to death in the cited source.

Table 29: Transition probabilities (CS Table 51)

From	To	TP (annual probabilities)	Source
Non-cirrhotic, mono-infected	Compensated cirrhosis	GT1: 0.0213 GT2: 0.0165 GT3: 0.0296 GT4: 0.0202 GT5: 0.0202 GT6: 0.0202	Kanwal *et al* 2014[42]
Compensated cirrhosis	Decompensated cirrhosis	0.0438	Cardoso *et al.* 2010[43]
	HCC	0.0631	Cardoso *et al.* 2010[43]
Compensated cirrhosis SVR	Decompensated cirrhosis	0.0064	Cardoso *et al.* 2010[43]
	HCC	0.0128	Cardoso *et al.* 2010[43]
Decompensated cirrhosis	HCC	0.0631	Cardoso *et al.* 2010[43]
	Liver transplant	0.0220	Siebert *et al.* 2005[47]
	Death	0.2400	EAP data (EASL 2016) European Association for Study of Liver, 2017 #44}
HCC	Death	0.4300	Fattovich *et al.*, 1997[46]
Liver transplant	Death, Yr1	0.2100	Bennett *et al.* 1997[48]
Post-liver transplant	Death, Yr2	0.0570	Bennett *et al.* 1997[48]

GT: genotype; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; SVR: sustained virological response; TP: transition probability; Yr: Year.

Adverse event rates

Treatment-related AEs are included within the economic model by inclusion of AE costs. The treatment-related AEs are shown in CS Table 62. The key AEs are nausea and diarrhoea. The treatment related AEs are taken from the same trials as the SVR values. The company has included all treatment related AEs, although it is more usual to only include grade 3 or 4 AEs.

Summary of treatment effectiveness and extrapolation

Overall, the ERG considers that the company's approach to the clinical effectiveness parameters and transition probabilities used in the model is appropriate. We consider that the SVR rates chosen by the company are generally appropriate. The transition probabilities used in the model are based upon a previous model and have been used in several previous NICE technology appraisals for CHC. However, some of these data may now be out of date and we recommend a full review and update of the transition probabilities.

4.3.6 Health related quality of life

The cost-effectiveness model incorporates the impact of the different treatments on HRQoL as utilities. Utilities are associated with the different health states in the model (Table 30), and in addition the adverse impact of treatment is accounted for by applying utility decrements.

A systematic search for HRQoL evidence was undertaken (see section 3.1.1 for a critique of the search strategy) and is presented in CS Appendix H. The inclusion criteria for the searches are shown in Table 25 of Appendix H. The ERG notes that the inclusion criteria includes adults with CHC with or without compensated cirrhosis and includes a list of interventions and comparators used to treat CHC. These inclusion criteria are therefore not able to capture studies that relate to more severe health states such as decompensated cirrhosis, HCC and liver transplant. The search resulted in 28 records which were data extracted and are shown in Table 27 of Appendix H. Of these studies, the company reports that eight studies were suitable for use in cost effectiveness analyses as they include utility values.

The company included HRQoL outcomes in the POLARIS clinical trials (see section 3.3.3). However, the HRQoL measures chosen did not include a utility based measure suitable for economic evaluation and so these were not used in their economic evaluation.

The base case utility values for the health states were derived from the study by Wright et al. (the mild chronic hepatitis C trial)[44] and are shown in Table 30. The company justifies the use of these utilities by stating that these utilities use EQ-5D, as preferred by the NICE reference case, and have been used in publications by Hartwell et al.,[49] Grischenko et al.[50] and Shepherd et al.[51]

The ERG notes that these utilities values have also been used predominantly by previous NICE technology appraisals for CHC.

The company uses a utility value for non-cirrhotic patients of 0.75. The company estimated this value using a weighted average of the proportion of mild and moderate patients with the original utility values for patients with mild and moderate HCV. The ERG discusses the proportions used for mild and moderate disease in section 4.3.7. There is a utility increment of 0.04 for patients who achieve SVR, based on data from Vera-Llonch et al.[52] Vera-Llonch et al. measured EQ-5D utility values of HCV GT1 treatment-naïve CHC patients receiving telaprevir combination in the ADVANCE study.

The ERG considers that the company's search for utility values is inadequate as it does not consider utility values for the more severe liver disease health states and therefore the sources chosen may not necessarily be the most appropriate. An ad hoc search by the ERG found three European studies that measured EQ-5D in patients with hepatitis C and liver disease.[53-55] Whilst these studies are not for UK patients, they all show higher utility values for cirrhosis and post-liver transplantation than reported in Wright at al.[44] However, the values used in this submission are consistent with those chosen in previous NICE technology appraisals, including for SOF/VEL (TA430).[14]

Table 30: Summary of utility values for cost-effectiveness analysis (CS Table 52)

Health-state	Utility	Source
Baseline – non-cirrhotic	0.75	Wright et al, 2006[44]
Baseline – compensated cirrhosis	0.55	Wright et al, 2006[44]
SVR (utility increment)	0.04	Vera-Llonch et al, 2013[52]
Non-cirrhotic with SVR	0.79	Calculation
Compensated cirrhotic with SVR	0.59	Calculation
Decompensated cirrhosis	0.45	Wright et al, 2006[44]
HCC	0.45	Wright et al, 2006[44]
Liver transplant	0.45	Wright et al, 2006[44]
Post-liver transplant	0.67	Wright et al, 2006[44]

EQ-5D, EuroQol-5 dimension; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virological response.

Treatment-specific HRQoL for CHC patients receiving DAA treatment are shown in Table 31. The company did not provide a justification for the choice of utility decrements. In reply to Clarification question B9, the company stated that HRQoL data collected in the ASTRAL-3 trial[1] indicated that no on-treatment decrements were observed in patients receiving 12 weeks of treatment with SOF/VEL.[1] On the basis of this, the following treatments were associated with zero utility decrement: SOF/VEL/VOX, SOF/VEL, SOF/DCV. For the other treatments, the company bases its estimates for utility decrement on a study by Younossi et al.[56] Younossi et al. retrospectively collected SF-6D HRQoL data from clinical trials of sofosbuvir with and without interferon or ribavirin. Patients treated with an interferon and ribavirin containing regime (Peg-IFN2a/RBV, SOF/Peg-IFN2a/RBV) were associated with a 4.7% utility decrement and those treated with an interferon-free, ribavirin containing regime (SOF/DCV/DCV, SOF/RBV) were associated with a 2.5% decrement. The ERG's clinical experts considered that the decrements chosen were in line with the change in quality of life for patients in clinical practice whilst on these treatments.

Table 31: Treatment-specific QOL for DAA-experienced (all GTs) and DAA-naïve patients with GT3 infection (with or without cirrhosis) (From CS Table 63)

Strategy	Utility increment/decrement	Source
DAA-experienced (All GTs, CC/NC)		
SOF/VEL/VOX (12 weeks)	0.0%	Assumed equal to SOF/VEL (12 weeks)
DAA-naïve (GT3, CC)		
SOF/VEL/VOX (8 weeks)	0.0%	Assumed equal to SOF/VEL (12 weeks)
SOF/VEL (12 weeks)	0.0%	Foster et al.[1]
SOF/DCV + RBV (12 weeks)	-2.5%	Assumed equal to SOF + RBV from Younossi et al. 2016[56]
SOF + RBV (24 weeks)	-2.5%	Younossi et al. 2016[56]
Peg-IFN2a + RBV (24 weeks)	-4.7%	Younossi et al. 2016[56]
SOF + Peg-IFN2a + RBV (12 weeks)	-4.7%	Younossi et al. 2016[56]
DAA-naïve (GT3, NC)		

Strategy	Utility increment/decrement	Source
SOF/VEL/VOX (8 weeks)	0.0%	Assumed equal to SOF/VEL(12 weeks)
Peg-IFN2a + RBV (24 weeks)	-4.7%	Younossi et al. 2016[56]
SOF + Peg-IFN2a + RBV (12 weeks)	-4.7%	Younossi et al. 2016[56]
SOF/VEL (12 weeks)	0.0%	Foster et al.[1]
SOF + DCV (12 weeks)	0.0%	Assumed equal to SOF/VEL Foster et al.[1]

CC, cirrhotic; DAA, direct-acting antiviral; DCV, daclatasvir; GT, genotype; HCV, hepatitis C virus; NC, non-cirhottic; Peg-IFN2a, pegylated-interferon alfa-2a; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

Summary of HRQoL model inputs

Overall, the ERG considers that the company's approach to HRQoL is appropriate and follows NICE methodological guidelines. However, some of these data may now be out of date and we recommend of a full review and update of the health state utility values.

4.3.7 Resource use and costs

The costs and resources used in the economic model consisted of drug costs, monitoring costs (including outpatient appointments, inpatient care, tests and investigations), health state costs, AE unit costs as well as AE management costs. The company did not perform any additional systematic review of the literature to identify sources for resource use and costs, apart from the cost-effectiveness review (discussed earlier in section 4.2). Where relevant, the company extracted data from the sources in their cost-effectiveness review to inform parameters for resource use and costs in the cost-effectiveness model. Further, the company stated that no additional sources, other than those used in the previous NICE submission of SOF/VEL[14] were identified. Hence these sources and values were used in the economic model. These costs were inflated to the 2015/16 cost year using the HCHS Pay and Prices Index.[57]

Drug costs

The unit costs of the comparator regimens were obtained from the British National Formulary (August 2017).[58] The drug costs per pack are reproduced below in Table 32 from CS Table 53.

The company performed all the analyses with the list prices. It is to be noted that SOF/VEL/VOX, SOF/VEL and DCV have confidential discount prices.

