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

Sofosbuvir–velpatasvir–voxilaprevir for treating chronic hepatitis C

ERRATUM

Replacement pages for factual inaccuracies in Evidence Review Group report

13 November 2017

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Development of resistance

RAVs in the HCV NS3 or NS5A genes were present at baseline in both the POLARIS-2 and POLARIS-3 trial participants (POLARIS-2: SOF/VEL/VOX (8 weeks) 50.3%; SOF/VEL (12 weeks) 50.1%. POLARIS-3 SOF/VEL/VOX (8 weeks) 21.3%; SOF/VEL (12 weeks) 21.5%) 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 -

- 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), SOF/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 (until patients reach 100 years of age). With discounting at 3.5% per annum for costs and benefits, a cycle length of two weeks for the first 72 weeks, followed by a 24-week long cycle, 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 £29,884.66 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.

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Table 3: Base-case results: DAA-naïve, GT3 infection, with compensated cirrhosis (list price) (Shortened and edited version of 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) (Shortened and edited version of 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)

	£18,938	12.83	£6,682	-3.20	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 was 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

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, -3 and -4 n=1, 2, 1 and 0 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.

Equivalence of trial arms at baseline

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.

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).

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 1 January 2007 to 17 March 2017). An additional search was conducted for abstracts reporting treatment-related AEs in HCV in three conferences namely: AASLD, DDW and EASL in annual conferences held from 1 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

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) (Shortened and edited version of 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) (Shortened and edited version of 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 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.

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