NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sofosbuvir-velpatasvir-voxilaprevir for treating chronic hepatitis C [ID1055]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Sofosbuvir-velpatasvir-voxilaprevir for treating chronic hepatitis C [ID1055]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pre-meeting briefing

Sofosbuvir–velpatasvir–voxilaprevir for treating chronic hepatitis C [ID1055]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Common abbreviations

BOC	boceprevir
CC	compensated cirrhosis
CHC	chronic hepatitis C
D	dasabuvir
DAA	direct acting antivirals
DCC	decompensated cirrhosis
DCV	daclatasvir
GT	genotype
LDV	ledipasvir
NC	no cirrhosis
OPR	ombitasvir/paritaprevir/ritonavir
P	pegylated interferon;
R or RBV	ribavirin
SMV	simeprevir
SOF	sofosbuvir
SVR	sustained virologic response
TE	treatment-experienced
TN	treatment naïve
TVR	telaprevir
VEL	velpatasvir
VOX	voxilaprevir

Preview: Clinical effectiveness and treatment pathway issues

- The company's submission focused on the following populations:
  1. DAA-experienced (all GTs and cirrhotic & non-cirrhotic combined)
     - GT subgroups were small and limits reliability of the data: no results by GT and cirrhotic status provided.
  2. DAA-naïve (cirrhotic and non-cirrhotic) for GT3 because the risk of progressing from NC to CC is highest in GT3. No analyses for GT1, 2, 4, 5 and 6 provided.
- Individual trials used to estimate comparator SVR rates introduces uncertainty
- 8 wks SOF/VEL/VOX duration (based on POLARIS-2 & 3) modelled for DAA-naïve GT3 CC subgroup, but MA states 12 wks and to consider 8 wks:
  - Is 8 wks duration for DAA-naïve GT3 CC appropriate?

Key: CC, cirrhotic; DAA, direct-acting antivirals; DCV, daclatasvir; GT, genotype; R, ribavirin; SOF/VEL/VOX, Sofosbuvir/velpatasvir/voxilaprevir; wks, weeks.

Preview: Cost-effectiveness issues

- Does the committee accept the following assumptions and inputs?
  - model structure, comparator SVR 12 rates, transition probabilities and utilities
  - including re-infection and transmission as an exploratory analysis for DAA-naïve GT3 population only
- What is the most plausible ICER based on the committee's preferred assumptions?
- Innovation – any uncaptured health related benefits?
- Potential equality issues

Key: DAA, direct-acting antivirals; GT, genotype; TP, transition probability; SVR, sustained virologic response.

Hepatitis C

- Blood borne (people who inject drugs major source ≈90%)
- Causes inflammation of liver
- Acute infection usually asymptomatic:
  - 75-85% develop chronic hepatitis C (CHC)
  - 10-20% CHC progress to cirrhosis
  - 1-4% per year hepatocellular carcinoma (HCC)
- 214,000 people with CHC in UK, 160,000 in England (PHE, 2014)
- Six major genotypes (GT1-6)
  - GT1 and GT3 most common (approx. 90%)
  - GT3 (44% of Hep C population in England) associated with highest risk of disease progression (fibrosis, carcinoma) and death
- Aim of treatment is to cure the infection
- Historically, treatment included pegylated-interferon plus ribavirin regimens
- In recent times, direct-acting antivirals (DAAs) with better efficacy and improved safety profile have been recommended by NICE

Key: CHC, chronic hepatitis C; DAA, direct-acting antivirals; GT, genotype; HCC, hepatocellular carcinoma; Hep C, hepatitis C; NICE, National Institute for Health and Care Excellence; PHE, Public Health England; UK, United Kingdom.

RELEVANT NICE TECHNOLOGY APPRAISALS

GT	Recommended	Restrictions by cirrhosis & treatment history	NICE TA
GT1	P ± R	All	75, 106 & 200
	TVR + PR	All	252
	BOC + PR	All	253
	SOF + PR	NC TN; NC TE; CC TN; CC TE	330
	SMV + PR	All	331
	LDV/SOF	NC TN; NC TE; CC TN; CC TE[a]	**363**
	DCV + SOF ± R	NC TN[b]; NC TE[b]; CC[c]	**364**
	OPR + D ± R	NC TN; NC TE; CC TN; CC TE	**365**
	EBR + GZR	All	**413**
	SOF + VEL	All	**430**
GT2	P ± R	All	75, 106 & 200
	SOF + R	NC TN[c]; NC TE; CC TN[c]; CC TE	**330**
	SOF + VEL	All (except NC TN IFN-eligible)	**430**
GT3	P ± R	All	75, 106 & 200
	SOF + PR	NC TE; CC TN; CC TE	330
	SOF + R	CC TN[c]; CC TE[c]	**330**
	DCV + SOF ± R	NC[bc]; CC[c]	**364**
	SOF + VEL	All	**430**
GT4	P ± R	All	75, 106 & 200
	SOF + PR	CC TN; CC TE	330
	SMV + PR	All	**331**
	LDV/SOF	NC TE; CC TN; CC TE[a]	**363**
	DCV + PR	NC TN[b]; NC TE[b]; CC TN[b]; CC TE[b]	364
	DCV + SOF ± R	NC TE[b]; CC[c]	**364**
	OPR + R	NC TN; NC TE; CC TN; CC TE	**365**
	EBR + GZR	All	**413**
	SOF + VEL	All	**430**
GT5/6	P ± R	All	75, 106 & 200
	SOF + PR	CC TN; CC TE	330
	SOF + VEL	All	**430**

Key: [a] If certain clinical criteria are met; [b] Only for significant fibrosis; [c] Only if IFN-ineligible/intolerant

Sofosbuvir–velpatasvir–voxilaprevir (Gilead sciences)

Marketing authori-sation	For the treatment of chronic HCV infection in adults: • All genotypes GT1-GT6 • DAA naïve without cirrhosis or with compensated cirrhosis • DAA experienced* without cirrhosis or with compensated cirrhosis ** patients were treated with: daclatasvir, dasabuvir, elbasvir, grazoprevir, ledipasvir, ombitasvir, paritaprevir, sofosbuvir, velpatasvir, and voxilaprevir.*
Mechanism of action	Fixed-dose combination of 3 drugs: • sofosbuvir inhibits the non-structural protein 5B (NS5B); • velpatasvir is an NS5A inhibitor; • voxilaprevir is a second generation NS3/4A protease inhibitor.
Admini-stration	SOF/VEL/VOX (400 mg/100 mg/100 mg) film-coated tablet, taken orally, once daily: • DAA experienced patients: 12 weeks duration • DAA-naïve without cirrhosis: 8 weeks duration • DAA-naïve with comp. cirrhosis: 12 weeks & consider 8 for GT3
Acquisition cost	28 tablets: £14,942.33 • 8/12 weeks of treatment at list price: £29,884.66/£44,826.99 • The company have agreed a confidential pricing agreement with the commercial medicines unit

Key: DAA, direct-acting antivirals; GT, genotype; HCV, hepatitis-c virus; NS, non-structural protein; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir.

Patient Perspectives

- Submissions from Haemophilia Society, Hepatitis C Trust
- Experiences and feelings of people with Hepatitis C:
  - “chronic fatigue, memory problems, get muddled and depressed”
  - “some people cannot work and find their social/emotional/sexual life significantly impaired... encounter stigma and even discrimination,”
  - “people who were infected through the NHS often feel extremely angry and bitter” because never adequately compensated
  - “significant uncertainty about when they will have access to interferon-free therapy and hence a cure because NHS England has introduced a cap on the number to be treated in 2017/18”
- The SOF/VEL/VOX therapy:
  - “very high cure rates”...“works very well for people who have been unsuccessfully treated”
  - “of particular benefit to people with a bleeding disorder who were often infected with multiple genotypes via their NHS treatment”
  - “provides competition and drives the price down”

Key: NHS, National Health Service; SOF/VEL/VOX, Sofosbuvir/velpatasvir/voxilaprevir. .

Clinicians' perspectives

- Submissions from: RCP, British Society of Gastroenterology
- SOF/VEL/VOX would address unmet needs including:
  - "effective re-treatment options for all HCV genotypes treatment failures with previous DAA (particularly NS5A inhibitor) exposure"
  - "shorter treatment regimens-particularly special groups eg. prison population"
- SOF/VEL/VOX:
  - "Serious adverse events have been rare in trials (2%) and similar to placebo"
  - "RBV-free pan-genotypic treatment with response rates similar in cirrhotic & non cirrhotic patients" – no need to genotype, so cheaper, easier treatment
- No new infrastructure or training required
- Patients are treated via regional Operational Delivery Network:
  - "NHS England stipulates which drug regimens may be used on patients"
  - numbers of patients treated each month limited by the NHSE "run rate"
  - "not ideal for many of the patient sub-groups who suffer from chronic HCV infection e.g. prisoners and people who inject drugs "

Key: DAA, direct-acting antivirals; NHSE, National Health Service England; HCV, hepatitis C virus; NS, non-structural protein; RBV, ribavirin; SOF/VEL/VOX, Sofosbuvir/velpatasvir/voxilaprevir.