Table 32: Treatment unit costs (reproduced from CS Table 53)

Drug	Cost per pack (List)	Cost per pack (Confidential discount)	Unit dose	Quantity/ pack	Source	Assumption
SOF/VEL/VOX	£14,942.33	[redacted]	600 mg	28	Gilead	-
SOF/VEL	£12,993.33	[redacted]	500 mg	28	BNF, 3rd August 2017	Epclusa® 500mg tablets
SOF	£11,660.98	N/A	400 mg	28	BNF, 3rd August 2017	Sovaldi® 400mg tablets
RBV	£233.58		400 mg	56	BNF, 3rd August 2017	Copegus® 400mg Tablet
Peg-IFN2a	£124.40		180 µg	1	BNF, 3rd August 2017	Pegasys® Syringe
DCV	£8,172.61		60 mg	28	BNF, 3rd August 2017	Daklinza® 60mg tablets

µg, Micrograms; BNF, British National Formulary; DCV, Daclatasvir; DSV, Dasabuvir; GRZ/EBR, Grazoprevir/elbasvir; LDV, Ledipasvir; mg, milligrams; OBV, Ombitasvir; Peg-IFN2a, Pegylated-interferon 2a PTV, Paritaprevir; RTV, Ritonavir; RBV, Ribavirin; SMV, Simeprevir; SOF, Sofosbuvir; wks, Weeks

Monitoring costs

Unit costs associated with monitoring patients, whilst on treatment, were taken primarily from the study by Shepherd et al[51] and inflated to 2015/16 costs. This study conducted a systematic review and economic evaluation of interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C. Where data were unavailable, unit costs from other sources including National Reference Costs,[59] the studies by Stevenson et al. 2012[60] (which is a systematic review and economic evaluation of non-invasive diagnostic tools to detect liver fibrosis in patients with suspected alcohol-related liver disease) and Wright et al. 2006[44] (Mild Hepatitis C trial) were used to populate the model. A summary of the unit costs and their

sources are detailed in CS Table 54. In addition, the company presented a detailed summary of total costs for different treatment phases and cirrhotic states, an overview of which is presented in Table 33. For patients who received no treatment, the economic model assumed a monitoring phase of six weeks.

Table 33: Summary of monitoring cost in different monitoring phase and treatment (reproduced from CS Table 55)

Item	Treatment duration	Total cost
Initial evaluation of a new patient with confirmed HCV		
Total non-cirrhotic	-	£645
Total cirrhotic	-	£842
Further investigations for treatment group		
Total DAA-naïve non-cirrhotic	-	£482
Total DAA-naïve cirrhotic	-	£482
Total DAA-experienced non-cirrhotic	-	£482
Total DAA-experienced cirrhotic	-	£482
Monitoring during active treatment: Peg-IFN2a+RBV		
Total non-cirrhotic	4 weeks of treatment	£700
	6 weeks of treatment	£812
	8 weeks of treatment	£927
	12 weeks of treatment	£1,276
	16 weeks of treatment	£1,388
	24 weeks of treatment	£1,694
Total cirrhotic	4 weeks of treatment	£700
	6 weeks of treatment	£812
	8 weeks of treatment	£927
	12 weeks of treatment	£1,390
	16 weeks of treatment	£1,614
	24 weeks of treatment	£2,153
Monitoring during active treatment: All other treatments		
Total non-cirrhotic	4 weeks of treatment	£603
	6 weeks of treatment (excl. final visit)	£603

	6 weeks of treatment (incl. final visit)	£996
	8 weeks of treatment (excl. final visit)	£715
	8 weeks of treatment (incl. final visit)	£996
	12 weeks of treatment (excl. final visit)	£827
	12 weeks of treatment (incl. final visit)	£1,108
	16 weeks of treatment (excl. final visit)	£939
	16 weeks of treatment (incl. final visit)	£1,220
	24 weeks of treatment	£1,332
Total cirrhotic	4 weeks of treatment	£603
	6 weeks of treatment (excl. final visit)	£603
	6 weeks of treatment (incl. final visit)	£998
	8 weeks of treatment (excl. final visit)	£715
	8 weeks of treatment (incl. final visit)	£998
	12 weeks of treatment (excl. final visit)	£827
	12 weeks of treatment (incl. final visit)	£1,110
	16 weeks of treatment (excl. final visit)	£939
	16 weeks of treatment (incl. final visit)	£1,222
	24 weeks of treatment	£1,334

DAA, direct-acting antiviral; HCV, hepatitis C virus; Peg-IFN2a, pegylated-interferon alfa-2a; RBV, ribavirin

The ERG cross-checked all the unit costs reported in the CS against the sources as well as the economic model and noted a minor inconsistency in reporting the unit costs of gastroenterology-consultant led outpatient attendances. In CS Table 54, the associated unit cost was incorrectly reported as £144.44 whereas the economic model used the cost of £141.44. There is no impact on the overall cost-effectiveness results as the model used the correct value. For the unit costs of MRI liver and endoscopy diagnosis, the company used the average unit costs from three different unit prices reported in the study by Wright et al[44] where prices were reported separately for London, Newcastle and Southampton. The ERG considers this to be appropriate.

Health state costs

The company appropriately estimated the health state costs independent of monitoring costs as they are applied in health states outside of treatment administration. A summary of the health state costs along with their sources is reproduced from CS Table 56 and presented in Table 34.

The studies by Wright et al. 2006 (Mild Hepatitis C Trial),[44] Longworth et al. 2014[61] and Grischenko et al 2009[50] were used to estimate the health state costs in the economic model. Longworth et al. estimated the cost associated with liver transplantation in patients with chronic hepatitis B and C in the UK. Grischenko et al., on the other hand, estimated the cost-effectiveness of pegylated-interferon and ribavirin in patients withCHC. All the costs were inflated to the 2015/2016 costs using HCHS Pay and Prices Index.[57] The company used the same sources and assumptions to estimate cost parameters as the previous SOF/VEL technology appraisal to NICE.[14] Costs for the non-cirrhotic states (with and without SVR) were estimated as the weighted average of the mild and moderate hepatitis C states with 83% patients in the UK assumed to be in the mild state and the remaining 17% to be in the moderate state. Costs associated with the more severe liver disease health states (compensated cirrhosis with / without SVR, decompensated cirrhosis, HCC and liver transplant) included costs for pharmacy, hospitalisation and outpatients costs covering emergency and ambulatory services. For the costs associated with the post-liver transplantation stages, the company applied a 87:13 split between the first and second year respectively. This assumption (which has been previously used in the SOF/VEL TA430) is based on the relationship between these costs presented in the study by Wright et al.[44]

Table 34: Health state costs (reproduced from CS Table 56)

Health state ***Disaggregated costs***	**Inflated-values to £2015-2016**	**Source**
Non-cirrhotic, mild	£192	Wright et al, 2006[44]
Non-cirrhotic, moderate	£1,015	Wright et al, 2006 [44]
Non-cirrhotic[a]	£332	Calculation
Non-cirrhotic with SVR (mild)	£240	Grishchenko et al, 2009[50]
Non-cirrhotic with SVR (moderate)	£294	Grishchenko et al, 2009[50]
Non-cirrhotic with SVR[a,b]	£249	Calculation
Compensated cirrhosis	£1,582	Wright et al, 2006[44]
Compensated cirrhosis with SVR	£520	Grishchenko et al, 2009[50]
Decompensated cirrhosis	£12,676	Wright et al, 2006[44]
HCC	£11,295	Wright et al, 2006 [44]
Liver transplant	£86,324	Longworth et al 2014[61]

Health state ***Disaggregated costs***	**Inflated-values to £2015-2016**	**Source**
Post-liver transplant follow-up phase (0-12 months)	£28,441	Longworth et al 2014[61]; Split between post-liver transplant year 1 and year 2 cost based on Wright et al 2006 [44]
Post-liver transplant follow-up phase (12-24 months)	£4,250	

HCC, hepatocellular carcinoma; SVR, sustained virological response.

[a]Weighted average of mild and moderate health state costs; 83% of patients with F0-3 in the UK were mild (F0-F2) and 17% (F3) moderate; Patients are followed-up for 2 years;

[b]The same percentage split of mild and moderate in non-cirrhotic was applied to the non-cirrhotic with SVR health states.

In general, the company estimated the health states costs by using the same methodologies and assumptions as in the SOF/VEL submission (TA 430). Overall, the ERG views the methods to be reasonable, with the following exceptions. With regard to the percentage split of patients in the non-cirrhosis states of mild and moderate, we view that an equal percentage split (i.e. 50:50) instead of a split of 83:17 (as has been used in the company analyses) may be a better reflection of clinical experience, on the basis of expert clinical advice and a previous study by Hartwell et al. 2011,[49]

Furthermore, the company applies the costs associated with the non-cirrhotic patients with SVR health state across all the time periods. Based on our clinical expert advice, the ERG understands that non-cirrhotic patients with SVR are usually only followed up for one year after the end of treatment. This is not the case for cirrhotic patients with SVR, who are followed up long term with ultrasound screening every six months as they have a risk of HCC. We view this as a conservative assumption

We explore the impacts of these changes (i.e the change in the percentage split of patients in the non-cirrhotic states of mild and moderate and the follow-up costs for SVR non-cirrhotic patients) to the company's base case model in section 4.4.

Adverse events unit costs and resource use

Adverse event management costs consisted of:

- AE drug treatment unit costs

- Costs associated with outpatient care, GP visits and visits to specialists
- AE drug treatment dosing and duration

The unit costs of treatment-related AEs were obtained from the British National Formulary (BNF)[58] and NHS Reference Costs[59] (CS Table 57). Costs associated with outpatient, GP and specialist visits were obtained from clinical expert opinions, the Personal Social Services Research Unit (PSSRU),[57] NHS Reference Costs,[59] and BNF[58] (CS Table 59). Information on AE costs and resource use for treatment dosing and duration were obtained from a number of sources including a previous NICE submission (TA 252[62]), BNF, clinical expert opinion, PSSRU,[57] NHS Reference Costs[59](CS Table 58). The AE total costs (per episode) were estimated as the sum total of AE drug costs, inpatient costs, outpatient costs, GP costs and specialist costs. The results, obtained from the economic model, are presented in Table 35.

Table 35: AE total costs (per episode)

AE	Total costs
Nausea	£2.16
Vomiting	£2.16
Diarrhoea	£0.96
Pruritus	£3.04
Rash	£680.87
Anaemia (Erythropoietin)	£12.55
Anaemia (blood transfusion)	£8.41
Thrombocytopenia	£1,909.97
Neutropenia	£1,341.41
Depression	£107.48

Whilst verifying the costs reported in the CS against the values used in the economic model, we noted a few inconsistencies. First, the CS Table 58 reports the weekly cost of anaemia (erythropoietin) as £13.27 but the economic model uses a value of £2.21. Secondly, the cost of anaemia treatment (erythropoietin) in outpatient setting is reported as £240, that of a specialist visit as £129.97 and the total cost of anaemia treatment (blood transfusion) as £129.97 in CS Table 59 whereas the model uses values of £2.40, £1.30 and £0.91 respectively. On further clarification, the company stated that the values reported in the CS were typographical errors and that the model used the correct values (Company response Question B11).

Summary of resource use and costs

Overall, the ERG views the company's approach to modelling costs as reasonable. We identified a few minor reporting errors but these did not impact the base case cost-effectiveness results. The ERG had a few concerns over some of the assumptions used in estimating heath state costs which are explored further in section 4.4. Overall, we view that whilst the methods used to estimate the costs are reasonable, the data, in general, are now out of date and therefore should be reviewed for future appraisals.

4.3.8 Model validation

We checked the company's economic model for transparency and validity in line with the recommendations developed by a task force of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM).[63] Our checks cover internal and external validation and are discussed below.

Model transparency

The CS described the model's structure, parameter values and sources, model assumptions and data identification in clear terms. The submission appendices and submission summary were accessible. The model was technically transparent and the R codes and Visual basic codes used within the model were accessible. The CS clearly presented model results for the deterministic, probabilistic and scenario analyses.

Model validation

The CS states that the model is an updated version of one previously submitted and accepted previously by NICE (SOF/VEL (TA430),[14] LDV/SOF(TA363)[6] and SOF(TA330))[12] and these earlier versions had undergone internal and external validation. The company therefore adopted a minimalist approach to model validation. We describe the steps taken by the company and our approach in detail below.

Face validity

The company carried out literature reviews of published cost-effectiveness studies as well as existing NICE appraisals in Hepatitis C to inform its modelling approach. The model used by the company was a similar to the ones used in previous submissions to NICE and the CS states that given the consistent use of the model, further clinical expert opinion was not sourced for

this submission. Two clinical experts with prior experience in earlier submissions were consulted to inform the choice of a model annual transition probability and use of SVR rates from individual trials to inform model comparisons as an alternative to the results of the network meta-analysis. The ERG confirms that the model structure reflects current UK clinical practice and involved minor updates to a model for a recent NICE submission (SOF/VEL submission TA430,).[14]

Internal consistency

The approach used by the ERG for internal validity checks involved checking the individual equations within the model, and then verifying their accurate implementation in model codes and outputs.

The CS reports three steps in used for internal validation: first, a formal checklist (Phillips et al[64]) was used to assess the model; a health economist then conducted manual checking of formulas and model codes; finally model logic and internal calculations were tested by imputing extreme values into the model. The extreme value tests conducted by the company are summarised in Table 36 below.

Table 36: Tabulation of extreme checks for model internal validation reported in the CS

No.	Extreme check
1	Remove excess mortality for advanced liver disease
2	Remove background mortality in addition to excess mortality.
3	Test an equal rate of SVR between both arms of the model. 100% efficacy
4	Test an equal rate of SVR AND an equal treatment duration between both arms of the model. 50% efficacy
5	Set all health state utility values to 1.
6	Turn off probability of DCC
7	Model a non-cirrhotic cohort with a 100% SVR rate.

The CS does not report any adverse outcomes from these checks and it is implied that the results of the company checks further justified the use of the model. The outcomes of verification checks conducted by the ERG are reported in Appendix 1. The ERG checks reported are specifically for the genotype 3 treatment-naïve cirrhotic analyses with SOF/VEL/VOX (8 weeks) versus no treatment, however similar checks were conducted on other

subgroups. The ERG's verification checks did not reveal any potential errors in the company model. The conclusions from our checks in the table below apply to the other subgroups as well.

External consistency

As stated earlier, the model has been previously validated and the company did not carry out any further external validation. The ERG compared results for SOF/VEL for the company's model against those reported in the previous technology appraisal for SOF/VEL (TA430) for DAA-naïve patients. Cost and QALY results were redacted so we compared results for life years only. We used the SVR rates from the SOF/VEL technology appraisal (Non cirrhotic SVR 98.2%, cirrhotic SVR 93.0%). The life years were similar for the current model against those reported in the SOF/VEL technology appraisal (21.84 vs 21.85 years for non-cirrhotic patients; 16.89 vs 16.90 years for cirrhotic patients. Predictive validity checks were not relevant and were not performed by either the company or the ERG.

4.3.9 Cost effectiveness results

Base case results reported in the CS are for DAA-experienced patients and DAA-naïve patients with HCV GT3 infection. DAA-naïve patients are further split into a subgroup of patients with compensated cirrhosis and non-cirrhotic patients.

The company presented the base case results in terms of total costs, life years gained and total QALYs. The results are presented incrementally and also for treatment versus no treatment (see CS tables 64, 65 and 66). In the tables below, we summarise the incremental analyses for DAA-experienced and DAA-naïve patients.

The company does not present genotype-specific results for the DAA-experienced population and acknowledges this as a limitation of the model. For analyses involving DAA-experienced patients a blended SVR (incorporating efficacy data across all genotypes) was used. The ERG notes that although the company report SVR12 subgroup analyses results for all genotypes in DAA-experienced participants in the POLARIS trials, for some of these genotype subgroups the number of patients reported was small, which would have limited the reliability of these data. Therefore the ERG considers that the company's approach to report results for a pan-genotype group for DAA-experienced patients is appropriate. In DAA-experienced patients, the base-case

result showed that SOF/VEL/VOX 12 week is cost-effective with an incremental cost-effectiveness ratio (ICER) of £8,153 per QALY gained compared to no treatment.

Table 37: Base-case results: DAA-experienced (pan-GT and all non-cirrhotic/compensated cirrhosis) (list price) (CS Table 64)

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER Incremental (£)
No treatment	£23,262	10.01	-	-	-
SOF/VEL/VOX (12 wks)	£53,922	13.77	£30,660	3.76	£8,153

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

Table 38: Base-case results: DAA-naïve, GT3 infection, with compensated cirrhosis (list price) (CS Table 65)

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER Incremental (£)
No treatment	£36,262	4.98	-	-	-
Peg-IFN2a + RBV (24 wks)	£37,510	6.61	£1,248	1.63	£765
SOF/VEL/VOX (8 wks)	£51,289	9.98	£13,779	3.37	£4,088
SOF + Peg-IFN2a + RBV (12 wks)	£59,961	9.72	£8,672	-0.26	**Dominated** by SOF/VEL/VOX (8 wks)
SOF/VEL (12 wks)	£60,449	9.99	£9,160	0.01	£863,724
SOF + DCV + RBV (12 wks)	£83,447	9.31	£32,158	-0.67	**Dominated** by SOF/VEL/VOX (8 wks)
SOF+ RBV (24 wks)	£98,661	8.49	£47,372	-1.49	**Dominated** by SOF/VEL/VOX (8 wks)

DCV, daclatasvir; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN2a, pegylated-interferon alfa-2a; QALYs, quality-adjusted life years; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

[a] SOF/VEL (12 wks) has a smaller efficacy level than SOF/VEL/VOX. The model assumes that patients cannot die whilst on treatment; SOF/VEL has a longer treatment time than SOF/VEL/VOX. The difference in health outcomes can be attributed to modelling limitations.

Table 39: Base-case results: DAA-naïve, GT3 infection, non-cirrhotic (list price) (based on CS Table 66)

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER Incremental (£)
Peg-IFN2a + RBV (24 wks)	£12,256	16.03	-	-	-
No treatment	£18,938	12.83	£6,682	-3.20	**Dominated** by Peg-IFN2a + RBV (24 wks)
SOF/VEL/VOX (8 wks)	£32,917	17.27	£20,661	1.24	£16,654
Sofosbuvir + Peg-IFN2a + RBV (12 wks)	£41,303	17.13	£8,386	-0.14	**Dominated** by SOF/VEL/VOX (8 wks)
SOF/VEL (12 wks)	£42,519	17.17	£9,602	-0.10	**Dominated** by SOF/VEL/VOX (8 wks)
SOF + DCV (12 wks)	£62,698	17.20	£29,781	-0.07	**Dominated** by SOF/VEL/VOX (8 wks)

DCV, daclatasvir; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Peg-IFN2a, pegylated-interferon alfa-2a; QALYs, quality-adjusted life yeas; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

In non-cirrhotic DAA-naïve GT3 patients and DAA-naïve GT3 patients with compensated cirrhosis, the CS reports that SOF/VEL/VOX (8 weeks) is cost-effective and below the £20,000 threshold compared to Peg-IFN2a/RBV, with all other treatment options dominated. For cirrhotic DAA-naïve GT3 patients, against SOF/VEL, SOF/VEL/VOX is equivalent in efficacy and cost-saving. The CS notes there is a modelling limitation which has a small effect on this comparison (discussed in more detail in section 4.3.2). The CS results tally with the outputs of the company's model.

4.3.10 Assessment of uncertainty

To reflect methodological, structural and parameter uncertainties, the company conducted various deterministic, probabilistic and scenario analyses. Details are summarised and discussed below.

One-way sensitivity analyses

The CS reports deterministic sensitivity analysis (DSA) performed on input parameters. The parameters and their ranges are reported in CS Tables 73, 74 and 75. The choices of parameters explored in the CS DSA are summarised in Table 40 below. For the SVR rates, the ranges explored in the DSA were the upper and lower of 95% CIs. The ERG deemed that this was reasonable. For the other parameters, the company used a range of 25% above or below the base case for most parameters which appeared plausible.

Table 40: Input parameters and ranges used for deterministic sensitivity analysis (Adapted from CS Tables 73, 74 and 75)

Parameter	Range
Health state costs	+/- 25% of base-case value
Utility weights	+/- 20% of base-case value
Transition probabilities	95% CI estimated from the probabilistic sensitivity analysis (PSA)
Treatment-specific AE rates	Between 0% and 25%
SVR12 rates	95% CI

The company presents tornado diagrams to illustrate the DSA results in CS Figures 6 -10. The tornado diagram for DAA-experienced patients is shown in Figure 2. The tornado diagrams for DAA treatment naïve in the CS are for SOF/VEL/VOX compared to Peg-IFN2a/RBV and no treatment.