NHS England comments

- Fixed duration therapy for all genotypes with durations modified by the degree of liver fibrosis: 8 weeks for all patients with mild disease
  - ‘immediate access’ to therapy without the need for genotyping
  - access for people struggling to engage in traditional care pathways
  - due to experienced teams working in multi-disciplinary networks, the benefits of this approach are marginal.
- At present there is no licensed therapy for the very few patients who have failed to respond to currently available treatments.
- NHS England fund hepatitis C treatments via a managed access programme which will fund a target of 12,500 patients in 2017/2018 – it is not envisaged that extra resource will be required for this technology appraisal.
- The technology should be delivered by Operational Delivery Networks
- Current rules recommend stopping therapy if there is evidence of virological failure and we would recommend that these rules be applied to the new technology

Key: NHS England, National Health Service England.

Company's decision problem

	NICE scope	Company
Pop.	**1. treatment-experienced** **2. treatment-naïve**	**1. DAA-experienced (all GT, CC/NC combined)** **2. GT3 DAA-naïve NC** **3. GT3 DAA-naïve CC** • DAAs are 1st-line therapy • No licenced treatment for DAA-experienced (GT subgroups small and limits reliability of the data) • High unmet need for GT3 (44% of CHC) in highest risk of progressing from NC to CC.
Int.	SOF/VEL/VOX	Treatment duration: 12 weeks for DAA experienced (**1.**) and 8 weeks for DAA naïve (**2.** & **3.**)
Com.	• BSC (GT1-6) • SOF/DCV ± R (GT1, 3 or 4) • EBR/GZR (GT1 or 4) • LDF/SOF (GT1 or 4) • OBV/PTV/RTV + DCV ± R (GT1 or 4) • P + R (GT1-6) • SOF + R ± P (GT1-6) • SOF/VEL (GT1-6)	**1. BSC** (GT1-6) **2. SOF/VEL** (12 wks), **SOF + DCV + R** (12 weeks), **SOF + R** (24 wks), **P + R** (24 wks), **SOF + P + R** (12 weeks) **3. P + R** (24 wks), **SOF + P + R** (12 wks), **SOF/VEL** (12 wks), **SOF + DCV** (12 wks) Excluded comparators not used in current NHS practice
Out.	SVR, resistance to treatment Mortality, AE, HRQL	Notes that resistance does not impact cost or QALYs.

Key: BSC, best supported care; CC, cirrhotic patients; DAA, direct-acting antivirals; DCV, daclatasvir; EBR/GZR, elbasvir-grazoprevir; GT, genotype; LDV, ledipasvir; NC, non-cirrhotic patients; NHS, National Health Service; OBV/PTV/RTV, ombitasvir/paritaprevir/ritonavir; P, pegylated-interferon; QALYs, quality-adjusted life years; R, ribavirin; SOF, sofosbuvir; VEL, velparasvir; vox, voxilaprevir; wks, weeks.

ERG's critique of decision problem

- Population:
  - Narrower than scope: no results for DAA-naïve GT1, 2, 4, 5, 6
  - DAA experienced not presented by GT and cirrhotic status (CC/NC)
    - The ERG considers company's approach to report results for a pan-genotype group for DAA-experienced patients to be appropriate
- Intervention:
  - MA: 12 weeks and consider 8 weeks for CC GT3 DAA-naïve, CS based duration on POLARIS 2 & 3 (8 weeks and noted that12-weeks was not studied). However, clinicians may prefer to treat for 12 weeks.
- Comparators:
  - new off-label use of SOF/VEL (NHSE) for DAA-experienced
  - DAA-naïve GT3 CC: SOF+DCV ± R (TA364) & SOF+R (TA330) only recommended for P-ineligible/intolerant
  - SOF+DCV+R for CC modelled for 12 wks in DAA-naïve GT3 CC patients, but recommended for 24 weeks (TA364)
- Outcomes: as per the final NICE scope.

Clinical-effectiveness evidence

Company submission section B.2

Clinical evidence

Study	POLARIS-1 (N=415)	POLARIS-4 (N=333)	POLARIS-2 (N=941)	POLARIS-3 (N=219)
Study design	Multicentre (108 sites), double-blind, placebo-controlled, Phase III RCT	Multicentre (101 sites),open-label, active-controlled, Phase III RCT	Multicentre (117 sites), open-label, Phase III RCT	Multicentre (84 sites), open-label, Phase III RCT
UK sites	9 patients over 6 sites	12 patients over 5 sites	47 patients over 8 sites	15 patients over 6 sites
Population	DAA-experienced patients previously treated with an NS5A inhibitor (GT1 -6 or intermediate)	DAA-experienced patients not previously treated with an NS5A inhibitor (GT1-6 or intermediate)	DAA-naïve patients (GT1-6 or intermediate)	DAA-naïve patients with GT3 CHC and cirrhosis
Intervention	SOF/VEL/VOX for 12 weeks		SOF/VEL/VOX for 8 weeks	
Comparator	Placebo for 12 weeks	SOF/VEL for 12 weeks		
SVR12 (primary outcome)	HCV RNA<LLOQ12 weeks after cessation of treatment, in full analysis set in the SOF/VEL/VOX population. The LLOQ was 15 IU/mL			

Key: CHC, chronic hepatitis C; DAA, direct-acting antivirals; GT, genotype; HCV, hepatitis-c virus; LLOQ, lower limit of quantification; N, number of participants; NS, non-structural protein; RCT, randomised controlled trial; RNA, ribonucleic acid; SOF/VEL/VOX, Sofosbuvir/velpatasvir/voxilaprevir; SVR12, sustained virologic response at 12 months; UK, United Kingdom.

SVR12 results: NS5A-experienced POLARIS 1

Subgroups		SOF/VEL/VOX (12 weeks)	
		n/N (%)	95%CI
GT	All	**253/263 (96.2)**	**93.1, 98.2**
	GT1	146/150 (97.3)	[redacted]
	GT2	5/5 (100.0)	[redacted]
	GT3	74/78 (94.9)	[redacted]
	GT4	20/22 (90.9)	[redacted]
	GT5	1/1 (100.0)	[redacted]
	GT6	6/6 (100.0)	[redacted]
	unknown	1/1 (100.0)	[redacted]
Cirrhosis	yes	113/121 (93.4)	[redacted]
	no	140/142 (98.6)	[redacted]
DAA-experienced 253/263 (96.2%)	NS5A ± other DAA	252/262 (96.2)	[redacted]
	Others	1/1 (100.0)	[redacted]
	NS5A & NS5B	151/161 (93.8)	[redacted]
	NS5A & NS3 ± NS5B	83/83 (100.0)	[redacted]
	NS5A ± Others	18/18 (100.0)	[redacted]

Key: CI, confidence intervals; DAA, direct-acting antivirals; GT, genotype; NS, non-structural protein; SOF/VEL/VOX, Sofosbuvir/velpatasvir/voxilaprevir; SVR12, sustained virologic response at 12 months.

SVR12 results: DAA-experienced (not NS5A) POLARIS 4

Subgroups		SOF/VEL/VOX (12 weeks)		SOF/VEL (12 weeks)	
		n/N (%)	95%CI	n/N (%)	95%CI
GT	All	**178/182 (97.8)**[a]	[redacted][a]	136/151 (90.1)	[redacted]
	GT1	76/78 (97.4)	[redacted]	60/66 (90.9)	[redacted]
	GT2	31/31 (100.0)	[redacted]	32/33 (97.0)	[redacted]
	GT3	51/54 (94.4)	[redacted]	44/52 (84.6)	[redacted]
	GT4	19/19 (100.0)	[redacted]	NA	NA
	GT5	1/1 (100.0)	[redacted]	NA	NA
Cirrhosis	yes	81/84 (96.4)	[redacted]	59/69 (85.5)	[redacted]
	no	96/98 (98.0)	[redacted]	77/82 (93.9)	[redacted]
Prior treatment	DAA- naive	NA	NA	1/1 (100.0)	[redacted]
	DAA- experienced	177/182 (97.3)	[redacted]	135/150 (90.0)	[redacted]
	NS5B only	130/134 (97.0)	[redacted]	99/109 (90.8)	[redacted]
	NS5B & NS3	45/46 (97.8)	[redacted]	33/38 (86.8)	[redacted]
	others	18/18 (100.0)	[redacted]	3/3 (100.0)	[redacted]

Key: CI, confidence intervals; DAA, direct-acting antivirals; GT, genotype; NS, non-structural protein; SOF/VEL/VOX, Sofosbuvir/velpatasvir/voxilaprevir; SVR12, sustained virologic response at 12 months.

Notes: a, results updated with an achievement of SVR24 by 1 subject who had missed SVR12 assessment.

SVR12 results: DAA-naive POLARIS 2 & 3

Trial	Subgroup		SOF/VEL/VOX (8 weeks)		SOF/VEL (12 weeks)	
			n/N (%)	95%CI	n/N (%)	95%CI
Polaris 2	GT	All	**477/501 (95.2)**[a]	[a]	432/440 (98.2)	
		GT1	217/233 (93.1)		228/232 (98.3)	
		GT2	61/63 (96.8)		53/53 (100.0)	
		GT3	91/92 (98.9)		86/89 (96.6)	
		GT4	58/63 (92.1)		56/57 (98.2)	
		GT5	17/18 (94.4)		NA	NA
		GT6	30/30 (100.0)		9/9 (100.0)	
		other	2/2 (100.0)		NA	NA
	Cirrhosis	yes	82/90 (91.1)		83/84 (98.8)	
		no	394/411 (95.9)		349/356 (98.0)	
	Previous treatment	Naive	367/383 (95.8)		332/340 (97.6)	
		Exp.	109/118 (92.4)		100/100 (100.0)	
		P+R[b]				
Polaris 3 - GT3 CC	Overall		**106/110 (96.4)**	**91.0 to 99.0**	105/109 (96.3)	
	Previous treatment	Naive	72/75 (96.0)		76/77 (98.7)	
		Exp.	34/35 (97.1)		29/32 (90.6)	
		P+R[b]				

Notes: a, results updated 1 subject who had missed SVR12 but achieved SVR24; b, treatment experienced (exp.) treated with pegylated interferon.

Secondary outcomes: virologic failure

Trial	Outcome	SOF/VEL/VOX n/N (%)	Control arm n/N (%)
Polaris 1 NS5A-experienced	Did not achieve SVR12	10/263 (3.8)	-
	Overall virologic failure	7/263 (2.7)	-
	Other	3/263 (1.1)	-
Polaris 4 DAA-experienced (not NS5A)	Did not achieve SVR12	4/182 (2.2)	15/151 (9.9)
	Overall virologic failure	1/182 (0.5)	15/151 (9.9)
	Other	3/182 (1.6)	0/151 (0)
Polaris 2 DAA-naïve (all GT NC)	Did not achieve SVR12	25/501 (5) [a]	8/440 (1.8)[a]
	Overall virologic failure	21/501 (4.2)	3/440 (0.7)
	Other	4/501 (0.8)	5/440 (1.1)
Polaris 3 DAA-naïve (GT3 only and cirrhosis)	Did not achieve SVR12	4/110 (3.6)[a]	4/109 (3.7)[a]
	Overall virologic failure	2/110 (1.8)	2/109 (1.8)
	Other	2/110 (1.8)	2/109 (1.8)

Key: DAA, direct-acting antivirals; GT, genotype; NC, non-cirrhotic; NS, non-structural protein; SOF/VEL/VOX, Sofosbuvir/velpatasvir/voxilaprevir; SVR12, sustained virologic response at 12 months.
Notes: a, calculated by NICE technical team.

Adverse events

Trial	Outcome	SOF/VEL/VOX, n/N (%)	Control arm, n/N (%)
Polaris 1 NS5A-experienced	AEs	[redacted]	107/152 (70.4)
	Grade 3+	[redacted]	4/152 (2.6)
	Treatment related AE	[redacted]	63/152 (41.4)
	Discontinuation due AE	[redacted]	3/152 (2.0)
Polaris 4 DAA-experienced (not NS5A)	AEs	[redacted]	111/151 (73.5)
	Grade 3+	[redacted]	2/151 (1.3)
	Treatment related AE	[redacted]	77/151 (51.0)
	Discontinuation due AE	[redacted]	1/151 (0.7)
Polaris 2 DAA-naïve	AEs	[redacted]	303/440 (68.9)
	Grade 3+	[redacted]	6/440 (1.4)
	Treatment related AE	[redacted]	182/440 (41.4)
	Discontinuation due AE	[redacted]	2/440 (0.5)
Polaris 3 DAA-naïve (GT3 only and cirrhosis)	AEs	[redacted]	81/109 (74.3)
	Grade 3+	[redacted]	4/109 (3.7)
	Treatment related AE	[redacted]	51/109 (46.8)
	Discontinuation due AE	[redacted]	1/109 (0.9)

- headache, fatigue, diarrhoea and nausea were the most common AEs

Key: DAA, direct-acting antivirals; GT, genotype; NS, non-structural protein; SOF/VEL/VOX, Sofosbuvir/velpatasvir/voxilaprevir; AE, adverse events.

ERG: critique of the evidence

- POLARIS trials are of reasonable methodological quality
- only POLARIS-3 randomised all participants
- POLARIS-1, 3 and 4: trial arms not compared with each other. Individual arms was compared against a predefined SVR12 (85% for POLARIS-1 & -4, and 83% for POLARIS-3).
- POLARIS-2 was a non-inferiority trial comparing SOF/VEL/VOX 8 weeks with SOF/VEL 12 weeks
  - only GT3 subgroup included so not sufficiently powered
  - did not demonstrate non-inferiority, but GT3 patients with SOF/VEL/VOX had SVR12 of 98.9% and 96.6% with SOF/VEL
- POLARIS-4, -2 and -3 were open label trials, so there is scope for bias
- The company did explore the possibility of an NMA for the DAA-naïve HCV GT3 patient group but this was not feasible.
- The ERG agrees with the interpretation of clinical and safety evidence.

Key: DAA, direct-acting antivirals; GT, genotype; HCV, hepatitis C virus; NMA, network meta-analysis; SOF, sofosbuvir; SVR12, sustained virologic response at 12 moths; VEL, velparasvir; VOX, voxilaprevir.

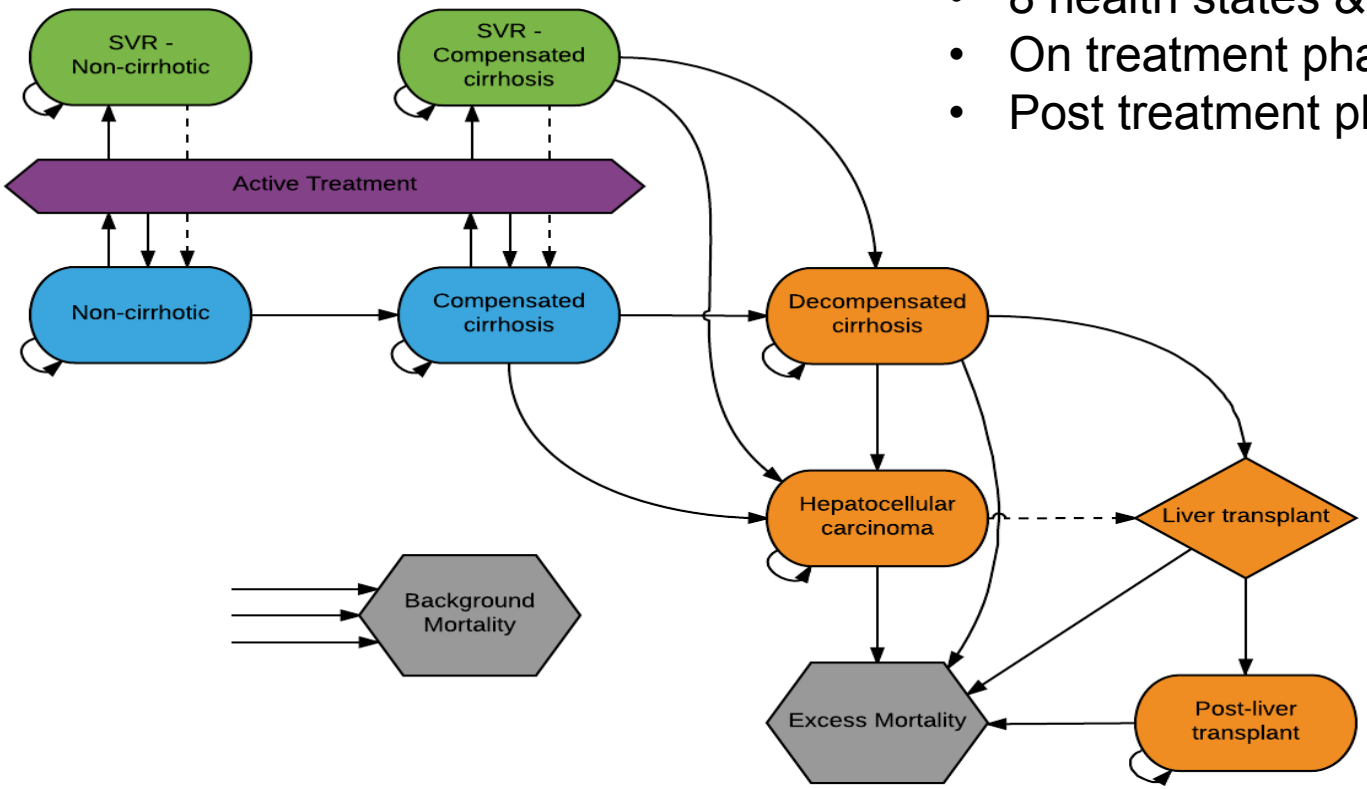
Cost-effectiveness evidence

Company submission section B.3

Company's model

Markov model

- 8 health states & death
- On treatment phase (green & blue)
- Post treatment phase (orange)



- Excess mortality: disease-specific (decompensated cirrhosis, liver transplant & HCC).
- Backroad mortality: mortality rate of the general population
- Dashed arrows represent transitions only investigated in sensitivity analysis

Key: HCC, hepatocellular carcinoma; SVR, sustained virologic response.