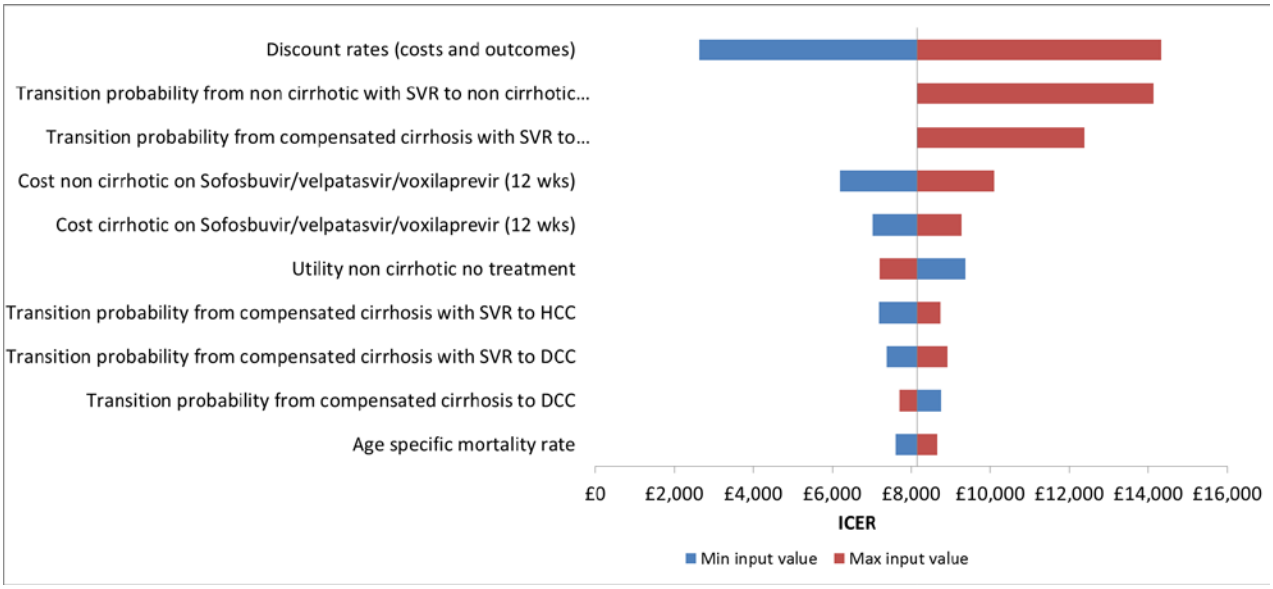


Figure 2: Tornado diagram: DAA-experienced (pan-GT and all non-cirrhotic/compensated cirrhosis): SOF/VEL/VOX 12 weeks vs no treatment (list price)

In DAA-experienced patients, the parameters with the most significant impact on the ICER were the discount rate, the transition probability from compensated cirrhosis with SVR to compensated cirrhosis (re-infection), and the cost of SOF/VEL/VOX administered for 12 weeks. None of these parameters increased the ICER beyond the £20,000 threshold (see CS Figure 6).

In the DAA-naïve patient group, transition probabilities from compensated cirrhosis with SVR to compensated cirrhosis (re-infection) and from non-cirrhotic with SVR to non-cirrhotic (re-infection) gave the biggest ICER changes. For the DAA-naïve cirrhotic population, SOF/VEL/VOX remains less costly than SOF/VEL but has similar QALYs for all sensitivity analyses except for changes to the SVR rates of SOF/VEL/VOX and SOF/VEL. For the DAA-naïve non-cirrhotic population, SOF/VEL/VOX dominates SOF/VEL for all sensitivity analyses except for changes to the cost of SOF/VEL and SVR rates of SOF/VEL/VOX and SOF/VEL

Scenario Analysis

The CS reports a number of scenario analyses for DAA-experienced and DAA-naïve patients. In addition the company conducts a dynamic transmission scenario. A list of the company's scenario analyses is shown in Table 41. A summary of the company's scenario analyses is shown in Table 42.

Table 41 List of company scenario analyses

Treatment group	Scenario	Base case	Changes made
DAA treatment experienced	Alternative SVR for SOF/VEL/VOX	SVR from POLARIS-1	SVR from POLARIS-4
	Alternative transition probability from non-cirrhotic to cirrhosis	Blended transition probability from all genotypes	Transition probability from genotype 3 only or genotype 1 only
	Alternative distribution of non-cirrhotic to compensated cirrhosis	Non-cirrhotic to cirrhotic 66.3:36.7	From POLARIS-1 58.6:41.4
DAA-naïve patients, GT3 infection, compensated cirrhosis	Alternative SVR for SOF/VEL	SVR from POLARIS-3	SVR from ASTRAL-3[1]
	Alternative treatment duration for SOF/VEL/VOX	8 weeks treatment	12 weeks treatment
DAA-naïve patients, GT3 infection, non-cirrhotic	Alternative SVR for SOF/VEL	SVR from POLARIS-3	SVR from ASTRAL-3[1]

Table 42 Summary of the results of the company scenario analyses

Treatment group	Scenario	Comparator	Base case ICER (£/QALY)	Scenario ICER (£/QALY)
DAA treatment-experienced	Alternative SVR for SOF/VEL/VOX	No treatment	£8,153	£8,021
	Alternative transition probability from non-cirrhotic to cirrhosis (GT3 only)	No treatment	£8,153	£7,171
	Alternative transition probability from non-cirrhotic to cirrhosis (GT1 only)	No treatment	£8,153	£8,399
	Alternative distribution of non-cirrhotic to compensated cirrhosis	No treatment	£8,153	£7,807

DAA-naïve patients, GT3 infection, compensated cirrhosis	Alternative SVR for SOF/VEL (ASTRAL-3)	SOF/VEL	£863,724[a]	SOF/VEL/VOX dominates
	Alternative treatment duration for SOF/VEL/VOX (12 weeks)	SOF/VEL	£863,724[a]	£3,394,377[b]
	Alternative SVR for SOF/VEL (ASTRAL-3)	SOF/VEL	£863,724[a]	SOF/VEL/VOX dominates

[a] ICER for SOF/VEL vs. SOF/VEL/VOX.

[b] ICER for SOF/VEL/VOX vs. SOF/VEL

In the scenarios for DAA-experienced patients, the ICER for SOF/VEL/VOX varied between £7,171 and £8,388 per QALY gained.

For DAA-naïve patients with compensated cirrhosis, in the scenario with an alternative SVR for SOF/VEL, SOF/VEL/VOX (8 weeks) dominates SOF/VEL (12 weeks). For the scenario with 12 weeks treatment for SOF/VEL/VOX, SOF/VEL/VOX was more expensive than SOF/VEL and the ICER of SOF/VEL/VOX changed significantly (£3,394,377 per QALY) compared to SOF/VEL.

For non-cirrhotic DAA-naïve patients, in the scenario with alternative SVR values for SOF/VEL, SOF/VEL continues to be dominated by SOF/VEL/VOX.

Company's dynamic transmission scenario

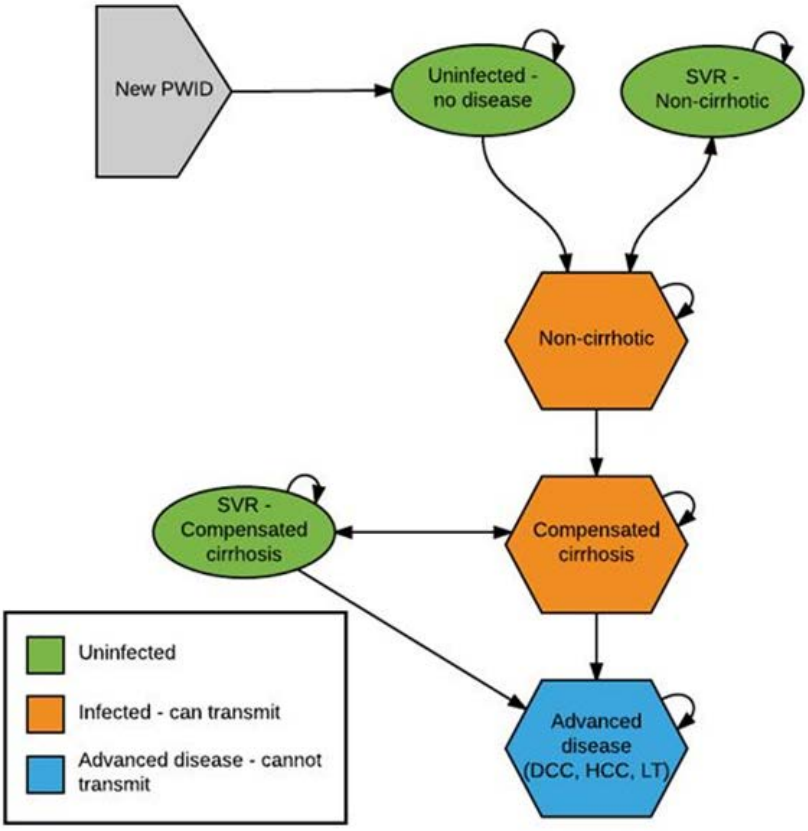
The company's dynamic transmission scenario explored the impact of Hepatitis C re-infection and onwards transmission in GT3 DAA-naïve patients. The CS stated that a similar analysis was not conducted on DAA-experienced patients as the impact of onward transmission and re-infection is expected to be minimal in this patient group.

The company conducted this scenario analysis in a separate model structure developed in R, which was then incorporated within the main Excel model. To account for the dynamic transmission, the model included uninfected persons along with the possibility of them becoming infected. The rate of transmission was estimated by a constant probability of infection (by genotype) and the number of currently infected persons who could transmit the disease

relative to persons at risk of infection. The model population is grouped into: People who inject drugs (PWID) and People who do not inject or have ceased injecting (ex-PWID). The company conducted a calibration model to address data gaps in the model inputs and fitted the model to match genotype prevalence data reported in a Public Health England (PHE) report.[65] This modelling approach, based on the study by M. Madin-Warburton et al.,[66] made the following assumptions:

- PWID could transmit the disease or become infected
- Ex-PWID are at no risk
- Following successful treatment, PWID could re-enter the pool of susceptible population and may be at risk of becoming re-infected
- PWID may stop using and become ex-PWID after an average of 11 years.
- All the populations within PWID and ex-PWID are homogenous.
- At baseline, 37.5% of PWID are infected with one of HCV GT1-4
- PWID are not given any treatment and GT prevalence remains constant over time
- The total population size and ratio of PWID to ex-PWID (1/6:5/6) remains constant over time.
- 5% of infected PWID and 7% of infected ex-PWID are treated per year.
- GT1, 2 and 4 are treated in line with current guidelines (assuming an SVR of 95%) as this analysis only considered GT3; costs associated with these GTs are not considered.