Company's model: patient characteristics

- Lifetime horizon (allowing to follow a patient until the ages of 60, 80 or 100 years), 2 weeks cycle length for 72 weeks, one 24-weeks cycle, and yearly cycles thereafter.
- Co-infected HCV/HIV patients not modelled separately (conservative approach)
- Post-liver transplant patients are not modelled separately (due to lack of data)
- Three sub-populations modelled (narrower than MA for SOF/VEL/VOX):

1. **DAA experienced: all GT and with/without cirrhosis combined**
   - 12 weeks treatment
2. **DAA-naïve GT3 only without cirrhosis:**
   - 8 weeks treatment
3. **DAA-naïve GT3 only with cirrhosis:**
   - 8 weeks treatment

Key: DAA, direct-acting antivirals; GT, genotype; HCV, hepatitis C virus HIV, human immunodeficiency virus; MA, marketing authorisation; SOF, sofosbuvir; VEL, velparasvir; VOX, voxilaprevir.

ERG: critique of company's model

- The structure is similar to previous NICE technology appraisals:
  - LDV/SOF (TA363), SOF+R (TA330) and SOF/VEL (TA430)
- Includes a scenario attempting to address re-treatment due to re-infection or treatment failure
- Does not account for mortality risk or disease progression for patients in active treatment phase (NC; also raised in TA430)
- Mortality assumption: treatment-related and background mortality is related to treatment duration and leads to counter-intuitive results:
  - QALYs for SOF/VEL are greater than SOF/VEL/VOX, but SVR rates are lower for SOF/VEL than SOF/VEL/VOX
  - it would be more appropriate for mortality to start at the same time.

Key: CC, compensated cirrhosis; LDV, ledipasvir; NC, non-cirrhotic; QALYs, quality-adjusted life years R, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velparasvir; VOX, voxilaprevir.

Model inputs: SVR rates

SG	GT	CC/ NC	Treatment	SVR Base-case/scenario	Source Base-case/scenario
DAA-experienced	**All**	**All**	SOF/VEL/VOX	96.2/97.8%	POLARIS-1/4
			No treatment	0%	POLARIS-1
DAA-naïve	**3**	**CC**	SOF/VEL/VOX	96.4%	POLARIS-3
			SOF/VEL	96.3%	POLARIS-3/ASTRAL 3
			SOF + DCV + R	83.3%	ALLY 3+
			SOF + R	66.3%	ASTRAL 3
			P + R	29.7%	SOF SmPC (TN population)
			SOF + P + R	91.3%	BOSON (TN population)
			No treatment	0%	POLARIS-1
		NC	SOF/VEL/VOX	98.9%	POLARIS-2
			P + R	71.2%	SOF SmPC (TN population)
			SOF + P + R	95.8%	BOSON (TN population)
			SOF/VEL	96.6%	POLARIS-2/ ASTRAL3 (TN population)
			SOF + DCV	97.3%	ALLY-3, DCV SmPC; TA364 limits this to F3 only
			No treatment	0%	POLARIS-1

Key: CC, cirrhotic; DAA, direct-acting antivirals; DCV, daclatasvir; F3, fibrosis stage 3; GT, genotype; NC, non-cirrhotic; P, pegylated interferon; R, ribavirin; SmPC, summary of product characteristics; SOF/VEL/VOX, Sofosbuvir/velpatasvir/voxilaprevir; TN, treatment naïve; wks, weeks.

Model inputs: transition probabilities

From	To	Annual TP	Source	Comments
NC	CC	GT1: 0.0213 GT2: 0.0165 GT3: 0.0296 GT4: 0.0202 GT5: 0.0202 GT6: 0.0202	Kanwal et al. 2014	Assumes GT5 and GT6 are equivalent to GT4
CC	DCC	0.0438	Cardoso et al. 2010	DCC: patients stage F3 & F4 included; DCC was defined as several liver-related complications HCC: calculated
	HCC	0.0631	Cardoso et al. 2010	
CC SVR	DCC	0.0064	Cardoso et al. 2010	
	HCC	0.0128	Cardoso et al. 2010	
DCC	HCC	0.0631	Cardoso et al. 2010	Calculated
	Liver trans.	0.0220	Siebert 2005	-
	Death	0.2400	EAP data (EASL 2016)	-
HCC	Death	0.4300	Fattovich et al. 1997	Obtained from Shepherd et al. 2007
Liver trans.	Death, Yr1	0.2100	Bennett et al. 1997	
Post-liver trans.	Death, Yr2	0.0570	Bennett et al. 1997	

Key: CC, cirrhotic patients; DCC, decompensated cirrhosis; NC, non-cirrhotic; GT, genotype; HCC, hepatocellular carcinoma; SVR: sustained virologic response; TP, transition probability; trans., transplant; Yr, year.

Model inputs: utilities

Health-state	Utility	Source
Baseline – non-cirrhotic	0.75	Wright et al. 2006; UK mild HCV trial
Baseline – compensated cirrhosis	0.55	
SVR (utility increment)	0.04	Vera-Llonch et al. 2013
Non-cirrhotic with SVR	0.79	0.75+0.04
Compensated cirrhotic with SVR	0.59	0.55+0.04
HCC	0.45	Wright et al, 2006; UK mild HCV trial
Liver transplant	0.45	
Post-liver transplant	0.67	

Strategy	decrement	Source
SOF/VEL/VOX	0%	Assumed equal to SOF/VEL
SOF/VEL	0%	Foster et al. 2015
SOF+ DCV	0%	Assumed equal to SOF/VEL
SOF+ R	-2.5%	Younossi et al. 2016
SOF+DCV + R	-2.5%	Assumed equal to SOF + R
P+R	-4.7%	Younossi et al. 2016
SOF+P+R	-4.7%	Younossi et al. 2016

Key: DCV, daclatasvir; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; P, pegylated-interferon; R, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; UK, United Kingdom; VEL, velparasvir; VOX, voxilaprevir.

ERG: critique of clinical inputs

- Use of SVR rates from individual trials were accepted in TA430
  - DAA naive GT3 CC: combined TN & TE rates for SOF+R (66.3%),
  - But rate for SOF + PR for TN only (CC 91.3% & NC 95.8%), thus combined TN & TE rates for SOF + PR more appropriate: CC 87.9% & NC 95.1%
- TPs: same as in TA430, but old sources (already raised in other HTAs) a full review and update is due
  - same TPs for all GTs, except NC to CC TPs (GT1-4, GT5/6 = GT4; based on 2000 - 2009 US veterans CHC data)
  - unable to confirm TP for decompensated cirrhosis to death
  - Current mortality rates for liver transplant decreased to 16% in year 1 and 5.2% in subsequent years (vs. CS: 21% and 5.7% respectively)
  - TA430 recommends also consider Fattovich et al. 1997 TPs:

From	To	CS TP	Fattovich TP
CC	DC	0.0438	0.039
	HCC	0.0631	0.014
DC	HCC	0.0631	0.014
	Death	0.2400	0.129
HCC	Death	0.4300	0.427

Key: CC, compensated cirrhosis; CS, company submission; DC, decompensated cirrhosis; GT, genotype; HCC, hepatocellular carcinoma; HTA, health technology assessment; NC, non-cirrhotic; P, pegylated interferon; QALYs, quality-adjusted life years; R, ribavirin; SOF, sofosbuvir; TE, treatment naïve; TN, treatment experienced; TP, transition probability; VEL, velparasvir; VOX, voxilaprevir.

ERG: critique of utilities

- ERG considers company's search for utility values inadequate:
  - studies related to more severe health states, decompensated cirrhosis, hepatocellular carcinoma and liver transplant, not included
- Utilities based on Wright et al. 2006 and 0.04 SVR-related utility increment from Vera-Llonch et al. 2013 (same as TA430)
- POLARIS trials collected HRQL (SF-36,CLDQ-HCV, FACIT-F, WPAI) although not EQ-5D
- Baseline utilities estimated using 83:17 percentage split for NC mild & moderate disease. 50:50 split is a better reflection of clinical experience, expert clinical advice and used by Hartwell et al. 2011.

Key: CLDQ-HCV, Chronic Liver Disease Questionnaire-Hepatitis C Virus; EQ-5D, European Quality of Life-5 Dimensions; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HRQL, health related quality of life; NC, non-cirrhotic; SF-36, Short Form Health Survey; WPAI, Work productivity and Activity Impairment.

Model inputs: resource use and costs

- Company model included costs associated with treatment, monitoring and adverse events (including management cost)
- The costs were based on most recent HTAs (mainly TA430), apart from the costs for patients who reached SVR which were from Wright et al, 2006, since these were based on UK studies.
- All costs have been updated to 2015/2016 costs
- SOF/VEL/VOX has a confidential commercial pricing arrangement
- Confidential commercial pricing arrangements also exist for:
  - Daclatavir (TA364)
  - Sofosbuvir/velpatasvir (TA430)

Key: HTA, health technology assessment; SOF/VEL/VOX, Sofosbuvir/velpatasvir/voxilaprevir; SVR, sustained virologic response; UK, United Kingdom; 3D, three drugs regimen; 2D, two drugs regimen.

ERG: critique of costs inputs

- Health states costs
  - ERG suggests follow-up for NC patients with SVR should be 1 year, (not 2 years as in CS)
  - Cost based on 50:50 split for NC moderate and mild disease more appropriate (not 83:17).
- Treatment cost
  - Base case: SOF/VEL/VOX for 8 weeks for DAA-naïve GT3 CC patients (exploratory analysis used 12 weeks)
  - Clinicians may prefer to treat some patients for longer. ERG explored scenarios where clinicians were able to "choose" treatment duration (75% 8 wks & 25% 12 wks, 50% 8 wks & 50% 12 wks, and 25% 8 wks & 75% 12 wks ratios).
- Methods used to estimate costs are reasonable, but data, in general, are out of date and should be reviewed for future appraisals.

Key: CC, cirrhotic; CS, company submission; DAA, direct-acting antivirals; DCV, daclatasvir; GT, genotype; NC, non-cirrhotic; SOF/VEL/VOX, Sofosbuvir/velpatasvir/voxilaprevir; SVR, sustained virologic response; wks, weeks.

Company's results: 1. DAA-experienced (all GTs, NC and CC combined)

- The company performed all analyses using list prices

Treatment	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER vs. no treatment (£)	ICER Incremental (£)
No treatment	23,262	14.83	10.01	-	-	-	-	-
SOF/VEL/VOX (12 wks)	**53,922**	**19.06**	**13.77**	**30,660**	**4.23**	**3.76**	**8,153**	**8,153**

Probabilistic sensitivity analysis (PSA)

- 100% probability of SOF/VEL/VOX to be cost-effective at £20,000

Results using discounted prices for intervention and comparators presented in a confidential appendix

Key: DAA, direct-acting antivirals; ICER, incremental cost-effectiveness ratio; Inc, incremental; LY, life years; QALYs, quality-adjusted life years; SOF/VEL/VOX, Sofosbuvir/velpatasvir/voxilaprevir; vs. versus.

Company's results (list price): 2. DAA-naïve, GT3 NC

Treatment	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER vs. P+R (£)	ICER Incremental (£)
P+R (24 wks)	12,256	20.85	16.03	-	-	-	-
SOF/VEL/VOX (8 wks)	**32,917**	**21.87**	**17.27**	**20,661**	**1.24**	**16,654**	**16,654**
No treatment	18,938	18.12	12.83	6,682	-3.20	Dominated by P+R (24 wks)	Dominated by P+R (24 wks)
SOF+P+R (12 wks)	41,303	21.76	17.13	29,047	1.09	26,596	Dominated by SOF/VEL/VOX (8 wks)
SOF/VEL (12 wks)	42,519	21.79	17.17	30,262	1.14	26,594	Dominated by SOF/VEL/VOX (8 wks)
SOF + DCV (12 wks)	62,698	21.81	17.20	50,441	1.17	43,137	Dominated by SOF/VEL/VOX (8 wks)

PSA result

- 36% probability of SOF/VEL/VOX to be cost-effective at £20,000

Key: DAA, direct-acting antivirals; DCV, daclatasvir; GT, genotype; ICER, incremental cost-effectiveness ratio; Inc., incremental; LY, life years; NC, non-cirrhotic; P, pegylated interferon; PSA, probabilistic analyses; QALYs, quality-adjusted life years; R, ribavirin; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; vs. versus; wks, weeks.

Company's results: 3. DAA-naïve, GT3 CC

Treatment	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER vs. no treatment (£)	ICER Incremental (£)
No treatment	36,262	9.36	4.98	-	-	-	-
P + R (24 wks)	37,510	11.94	6.61	1,248	1.63	765	765
SOF/VEL/VOX (8 wks)	**51,289**	**17.14**	**9.98**	**15,027**	**5.00**	**3,004**	**4,088**
SOF/VEL (12 wks)	60,449	17.16	9.99	24,187	5.01[a]	4,825	863,724
SOF + P+R (12 wks)	59,961	16.76	9.72	23,699	4.75	4,992	Dominated by SOF/VEL/VOX (8 wks)
SOF + DCV + R (12 wks)	83,447	16.12	9.31	47,185	4.34	10,873	Dominated by SOF/VEL/VOX (8 wks)
SOF+ R (24 wks)	98,661	14.86	8.49	62,399	3.51	17,760	Dominated by SOF/VEL/VOX (8 wks)

PSA result

- 49% probability of SOF/VEL/VOX to be cost-effective at £20,000

Key: CC, compensated cirrhosis; DAA, direct-acting antivirals; DCV, daclatasvir; GT, genotype; ICER, incremental cost-effectiveness ratio; Inc., incremental; LY, life years; P, pegylated interferon; PSA, probabilistic analyses; QALYs, quality-adjusted life years; R, ribavirin; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; vs. versus; wks, weeks.

Company's DSAs

- Key drivers were: treatment TPs from NC with SVR to NC (re-infection), the discount rate applied for costs and outcomes and treatment costs.
- However, only re-infection was considered in DSAs (not disease transmission). A separate dynamic transmission modelling exploratory analysis considered both.

- **DAA-experienced**: in all analyses ICER < £20,000
- **DAA-naïve GT3 NC**: SOF/VEL/VOX dominates SOF/VEL except for changes to the cost of SOF/VEL and SVR rates of SOF/VEL/VOX & SOF/VEL
- **DAA-naïve GT3 CC**: SOF/VEL/VOX remains less costly than SOF/VEL but has similar QALYs except for changes to the SVR rates of SOF/VEL/VOX & SOF/VEL

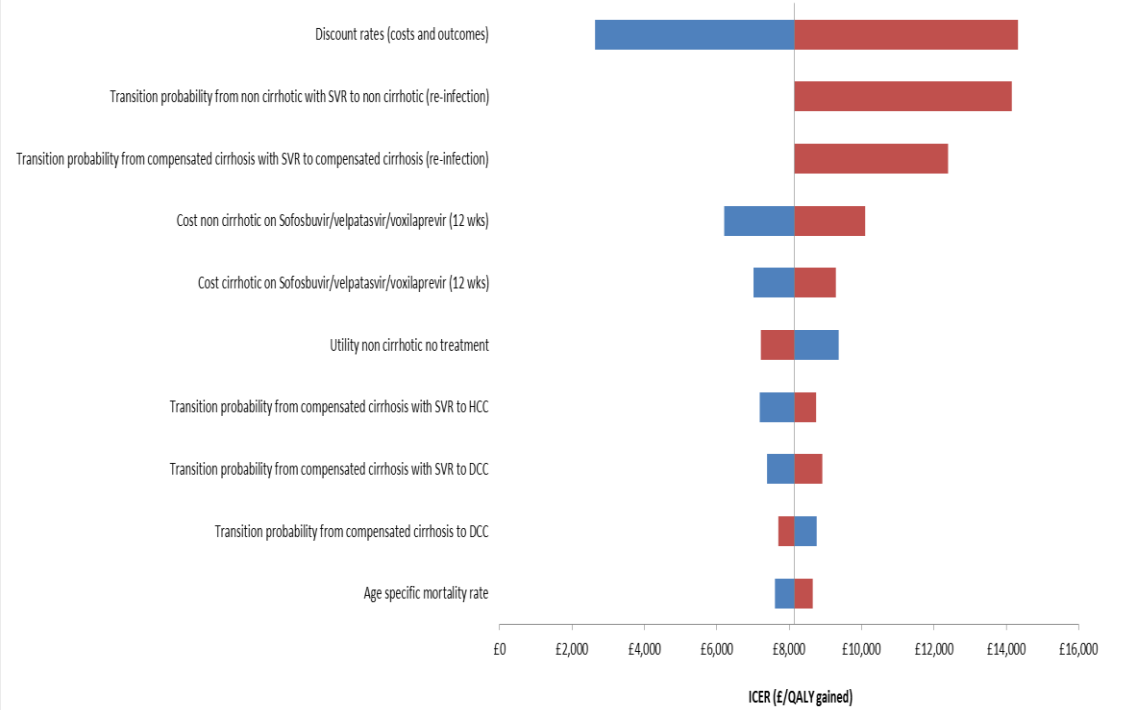


Figure: DAA-experienced DSAs

Key: CC, compensated cirrhosis; DAA, direct-acting antivirals; DCC, decompensated cirrhosis; DSA, deterministic analyses; GT, genotype; ICER, incremental cost-effectiveness ratio; NC, non-cirrhotic; QALYs, quality-adjusted life years; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SVR, sustained virologic response; TP transition probability.