A schematic of the dynamic transmission model structure is reproduced from CS Figure 11 and presented below in Figure 3 and the distribution of genotype among PWID is presented in Table 43.



Note: Advanced Disease in the structure above refers to the DCC, HCC and LT states described in the main model. All transitional probabilities used within the Markov model are utilised within the dynamic model above.

Figure 3: Dynamic transmission model structure (reproduced from CS Figure 11)

Table 43: Genotype distribution among PWID at baseline (reproduced from CS Table 83)

Genotype	Proportion of PWID infected
GT1	16.1%
GT2	1.7%
GT3	18.7%
GT4	1.1%
Any genotype of HCV	*37.5%*

GT, genotype, HCV, hepatitis C virus; PWID, people who inject drugs.

Results of the scenario analysis are presented in Table 44. As can be seen, the results of the analysis are broadly in line with the base case, with an improvement in ICERs for all treatments vs. no treatment.

Table 44: Scenario analysis: exploratory analysis using dynamic transmission modelling framework (CS Table 84)

Treatment	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER versus No treatment (£)	ICER Incremental (£)
No treatment	£6,078	20.84	-	-	-	-
Peg-IFN2a + RBV (24 weeks)	£5,625	21.11	-£453	0.27	**Dominates** no treatment	**Dominates** no treatment
SOF/VEL/VOX (8 weeks)	£7,142	21.24	£1,064	0.40	2,660	£11,489
SOF+ Peg-IFN2a + RBV (12 weeks)	£7,850	21.23	£1,772	0.39	4,544	**Dominated** by SOF/VEL/VOX (8 weeks)
SOF/VEL (12 weeks)	£7,934	21.23	£1,856	0.39	4,759	**Dominated** by SOF/VEL/VOX (8 weeks)
SOF + DCV (12 weeks)	£9,962	21.18	£3,884	0.34	11,424	**Dominated** by SOF/VEL/VOX (8 weeks)

DCV, daclatasvir; Peg-IFN2a, pegylated-interferon alfa-2a; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

ERG's conclusion

The ERG is of the opinion that this dynamic transmission model is useful in providing more robust estimates of the cost-effectiveness of SOF/VEL/VOX and the results of this scenario further reinforce the results of the base case. However we note that this scenario does not represent a truly population dynamic model and many simplifying assumptions have been made. The analysis did not include DAA-experienced patients so we are unable to comment on the impact on the cost-effectiveness results in this population. Furthermore, the company did not conduct any separate exploratory analysis for cirrhotic vs non-cirrhotic patients in the DAA-naïve GT3 patient population. In the company's instructions for running the transmission model, the user is directed to select 'Non-cirrhotic and compensated cirrhotic', but it is not clear what

drugs these two groups of patients receive in the model. The company presents results (CS Table 84) with the choice of drugs recommended for the management of DAA-naïve, non-cirrhotic infection while some choices for DAA-naïve, compensated cirrhotic, such as SOF+RBV (24 weeks) are excluded. The ERG notes that the options available in the model are those for compensated cirrhotic, and therefore it is not clear how results in CS Table 84 have been derived. Lastly, the company's estimated percentage of PWD infected was based on GT1-4, but the scenario is conducted for GT3 only.

Probabilistic Sensitivity Analysis

The CS reports probabilistic sensitivity analysis (PSA) performed on the base case analysis to assess parameter uncertainty (CS section B.3.8.1). The ERG's view is that the PSA was well conducted and accounted for most of the key input parameters. We present an abridged version of CS Tables 67 and 68 with comments on the choice of distributions used by the company in Table 45.

Table 45: PSA parameter groups and associated distributions (Adapted from tables 67 and 68 of the CS)

Type of parameter	Distribution	ERG Comments
Health state costs	Gamma	Appropriate; health care costs are usually skewed and constrained to positive values
Utility weights	Beta	Appropriate; utility weights are usually bounded between values minus infinity and 1
Utility increment	Gamma	Appropriate; bounded between zero and infinity and skewed
Transition probabilities	Beta	Appropriate; bounded between zero and 1

The number of PSA iterations is set to a default of 1000 iterations. PSA and base case deterministic results are compared and summarised in the tables below. The ERG notes that with 1000 iterations the PSA takes about 30 seconds to run per comparator and three minutes and 50 seconds to run for six comparators.

The ERG notes that the PSA results are fairly stable at 1000 iterations but there was some divergence between the PSA and deterministic results (see Table 46 and Table 47 below for the analyses for DAA-naïve GT3 cirrhotic patients). The ERG noted that there was an error in the

PSA input parameters (alpha and beta parameters) for the transition probabilities for cirrhosis to HCC, DCC to HCC, DCC with SVR to HCC, DCC with SVR to death and DCC to death. The ERG corrected the alpha and beta values using those reported in CS Table 67. The corrected PSA results are shown in Table 46 and Table 47 and can be seen to be similar to the deterministic results.

Table 46: Comparison of Total QALYs in deterministic and PSA results (genotype 3 treatment naïve cirrhotic, SOF/VEL/VOX 8 weeks)

	Deterministic	PSA	PSA corrected
Treatment	**Total QALYs**	**Total QALYs**	**Total QALYs**
SOF/VEL/VOX (8 wks)	9.98	10.11	10.00
Peg-IFN2a + RBV (24 wks)	6.61	6.92	6.68
SOF + DCV + RBV (12 wks)	9.31	9.43	9.34
SOF/Peg-IFN2a/RBV(12 wks)	9.72	9.88	9.71
SOF + RBV (24 wks)	8.49	8.75	8.55
SOF/VEL (12 wks)	9.99	10.17	10.05
No treatment	4.98	5.35	5.03

Table 47: Comparison of total costs in deterministic and PSA results (genotype 3 treatment naïve cirrhotic, SOF/VEL/VOX 8 weeks)

	Deterministic	PSA	PSA corrected
Treatment	**Total Costs (£)**	**Total Costs (£)**	**Total costs (£)**
SOF/VEL/VOX (8 wks)	£51,288	£54,707	£51,394
Peg-IFN2a + RBV (24 wks)	£37,509	£45,521	£37,958
SOF + DCV + RBV (12 wks)	£83,447	£87,526	£83,746
SOF/Peg-IFN2a/RBV(12 wks)	£59,960	£63,593	£60,216
SOF + RBV (24 wks)	£98,660	£102,920	£99,002
SOF/VEL (12 wks)	£60,449	£63,564	£60,513
No treatment	£36,261	£46,409	£36,921

The company produced cost-effectiveness acceptability curves (CEACs) for the DAA-experienced and DAA-naïve groups, shown in Figure 4 - Figure 6 (Figures 70, 71 and 72 of the CS). For the DAA treatment experienced patients, SOF/VEL/VOX has a 100% probability of being cost-effective at the willingness to pay (WTP) thresholds of £20,000 and £30,000 respectively. For the DAA-naïve GT3 patients with cirrhosis, SOF/VEL/VOX has a probability of being cost-effective at the WTP thresholds of £20,000 and £30,000 of 49% and 44% respectively. For the DAA-naïve GT3 patients with non-cirrhosis, SOF/VEL/VOX has a probability of being cost-effective at the WTP thresholds of £20,000 and £30,000 of 36% and 35% respectively.

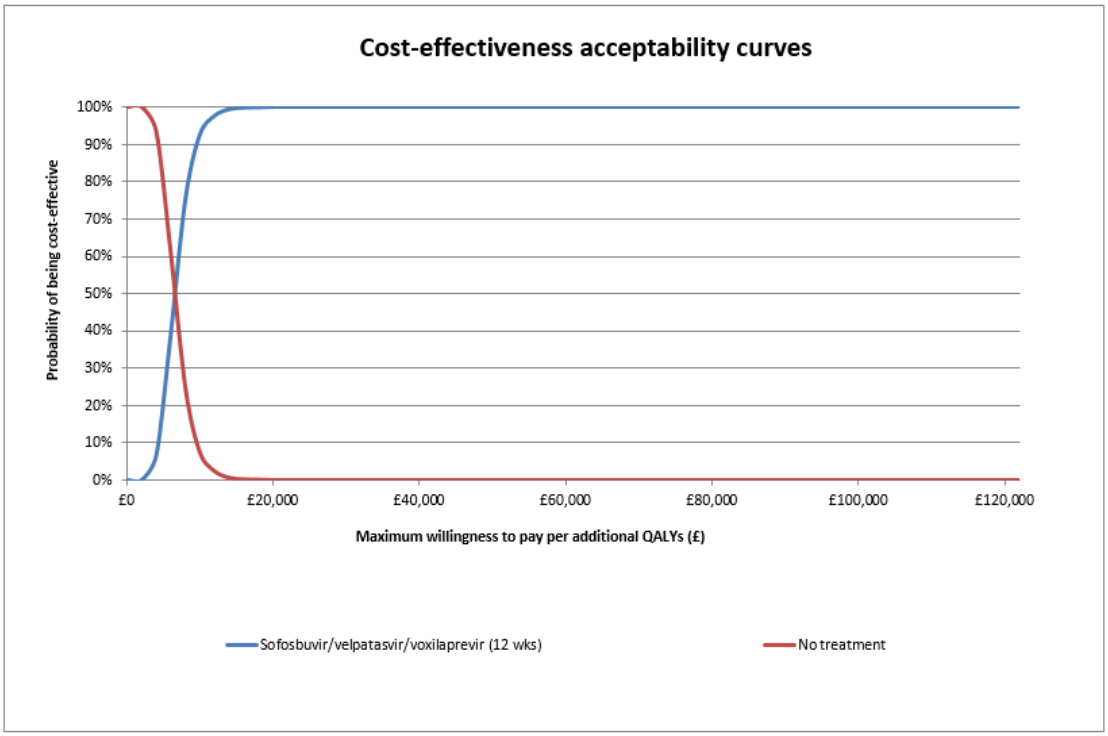


Figure 4: Cost-effectiveness acceptability curves for DAA-experienced patients (PAN genotypic and non-cirrhotic/cirrhotic)