Company's scenario analyses

- DAA-experienced:
  - Using POLARIS-4 SVR rates for SOF/VEL/VOX instead of POLARIS 1
  - Using POLARIS-1 NC/CC ratio (58.6:41.4) instead of 66.3:36.7 ratio
  - Using TPs for GT3 and GT1 only instead of using blended transition probability from all genotypes

  Results similar to base-case results
- DAA-naïve GT3 NC:
  - Using SVR rates for SOF/VEL from ASTRAL-3 instead of POLARIS 3

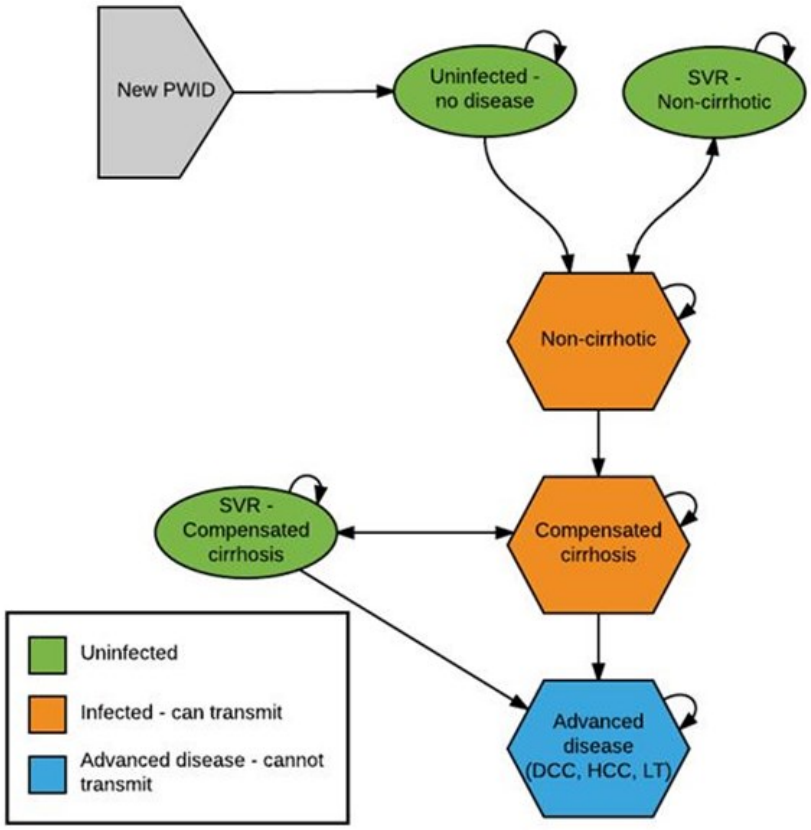
  Results similar to base-case results
- DAA-naïve GT3 CC:
  - Using SVR rates for SOF/VEL from ASTRAL-3 instead of POLARIS 3
  - Using 12 weeks duration for SOF/VEL/VOX instead of 8 weeks: SOF/VEL/VOX becomes more expensive than SOF/VEL with the same incremental QALYs) producing an ICER of £3,394,377

  Different results when 12 weeks SOF/VEL/VOX treatment duration is used

Key: CC, compensated cirrhosis; DAA, direct-acting antivirals; GT, genotype; ICER, incremental cost-effectiveness ratio; NC, non-cirrhotic; QALYs, quality-adjusted life years; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SVR, sustained virologic response; TP transition probability.

Company's exploratory analysis: Dynamic transmission modelling

- Conducted for GT3 DAA-naïve only as impact of onward transmission and re-infection is minimal for DAA-experienced
- Baseline: 37% of PWID infected
- Ratio of PWID to ex-PWID: 1/6 to 5/6
- The key modification from Markov model is inclusion of uninfected persons, and the possibility to become infected.
- Rate of infection is determined by a constant probability of infection (by GT) and the number of currently infected persons.
- Only PWID can transmit disease or become infected (and can get re-infected after a successful treatment)



Key: DAA, direct-acting antivirals; DCC, decompensated cirrhosis; GT, genotype; HCC, hepatocellular carcinoma; LT, liver transplant; PWID, people who inject drugs.

Company's results: Dynamic transmission modelling

Treatment	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER vs. no treatment (£)	ICER Incremental (£)
No treatment	6,078	25.50	20.84	-	-	-	-
P+R (24 weeks)	5,625	25.73	21.11	-453	0.27	Dominates no treatment	Dominates no treatment
SOF/VEL/VOX (8 wks)	**7,142**	**25.86**	**21.24**	**1,064**	**0.40**	**2,660**	**11,489**
SOF+ P+R (12 wks)	7,850	25.85	21.23	1,772	0.39	4,544	Dominated by SOF/VEL/VOX
SOF/VEL (12 wks)	7,934	25.86	21.23	1,856	0.39	4,759	Dominated by SOF/VEL/VOX
SOF + DCV (12 wks)	9,962	25.76	21.18	3,884	0.34	11,424	Dominated by SOF/VEL/VOX

Key: DCV, daclatasvir; ICER, incremental cost-effectiveness ratio; Inc., incremental; LY, life years; P, pegylated-interferon; QALYs, quality-adjusted life years; R, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir; vs. versus; wks, weeks.

ERG: dynamic transition scenario

- The scenario is useful in providing more robust estimates of the cost-effectiveness of SOF/VEL/VOX
- The results reinforce the results of the base case
  - with an improvement in ICERs for all treatments vs. no treatment.
- However it does not address re-treatment due to re-infection or treatment failure fully and makes simplifying assumptions.
- Conducted for GT3 DAA-naïve only
  - No results for CC vs NC in the DAA-naïve GT3 population, it is unclear how results in company's submission were calculated
- The company's estimated percentage of PWID infected was based on GT1-4, but the scenario is conducted for GT3 only

Key: cc, compensated cirrhosis; DAA, direct-acting antivirals; GT, genotype; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; LT, liver transplant; NC, non-cirrhotic; PWID, people who inject drugs.

ERG: exploratory analyses

#	Change	Justification
1	Follow-up for non-cirrhotic patients with SVR should be for 1 year only	Clinical advice to the ERG
2	SVR for SOF+P+R changed to 95.1% for DAA naive NC patients and 87.9% for CC patients	DAA estimates include both TN and TE (not DAA) patients
3	TP from liver transplant to death in year 1 is 16% and 5.2 % in subsequent years	More recent mortality estimates
4	The proportion of mild and moderate patients for non-cirrhotic patients is 50:50	Clinical advice to the ERG
5	Using transition probabilities from Fattovich et al. 1997	requested by TA430 NICE committee
6	Different proportions of patients receiving SOF/VEL/VOX for 8 and 12 weeks for DAA-naïve GT3 cirrhotic patients	MA allows treatment with 8 or 12 weeks
1-4	**Scenarios 1-4 combined**	**ERG base-case**

Key: DAA, direct-acting antivirals; MA, marketing authorisation; P, pegylated interferon; R ribavirin; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SVR, sustained virologic response; TE, treatment experienced, TN, treatment naïve; TP, transition probabilities.

ERG: exploratory analyses results

- The ERG base case (scenarios #1-4 combined) did not change the conclusions on cost-effectiveness of SOF/VEL/VOX (8 wks) for DAA-naïve NC, and of SOF/VEL/VOX (12 wks) for DAA-experienced patients remained cost-effective.
- Using TPs from Fattovich et al. 1997 (#5) only had a minimal impact and results are similar to company's base case.
- Changing proportions of DAA-naïve CC patients treated with 8 and 12 weeks (# 6) had a significant impact:
  - 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:

	SOF/VEL/VOX		SOF/VEL		
SOV/VEL/VOX duration:	Total costs	Total QALYs	Total costs	Total QALYs	ICER vs. SOF/VEL
8 wks	£51,289	9.978	£60,449	9.988	£863,724 (SW)
75% 8wks & 25% 12wks	£55,038	9.981	£60,449	9.988	£719,153 (SW)
50% 8wks & 50% 12wks	£58,787	9.984	£60,449	9.988	£374,066 (SW)
25% 8wks & 75% 12wks	£62,536	9.987	£60,449	9.988	SOF/VEL dominates
(12 wks)	£66,285	9.990	£60,449	9.988	£3,394,377

Key: CC, compensated cirrhosis; DAA, direct-acting antivirals; ICER, incremental cost-effectiveness ratio; NC, non-cirrhotic; QALYs, quality-adjusted life years; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SW, south-west ICER; TP, transition probability; vs., versus; wks, weeks.