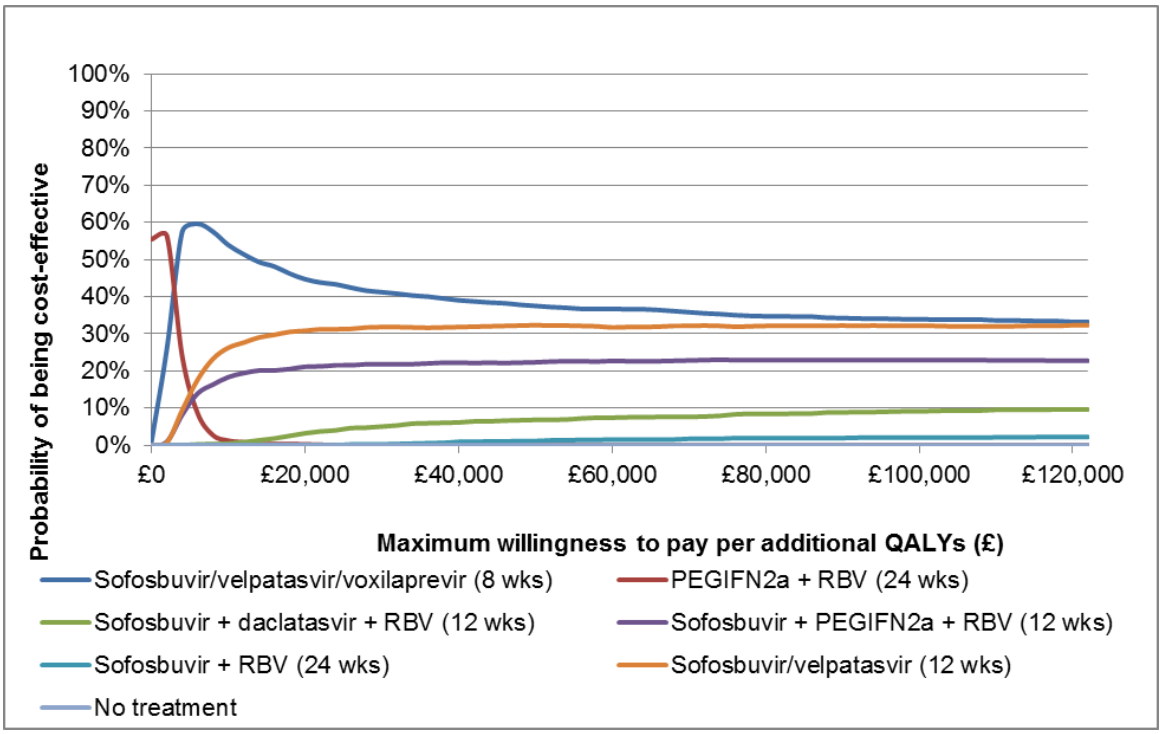


Figure 5: Cost-effectiveness acceptability curves for all treatments (genotype 3 treatment naïve cirrhotic, SOF/VEL/VOX 8 weeks)

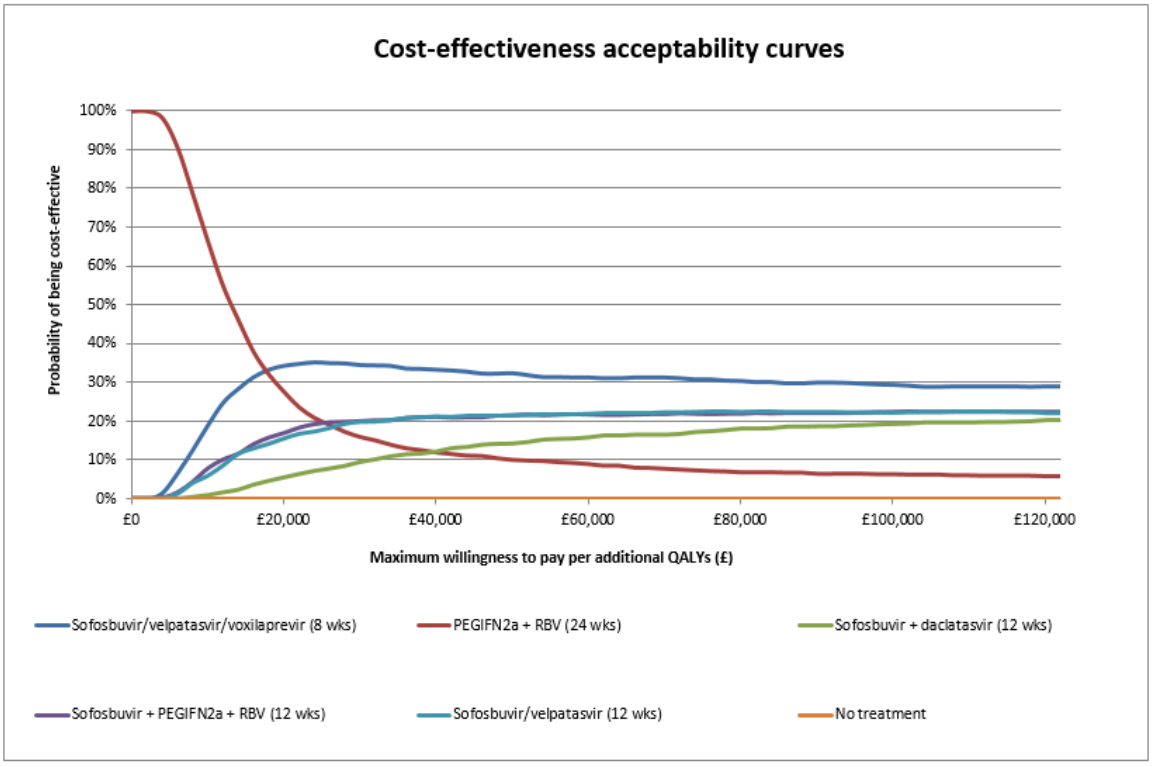


Figure 6: Cost-effectiveness acceptability curves for all treatments (genotype 3 treatment naïve non-cirrhotic, SOF/VEL/VOX 8 weeks)

4.4 Additional work undertaken by the ERG

This section details the ERG's further exploration of the issues and uncertainties raised in the review and critique of the company's cost-effectiveness analyses. This consists of changes to the follow-up costs for non-cirrhotic patients with SVR, the SVR rates for SOF/Peg-IFN2a/RBV, the mortality rates after liver transplant, the proportion of mild and moderate patients for non-cirrhotic patients, the source of the transition probabilities and the duration of treatment for SOF/VEL/VOX for cirrhotic patients. Table 48 shows the ERG scenarios with an explanation of the changes implemented.

Our results are reported below. With the exception of scenario 2, we do not report results for treatments including Peg-IFN2a or no treatment as these are no longer prescribed in current UK practice.

Table 48: Description of the ERG analyses

Scenario #'	Description	Justification
1	Follow-up for non-cirrhotic patients with SVR should be for 1 year only	As per clinical advice to the ERG (section 4.3.7).
2	SVR for SOF/Peg-IFN2a/RBV changed to 95.1% for DAA-naïve non-cirrhotic patients and 87.9% for cirrhotic patients	DAA estimates include both treatment naïve and treatment experienced (not DAA) patients (section 4.3.5)
3	The transition probability from liver transplant to death in year 1 changed to 16%; and in subsequent years is 5.2%	More recent mortality estimates (section 4.3.5)
4	The proportion of mild and moderate patients for non-cirrhotic patients is 50:50	As per clinical advice to the ERG (section 4.3.7)
5	Using transition probabilities from Fattovich et al.	As requested by NICE committee for SOF/VEL appraisal (section 4.3.5)
6	Different proportions of patients receiving SOF/VEL/VOX for 8 and 12 weeks for DAA-naïve GT3 cirrhotic patients	Marketing authorisation allows treatment with 8 or 12 weeks (section4.3.4)
7	ERG base case consisting of scenarios i-iv	See above

ERG scenario 1: Reducing follow-up for non-cirrhotic patients with SVR to 1 year only

This scenario reduced the follow-up costs for non-cirrhotic patients to one year only (as discussed in section 4.3.7. This marginally reduced the cost of SOF/VEL/VOX and the ICER in both DAA-experienced (Table 49) and DAA-naïve, GT3 infection, non-cirrhotic groups (Table 50) without changing the conclusions on cost-effectiveness. This scenario does not apply to the cirrhotic group.

Table 49: ERG scenario 1 DAA-experienced, PAN genotypic

Treatments	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
No treatment	£23,262	10.01	-	-	

SOF/VEL/VOX (12 wks)	£53,677	13.77	30,415	3.76	£8,088

Table 50: ERG scenario 1 DAA-naïve, GT3 infection, non - cirrhotic

Treatments	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
SOF/VEL/VOX (8 weeks)	£32,499	17.27	-	-	-
SOF/VEL (12 wks)	£42,129	17.17	£9,630	-0.10	Dominated by SOF/VEL/VOX (8 weeks)
SOF/DCV (12 wks)	£62,306	17.2	£29,807	-0.07	Dominated by SOF/VEL/VOX (8 weeks)

ERG scenario 2: Reducing SVR for SOF/Peg-IFN2a/RBV to 95.1% for DAA-naïve non-cirrhotic patients and 87.9% for cirrhotic patients

The ERG considered that the company had not used the appropriate values for SVR for SOF/Peg-IFN2a/RBV (section 4.3.5) and changed them to 95.1% for DAA-naïve non-cirrhotic patients and 87.9% for cirrhotic patients in this scenario. In both DAA-naïve GT3 cirrhotic (Table 51) and non-cirrhotic groups (Table 52), SOF/VEL/VOX (8 weeks) remained cost-effective.