Company: Innovation

- The EMA adopted an accelerated regulatory process granted to those medicines of major public health interest.
- SOF/VEL/VOX fulfils a number of criteria identified by the Kennedy Report as constituting innovation
- DAA-experienced
  - Currently no licensed and reimbursed pharmacologic treatment option for this group
  - SOF/VEL/VOX is the only pan-genotypic STR available (regardless of cirrhosis status)
  - SOF/VEL/VOX address a substantial current unmet need
- DAA-naïve GT3
  - GT3 represents a large (44%) and difficult to treat group
  - patients have typically worse virologic response to DAA therapy
  - SOF/VEL/VOX demonstrated high cure rates in NC and CC patients
  - short duration treatment (8 weeks)

Key: CC, compensated cirrhosis; DAA, direct-acting antivirals; NC, non-cirrhotic; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; STR, single tablet regime.

Equalities

- Company and ERG: no issues identified.
- Scope development:

During the scoping process, it was noted that chronic hepatitis C disproportionately affects certain populations such as certain immigrant populations, prison populations, and drug users, in terms of accessing the healthcare system and having access to innovative new treatments.

The appraisal committee have previously discussed these issues in previous hepatitis C appraisals, and concluded that its recommendations were fair regarding these groups of people.

Any recommendations on the use of sofosbuvir-velpatasvir-voxilaprevir would be irrespective of whether or not the person is in prison, or uses injectable drugs

- Clinical expert:

Nil specific – however technology would not be recommended for those with severe renal impairment (eGFR<30) (as it contains Sofosbuvir which is contra-indicated in such patients) or those with decompensated liver disease (as it contains an NS3/4 protease inhibitor which as a class are contra-indicated in such patients even though there is no specific data for Voxilaprevir in this scenario)*

Key: eGFR, estimated glomerular filtration rate; NS, non-structural protein; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir.
Note: * corrected spelling.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Sofosbuvir-velpatasvir-voxilaprevir for treating chronic hepatitis C [ID 1055]

Document B

Company evidence submission

August 2017

File name	Version	Contains confidential information	Date
ID1055_SOF-VEL-VOX _evidence_submission_REDACTED	1	Redacted	24 August 2017

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Contents

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B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. *Decision problem*

The submission focuses on part of the technology's marketing authorisation, and specifically for patients who:

- Have previously failed to achieved sustained virologic response (SVR) with a direct-acting antiviral (DAA), DAA-experienced, or
- Have received no DAA treatment for chronic hepatitis C (CHC), DAA-naïve, and who have genotype 3 (GT3) chronic hepatitis C (CHC) with or without compensated cirrhosis

The proposed sub-populations are narrower than the pan-genotypic marketing authorisation for sofosbuvir-velpatasvir-voxilaprevir (SOF/VEL/VOX). These sub-populations reflect where SOF/VEL/VOX provides the most clinical benefit. In DAA-experienced population, there are currently no licensed and reimbursed treatment options. In the DAA-naïve population with GT3 infection there is a need for a more efficacious and shorter duration treatment option for first-line therapy.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with CHC: • who have had treatment for CHC before (treatment-experienced) • who have not had treatment for CHC before (treatment-naïve)	Adults with CHC: • who have had previous treatment with DAA agents for chronic hepatitis C (DAA-experienced) • with GT3 (cirrhotic and non-cirrhotic), who have no previous treatment with DAA agents for chronic hepatitis C (DAA-naïve)	DAAs are considered first line of therapy in CHC in UK current practice, based on the UK Consensus Guidelines 2017 (1); patients will therefore not be treated with Peg-IFN or PI. Patients who have failed on Peg-IFN or early generation PI therapy are eligible for DAAs and can be grouped with true treatment-naïve patients. EASL guidance also recognises the CHC population as DAA-naïve (treatment-naïve and IFN-experienced) and DAA-experienced (2) **DAA-experienced** • IFN-free regimens should be used in DAA-experienced patients (2) • In those patients who have failed to achieve SVR with a DAA, there are no licensed or reimbursed treatment options available for re-treatment[a]. This sub-population reflects where SOF/VEL/VOX would provide the greatest clinical benefit **DAA-naïve** • GT3 infection is regarded as a difficult to treat population, with high unmet need. Approximately 44% of the total CHC population

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			have GT3 infection (3), and are at the highest risk of progressing from non-cirrhotic to cirrhotic (4) • For those with and without compensated cirrhosis the option of 8 weeks of treatment compared with 12-24 weeks is likely to offer benefits in terms of efficacy, adherence and tolerability due to shorter treatment duration
Intervention	SOF/VEL/VOX	SOF/VEL/VOX • DAA-experienced patients: SOF/VEL/VOX (12 weeks) • DAA-naïve patients with GT3 who are: o Non-cirrhotic – SOF/VEL/VOX (8 weeks) o Cirrhotic – SOF/VEL/VOX (8 weeks)	The license for SOF/VEL/VOX has been confirmed as: • DAA-experienced patients: SOF/VEL/VOX (12 weeks) • DAA-naïve patients who are: o Non-cirrhotic – SOF/VEL/VOX (8 weeks) o Cirrhotic – SOF/VEL/VOX (12 weeks, and to consider 8 weeks in GT3[b])
Comparator(s)	• Best supportive care (no active pharmacological treatment) (GT1-6) • SOF/DCV, +/- RBV (for specific people with GT1, 3 or 4; as recommended by NICE) • EBR/GZR (for GT1 or 4) • LDF/SOF (for specific people with	• DAA-experienced patients: o Best supportive care (defined as no active pharmacological treatment) (GT1-6) • DAA-naïve GT3 patients: - Cirrhotic o SOF/VEL (12 weeks)	These changes align with the sub-populations in this appraisal, and most recent European and UK guidance

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	GT1 or 4; as recommended by NICE) • OBV/PTV/RTV + DSV ± RBV (for GT1 or 4) • Peg-IFN2a + RBV (for GT1-6) • SOF + RBV +/- Peg-IFN2a (for specific people with GT1-6; as recommended by NICE) • SOF/VEL (for specific people with GT1-6; as recommended by NICE)	○ SOF + DCV + RBV (12 weeks) ○ SOF + RBV (24 weeks) ○ Peg-IFN2a + RBV (24 weeks) ○ SOF + Peg-IFN2a + RBV (12 weeks) - Non-cirrhotic ○ Peg-IFN2a + RBV (24 weeks) ○ SOF + Peg-IFN2a + RBV (12 weeks) ○ SOF/VEL (12 weeks) ○ SOF + DCV (12 weeks)	
Outcomes	The outcome measures to be considered include: • SVR • development of resistance to treatment • mortality • adverse effects of treatment • HRQL	As per final scope, except: • The development of resistance to SOF/VEL/VOX is discussed only in section 2.10	Development of resistance does not impact the cost-effectiveness of SOF/VEL/VOX; i.e. it has not impact on cost or QALYs. Furthermore, treatment-emergent resistance mutations was observed in 2 patients, who did not respond to SOF/VEL/VOX
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should	As per final scope	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • GT • co-infection with HIV • people with and without cirrhosis • previous treatment received (with or without DAA-containing regimens) • people who have received treatment before liver transplantation, and those who have received it after liver transplantation • response to previous treatment (non-response, partial response, relapsed) • people who are intolerant to or ineligible for IFN treatment If the evidence allows, the impact of treatment on reduced onward HCV transmission will also be considered. Guidance will only be issued in	Evidence allowed subgroup analyses including: • GT • Patients with and without cirrhosis • Previous treatment received (with or without DAA-containing regimens)	Sub-group evidence provided was based on data reported within the POLARIS clinical trial program In addition based on the UK Consensus Guidelines 2017 (5): • IFN is not recommended as a treatment option for any GT HCV infection and RBV should be avoided where possible • Patients with HCV-HIV coinfection: ○ Should be treated for CHC with the same DAA-based treatment regimens as patients with HCV mono-infection, although consideration of DDI between DAAs and antiretrovirals should be taken into account ○ Where HIV therapy cannot be switched to avoid DDI, an appropriate alternate DAA-based regimen should be identified • Liver transplant:

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.		○ SOF/VEL/VOX is not indicated for use in decompensated patients and has not been studied in liver transplant population (6)
Special considerations including issues related to equity or equality	N/A	N/A	N/A

CHC, chronic hepatitis C; DAA, direct-acting antiviral; DCV, daclatasvir; DDI, drug-drug interactions; DSV, dasabuvir; EASL, European Association for the Study of the Liver; EBR, elbasvir; GT, genotype; GZR, grazoprevir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQL, health-related quality of life; IFN, interferon; LDF, ledipasvir; N/A, not applicable; NHS, National Health Service NICE, National Institute for Health and Care Excellence; OBV, ombitasvir; Peg-IFN(2a); pegalated interferon (alfa-2a); PI, protease inhibitors; PTV, paritaprevir; QALY, quality-adjusted life-year; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; UK, United Kingdom; VEL, velpatasvir; VOX, voxilaprevir.