Table 51: ERG Scenario 2 DAA-naïve, GT3 infection, cirrhotic

Treatments	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
SOF/VEL/VOX (8 weeks)	£51,289	9.98	-	-	-
SOF/VEL (12 wks)	£60,449	9.99	£9,160	0.01	£863,724
SOF/Peg-IFN2a/RBV(12 wks)	£60,553	9.55	£9,264	-0.43	Dominated by SOF/VEL/VOX (8 weeks)
SOF/DCV/RBV (12 wks)	£83,447	9.31	£32,158	-0.66	Dominated by SOF/VEL/VOX (8 weeks)

SOF/RBV (24 wks)	£98,661	8.49	£47,372	-1.49	Dominated by SOF/VEL/VOX (8 weeks)

Table 52: ERG Scenario 2 DAA-naïve, GT3 infection, non-cirrhotic

Treatments	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
SOF/VEL/VOX (8 wks)	£32,917	17.27	-	-	-
SOF/Peg-IFN2a/RBV(12 wks)	£41,430	17.09	£8,512	-0.18	Dominated by SOF/VEL/VOX (8 weeks)
SOF/VEL (12 wks)	£42,519	17.17	£9,601	-0.10	Dominated by SOF/VEL/VOX (8 weeks)
SOF/DCV (12 wks)	£62,698	17.20	£29,780	-0.07	Dominated by SOF/VEL/VOX (8 weeks)

ERG scenario 3: The mortality after liver transplant in year 1 changed to 16%; and in subsequent years is 5.2%

The ERG noted that there were more recent estimates of the mortality rates after liver transplant (section 4.3.5) and these are used in this scenario. SOF/VEL/VOX (12 weeks) in DAA-experienced patients (Table 53) and SOF/VEL/VOX (8 weeks) in DAA-naïve patients (Table 54 and Table 55) remained cost-effective in this scenario.

Table 53: ERG Scenario 3, PAN genotypic, DAA-experienced

Treatments	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
No treatment	£23,305	10.01	-	-	-
SOF/VEL/VOX (12 wks)	£53,932	13.77	£30,627	3.76	£8,153

Table 54: ERG Scenario 3, DAA-naïve, GT3 infection, cirrhotic

Treatments	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
SOF/VEL/VOX (8 weeks)	£51,317	9.98	-	-	
SOF/VEL (12 wks)	£60,477	9.99	£9,160	0.01	£864,558
SOF/DCV/RBV (12 wks)	£83,483	9.32	£32,166	-0.66	Dominated by SOF/VEL/VOX (8 weeks)
SOF/RBV (24 wks)	£98,707	8.49	£47,389	-1.49	Dominated by SOF/VEL/VOX (8 weeks)

Table 55: ERG Scenario 3, DAA-naïve, GT3 infection, non-cirrhotic

Treatments	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
SOF/VEL/VOX (8 wks)	£32,918	17.27	-	-	-
SOF/VEL (12 wks)	£42,520	17.17	£9,602	-0.10	Dominated by SOF/VEL/VOX (8 weeks)
SOF/DCV (12 wks)	£62,698	17.20	£29,780	-0.07	Dominated by SOF/VEL/VOX (8 weeks)

ERG scenario 4: The proportion of mild and moderate patients for non-cirrhotic patients changed to 50:50.

In this scenario we changed the proportion of mild and moderate patients for non-cirrhotic patients to 50:50, based on clinical advice (section 4.3.7). SOF/VEL/VOX (12 weeks) in DAA-experienced patients (Table 56) and SOF/VEL/VOX (8 weeks) in DAA-naïve patients (Table 57) remained cost-effective in this scenario.

Table 56: ERG Scenario 4, Pan-genotypic, DAA-experienced

Treatments	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
No treatment	£25,869	10.01	-	-	-
SOF/VEL/VOX (12 wks)	£54,088	13.77	£28,219	3.76	£7,504

Table 57: ERG Scenario 4, DAA-naïve, GT3 infection, non-cirrhotic

Treatments	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
SOF/VEL/VOX (8 weeks)	£33,071	17.27	-	-	-
SOF/VEL (12 wks)	£42,757	17.17	£9,686	-0.10	Dominated by SOF/VEL/VOX (8 weeks)
SOF/DCV (12 wks)	£62,909	17.20	£29,838	-0.07	Dominated by SOF/VEL/VOX (8 weeks)

ERG scenario 5: Using transition probabilities from Fattovich et al.

The NICE committee for the SOF/VEL technology appraisal (TA430) requested that a scenario should be conducted using the transition probabilities from Fattovich et al.[46] These are shown in Table 58. The following transition probabilities were changed: compensated cirrhosis to decompensated cirrhosis, compensated cirrhosis to HCC, decompensated cirrhosis to HCC, decompensated cirrhosis to liver death and HCC to liver death (Table 59 - Table 61).

Table 58: Transition probabilities (CS Table 51)

From	To	TP (annual probabilities)	
		Company base case	Fattovich et al.[46]
Compensated cirrhosis	Decompensated cirrhosis	0.0438	0.039
	HCC	0.0631	0.014
	HCC	0.0631	0.014

Decompensated cirrhosis	Death	0.2400	0.129
HCC	Death	0.4300	0.427

HCC: hepatocellular carcinoma; HCV: hepatitis C virus;

Table 59: ERG Scenario 5, DAA-experienced, pan genotypic

Treatments	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
No treatment	£31,878	11.30	-	-	-
SOF/VEL/VOX (12 wks)	£55,243	13.85	£23,365	2.56	£9,140

Table 60: ERG Scenario 5, DAA-naïve, GT3 infection, cirrhotic

Treatments	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
SOF/VEL/VOX (8 wks)	£54,886	10.18	-	-	-
SOF/VEL (12 wks)	£64,037	10.19	£9,151	0.01	£858,954
SOF/DCV/RBV (12 wks)	£88,986	9.83	£34,100	-0.34	Dominated by SOF/VEL/VOX (8 weeks)
SOF/RBV (24 wks)	£106,653	9.41	£51,767	-0.76	Dominated by SOF/VEL/VOX (8 weeks)

Table 61: ERG Scenario 5, DAA-naïve, GT3 infection, non-cirrhotic

Treatments	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
SOF/VEL/VOX (8 weeks)	£32,978	17.28	-	-	-
SOF/VEL (12 wks)	£42,703	17.20	£9,725	-0.08	Dominated by SOF/VEL/VOX (8 weeks)
SOF/DCV (12 wks)	£62,843	17.23	£29,865	-0.06	Dominated by SOF/VEL/VOX (8 weeks)

SOF/VEL/VOX (8 weeks) in DAA-naïve patients and SOF/VEL/VOX (12 weeks) in DAA-experienced patients remained cost-effective.

ERG scenario 6: Different proportions of patients receiving SOF/VEL/VOX for 8 and 12 weeks

In this scenario, we investigate the situation where clinicians are able to choose whether to prescribe SOF/VEL/VOX for either 8 weeks or 12 weeks. We then run analyses with varying proportions of patients treated with 8 weeks or 12 weeks, as shown in Table 62.

Table 62: ERG scenario 6, DAA-naïve, GT3, cirrhotic patients varying the proportions of patients receiving SOF/VEL/VOX for 8 and 12 weeks

	SOF/VEL/VOX		SOF/VEL		
Treatments	**Total costs (£)**	**Total QALYs**	**Total costs (£)**	**Total QALYs**	**ICER vs. SOF/VEL (12wks)**
SOV/VEL/VOX (8 wks)	£51,289	9.978	£60,449	9.988	£863,724
SOV/VEL/VOX- 75% 8 weeks /25%12weeks	£55,038	9.981	£60,449	9.988	£719,153
SOV/VEL/VOX- 50% / 8weeks / 50% 12weeks	£58,787	9.984	£60,449	9.988	£374,066
SOV/VEL/VOX - 25% 8 weeks / 75% 12weeks	£62,536	9.987	£60,449	9.988	Dominated by SOF/VEL (12wks
SOV/VEL/VOX (12 wks)	£66,285	9.990	£60,449	9.988	£3,394,377[a]

[a] In this case the ICER is for SOF/VEL vs. SOF/VEL/VOX

The QALYs for SOF/VEL and SOF/VEL/VOX for DAA-naïve cirrhotic GT3 patients are similar. SOF/VEL/VOX is less expensive than SOF/VEL when treatment is for 8 weeks and remains cost saving until 75% of patients are treated for 12 weeks.

ERG scenario 7: ERG base case consisting of scenarios i-iv

The ERG base case consists of changes to the follow-up costs for non-cirrhotic patients with SVR, the SVR rates for SOF/Peg-IFN2a/RBV, the mortality rates after liver transplant, the proportion of mild and moderate patients for non-cirrhotic patients (Table 63 - Table 65).

Table 63: ERG base case, DAA-experienced patients

Treatments	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
No treatment	£25,912	10.01	-	-	-
SOF/VEL/VOX (12 wks)	£53,835	13.77	£27,923	3.76	£7,433

Table 64: ERG base case DAA-naïve cirrhotic patients

Treatments	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
SOF/VEL/VOX (8 wks)	£51,317	9.98	-	-	-
SOF/VEL (12 wks)	£60,477	9.99	£9,160	0.01	£864,558
SOF/Peg-IFN2a/RBV(12 wks)	£60,587	9.55	£9,269	-0.43	Dominated by SOF/VEL/VOX (8 weeks)
SOF/DCV/RBV (12 wks)	£83,483	9.32	£32,166	-0.66	Dominated by SOF/VEL/VOX (8 weeks)
SOF/RBV (24 wks)	£98,707	8.49	£47,389	-1.49	Dominated by SOF/VEL/VOX (8 weeks)

Table 65: ERG base case, DAA-naïve non-cirrhotic patients

Treatments	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
SOF/VEL/VOX (8 wks)	£32,624	17.27	-	-	-
SOF/Peg-IFN2a/RBV(12 wks)	£41,317	17.09	£8,693	-0.18	Dominated by SOF/VEL/VOX (8 weeks)
SOF/VEL (12 wks)	£42,341	17.17	£9,717	-0.10	Dominated by SOF/VEL/VOX (8 weeks)

SOF/DCV (12 wks)	£62,490	17.20	£29,866	-0.07	Dominated by SOF/VEL/VOX (8 weeks)

The ERG base case which involved making the first four scenario changes simultaneously to the model did not change the conclusions on cost-effectiveness as SOF/VEL/VOX (8 wks) for DAA-naïve patients and SOF/VEL/VOX (12 wks) for DAA-experienced patients remained cost-effective.

In summary, the ERG scenarios 1 – 5 and the ERG base case only had a minimal impact on the model results and are similar to those reported for the company base case. ERG scenario 6 in which the proportions of DAA-naïve cirrhotic patients who were treated with either 8 or 12 weeks was varied showed a significant impact on the model results for SOF/VEL/VOX compared to SOF/VEL.

4.5 Conclusions of cost effectiveness

The company used a model structure commonly used for economic models of hepatitis C with health states that reflect the clinical progression of the disease. The ERG considers the model structure to be appropriate for the decision problem. The company used methods for the economic evaluation that are consistent with NICE methodological guidelines. The population in the economic evaluation is more restricted than described in the NICE scope as it is limited to genotype 3 in DAA-naïve patients. The intervention and comparators used in the economic evaluation are appropriate for the population considered.

The company compares SOF/VEL/VOX with SOF/VEL and no treatment for DAA-experienced and DAA-naïve patients using SVR rates from the company's POLARIS-1 to -4 head-to-head trials. For the other comparators, the company uses SVR rates from individual trials to inform the model rather than the results of a network meta-analysis. The ERG considers this an appropriate approach for hepatitis C as it has been accepted by NICE in previous hepatitis C technology appraisals. The ERG considers that the SVR rates chosen by the company are generally appropriate.

Clinical advice to the ERG suggests that of the comparators used for DAA-naïve patients with HCV GT3, Peg-IFN2a is no longer used in clinical practice, and so the ERG considers that the

comparators Peg-IFN2a/RBV, SOF/Peg-IFN2a/RBV and no treatment are of less relevance than the other comparators in this patient group.

The transition probabilities and utility values used in the model are based upon a previous model published several years ago. Whilst there is some consistency between previous technology appraisals, some of these data may now be out of date and a full review and update of the transition probabilities and utility values would be preferred.

There is some uncertainty around the treatment duration that would be used for DAA-naïve cirrhotic patients with HCV GT3 who are treated with SOF/VEL/VOX. Whilst the treatment duration used in the POLARIS-3 is for 8 weeks, the SmPC for SOF/VEL/VOX recommends 12 weeks treatment (for all genotypes) with an option of considering 8 weeks treatment for patients infected with HCV GT3. Clinical advice to the ERG suggests that, if they are given a choice, clinicians may prescribe 12 weeks treatment for DAA treatment-naïve patients with HCV GT3 and compensated cirrhosis as cirrhosis patients are at a high risk of problems (e.g. progression towards decompensated liver disease) if they fail to achieve SVR12. However, it is unclear to the ERG what proportion of clinicians would treat DAA treatment-naïve patients with HCV GT3 and compensated cirrhosis for 8 weeks or 12 weeks or if NICE guidance or NHS England policy will stipulate either only 8 weeks or only 12 weeks of treatment for these patients. However our clinical expert considered that the majority of patients with cirrhotic disease would be treated for 8 weeks with SOF/VEL/VOX in clinical practice.

5 End of life

NICE end of life treatment criteria were not applicable and not included in the CS.

6 Innovation

The CS makes the case that SOF/VEL/VOX is the only pan-genotypic single tablet regimen (STR) available for the treatment of all DAA-experienced patients, those with or without decompensated cirrhosis.

For the DAA-naïve patient group with HCV GT3 the CS highlights that the size of this group (approximately 44% of the patient population) and that it has been a difficult to treat group in

comparison to the other HCV genotypes. In the DAA-naïve HCV GT3 group high SVR12 rates have been achieved with 8-weeks of therapy in the POLARIS-2 and POLARIS-3 trials of non-cirrhotic and cirrhotic patients respectively. SOF/VEL/VOX is the first 8-week therapeutic option for this patient group. The ERG views the 8-week treatment option (which clinical advice to the ERG suggests will be suitable for the majority of DAA-naïve HCV GT3 patients) as an innovation.

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The POLARIS trials have shown that SOF/VEL/VOX treatment leads to high SVR rates in the two population groups defined in the company's decision problem (DAA-experienced with all HCV genotypes and DAA-naïve with HCV GT3). Furthermore there appear to be no major safety concerns about treatment of CHC patients with SOF/VEL/VOX. The four POLARIS trials are of reasonable methodological quality and the ERG believes that the results from these trials will be generalisable to the UK CHC population.

In the DAA-naïve CHC population with HCV GT3 the CS makes the case that the added benefit of therapy with SOF/VEL/VOX is that high SVR rates can be achieved with 8-weeks of treatment in comparison to SOF/VEL 12-week treatment. However, the non-inferiority trial POLARIS-2 included patients of all HCV genotypes, whereas the company have focussed on the GT3 subgroup in their submission. In POLARIS-2 overall (all genotypes) the inferiority of SOF/VEL/VOX 8-weeks was not established and the trial was not powered to test for non-inferiority in the GT3 subgroup. Nevertheless in the HCV GT3 subgroup of POLARIS-2 after 8-weeks of treatment with SOF/VEL/VOX the SVR12 rate was high 98.9% (and slightly higher than the SVR12 rate for SOF/VEL 12-week of 96.6%).

In summary high SVR rates have been achieved in the POLARIS trials with SOF/VEL/VOX treatment. In the DAA-naïve population with HCV GT3 high SVR rates have been achieved with 8-weeks of treatment and this shorter treatment duration may be appealing to patients.

7.2 Summary of cost effectiveness issues

The CS includes evidence on the cost-effectiveness of SOF/VEL/VOX in DAA treatment experienced and DAA treatment naïve patients. The model structure is appropriate and is consistent with the clinical disease pathway and is the same as those used for previous NICE technology appraisals for hepatitis C. The model transition probabilities, costs and quality of life are consistent with those used for the previous NICE technology appraisal for SOF/VEL (TA 430). The clinical evidence consists of the POLARIS trials for comparison between SOF/VEL/VOX and SOF/VEL and no treatment for DAA-naïve and DAA-experienced patients. For the other comparators, the company uses SVR rates from individual trials.

The CS model produces an ICER of £8,153 per QALY for SOF/VEL/VOX compared to no treatment in DAA-experienced patients. In non-cirrhotic DAA-naïve GT3 patients, SOF/VEL/VOX dominates treatment with SOF/VEL, SOF/Peg-IFN2a/RBV and SOF/DCV (i.e. SOF/VEL/VOX is more effective and less costly) and produces and ICER of £16,654 per QALY compared to Peg-IFN2a/RBV. In DAA-naïve GT3 patients with compensated cirrhosis SOF/VEL/VOX dominates SOF/Peg-IFN2a/RBV, SOF/DCV/RBV and SOF/RBV and produces ICERs of less than £4500 per QALY compared to no treatment and Peg-IFN2a/RBV. SOF/VEL has an ICER of £863,724 per QALY compared to SOF/VEL/VOX.

For the DAA treatment experienced patients, SOF/VEL/VOX has a 100% probability of being cost-effective at the willingness to pay (WTP) thresholds of £20,000 and £30,000 respectively. For the DAA-naïve GT3 patients with cirrhosis, SOF/VEL/VOX has a probability of being cost-effective at the WTP thresholds of £20,000 and £30,000 of 49% and 44% respectively. For the DAA-naïve GT3 patients with non-cirrhosis, SOF/VEL/VOX has a probability of being cost-effective at the WTP thresholds of £20,000 and £30,000 of 36% and 35% respectively.
In general, the model results were robust to changes in parameters and SOF/VEL/VOX dominated other DAA treatments for DAA-naïve patients in the majority of the sensitivity analyses. For treatment experienced patients the ICER remains below £20,000 per QALY in all sensitivity analyses. The ERG conducted several scenarios but these had limited impact on the model results.

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9 APPENDICES

Appendix 1: List of verification checks conducted by the ERG

Checks conducted	**Model outcome (in genotype 3 treatment naïve cirrhotic, SOF/VEL/VOX 8 weeks versus no treatment)**
Does the model provide a brief background on the model structure and design?	Yes

Are the different components of the model well presented?	The dynamic transmission aspect was clarified with the company and found to work correctly
Is it possible to navigate through the model easily?	For the most part, yes. Certain cells, formulas and sheets used in the model were hidden
Are the inputs used in the model clearly referenced?	For the most part, yes. The company clarified a few inputs in their later clarifications
Is the model is transparent with respect to its layout and technicalities?	Yes
Are there any of the key model outputs missing from the analysis?	No- dynamic transmission and Pan GT results were clarified with the company
Can the model results be reproduced (including any scenario analyses) as presented in the CS?	Yes
Set all the values to "0" and check if the results still pull through some figures	No
Does the sum total of the number of patients in each of the health states at any given point (dead or alive) in time (time t+ n) equate to the total number of patients entering the model?	Yes
Was an exhaustive list of parameters included within the DSA and PSA?	Yes
Are appropriate distributions used for the parameters included in the sensitivity analyses?	Yes
Is the deterministic mean ICER approximately equal/close to the probabilistic mean ICER?	Yes
Set difference in efficacy for all drugs to 0 ' equal health outcomes in all model arms	When all SVRs are set to "0", base case ICER is £1,976,312 per QALY gained (GT3 treatment naïve cirrhotic)

Set adverse event rate to 0%. No adverse events should occur	When all adverse events are set to 0%, base case ICER is £3,004 per QALY gained (GT3 treatment naïve cirrhotic)
Set unit cost for drugs and administration to 0. Total costs of drugs should be zero.	Correct
Use different discount rates (e.g. 0%, 3%, 7%)	At 0% ICER is £1,504, difference in cost (discounted) is £15,910 and difference in QALYs (discounted) per patient is 10.58. At 3% ICER is £2,704, difference in cost (discounted) is £14,886 and difference in QALYs (discounted) per patient is 5.50. At 7% ICER is £5,996, difference in cost (discounted) is £16,764 and difference in QALYs (discounted) per patient is 2.80
For costs, total costs should decrease with increasing discount rates	Yes
For health benefits, total number of events should decrease with increasing discount rates	Yes
Set utility values to 0, utility adjusted health outcomes should be zero	QALYs gained is 0, while LYG is 7.78
Set utility values to 1, utility adjusted health outcomes should be equal to unadjusted life years	Both QALYs gained and LYG are 7.78