[a] Although the UK Consensus Guidelines 2017 recommends the use of GLE/PIB (and SOF/VEL/VOX) in DAA-experienced patients when available in the UK, these recommendations were compiled before the license for GLE/PIB was known; it is not licensed in Europe for patients who failed on a NS5A-based therapy; [b] Based on the study of 8 weeks of therapy in POLARIS-2 and POLARIS-3. Note that 12 weeks was not studied.

B.1.2. *Description of the technology being appraised*

Table 2: Technology being appraised

UK approved name and brand name	Sofosbuvir velpatasvir voxilaprevir (SOF/VEL/VOX) 400 mg/100 mg/100 mg film coated tablets Brand name: Vosevi
Mechanism of action	SOF is a pan-GT inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication. SOF is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analogue triphosphate (GS 461203), which can be incorporated into HCV ribonucleic acid (RNA) by the non-structural protein 5B (NS5B) polymerase and acts as a chain terminator. In a biochemical assay, GS 461203 inhibited the polymerase activity of the recombinant NS5B from HCV GT1b, 2a, 3a and 4a with an IC50 value ranging from 0.36 to 3.3 x 10^{-6} mol/L. GS-461203 is neither an inhibitor of human deoxyribonucleic acid (DNA) and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase. VEL is a pan-genotypic HCV inhibitor targeting the HCV NS5A protein, which is required for viral replication. Resistance selection in cell culture and cross-resistance studies indicate VEL targets NS5A as its mode of action. VOX is a pan-genotypic inhibitor of the HCV NS3/4A protease. VOX acts as a noncovalent, reversible inhibitor of the NS3/4A protease.
Marketing authorisation/CE mark status	Marketing authorisation for SOF/VEL/VOX has been sought from the European Medicines Agency (EMA) via the centralised process for a new active substance. Regulatory submission: January 2017 Committee for Medicinal Products for Human Use (CHMP): Positive opinion (June 22 2017) Marketing authorisation: 27 July 2017
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	SOF/VEL/VOX is indicated for the treatment of chronic HCV in adults. The licensed indication for SOF/VEL/VOX covers chronic HCV infection of any genotype (GT1–6) in patients with or without cirrhosis, regardless of treatment experience. Eligible patients may also include those with HCV/HIV co-infection. Contraindications, special warnings and precautions for use are listed as per the draft SmPC (see Appendix C).
Method of administration and dosage	Each film-coated tablet contains 400 mg SOF, 100 mg VEL and 100 ml VOX. SOF/VEL/VOX is taken orally, as a single tablet, once daily.
Additional tests or investigations	N/A
List price and average cost of a course of treatment	Pack price: £14,942.33 8 weeks of treatment: £29,884.66 12 weeks of treatment: £44,826.99
Patient access scheme (if applicable)	[redacted] Pack price: [redacted]

	8 weeks of treatment: [redacted] 12 weeks of treatment: [redacted]

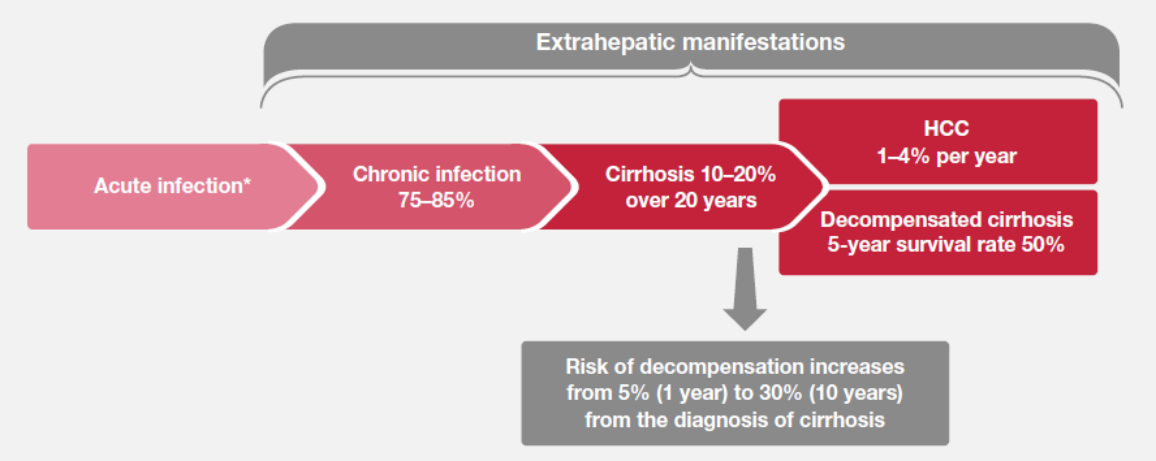
B.1.3. *Health condition and position of the technology in the treatment pathway*

B.1.3.1. *Disease overview*

Hepatitis C is a progressive infectious life-threatening disease caused by hepatitis C virus (HCV) infecting the liver (7). Six major HCV RNA GTs are prevalent (GT1-6) with GT1 (47%) and GT3 (44%) predominating in England (3).

Acute infection is generally asymptomatic and 15-25% of acutely affected individuals will spontaneously clear the virus (7). The remaining 75-85% will go on to develop CHC (Figure 1), defined as persistent, detectable serum HCV RNA for a period greater than 6 months.

Figure 1: Hepatitis C disease progression



Adapted from Chen and Morgan, 2006 (7).
HCC, hepatocellular carcinoma
*20-30% of individuals are symptomatic. Spontaneous clearance of HCV RNA occurs in 15-25% of patients with acute infection.

CHC is curable, and the primary goal of treatment for CHC is to cure the infection by eradicating the hepatitis C virus (8). Treatment efficacy for CHC is measured as the proportion of patients in whom the virus is undetectable at a defined time point, typically 12 or 24 weeks following treatment cessation; this is referred to as a sustained virologic response (SVR) (8).

If left untreated, or there is non-response to therapy, patients with CHC are at progressive risk of liver fibrosis, compensated cirrhosis, decompensated cirrhosis (leading to end-stage liver disease [ESLD]), hepatocellular carcinoma (HCC) and death (7), as well as extrahepatic diseases including circulatory diseases, renal diseases, autoimmune disorders, cutaneous manifestations and non-liver cancers (9, 10).

The rate at which liver disease progresses is unpredictable and related to a range of environmental and host factors, including alcohol consumption, age at infection, gender, the presence of co-morbidities such as obesity or insulin resistance, and co-infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV) (7).

B.1.3.2. *Burden to patients, carers and society*

CHC is associated with considerable burden to patients and society with approximately 214,000 (1) people chronically infected with HCV in the UK currently, including 160,000 (11) people in England. In England, the number of laboratory confirmed cases of HCV infection has risen more than 500% over nearly two decades from around 2,000 in 1996 to 11,605 in 2015 (11). Approximately two-thirds of laboratory reports (67%) were in men and almost half (45%) were in individuals aged 25-39 years (11).

Health burden

The prevalence of HCV-related liver disease has risen substantially in recent decades, with transmission among risk groups remaining prominent and significant numbers of patients remaining undiagnosed and untreated (1, 11, 12). The number of people living with cirrhosis and HCC in England rose by approximately 45% from 7,210 cases in 2005 (13) to 10,470 cases in 2015 (3). Correspondingly, the number of registrations for liver transplants in England resulting from CHC-related cirrhosis increased almost threefold from 43 in 1996 to 122 in 2014 (3).

HRQL

CHC is associated with reduced HRQL (14). The main independent predictors of HRQL impairment in untreated patients are fatigue and psychological issues, including depression and anxiety (14). Activities of daily living can be impaired and work productivity can be affected, with significantly greater levels of absenteeism and overall work impairment reported compared with those without CHC (15). The degree of impairment observed with patients with CHC is higher than with patients with other liver diseases and other chronic diseases including type II diabetes mellitus and irritable bowel syndrome (16). Progression to cirrhosis is often clinically silent, apart from non-specific symptoms such as fatigue, upper right quadrant pain or, sometimes, arthralgia and myalgia (17). Some patients are not known to have CHC until they present with the complications of ESLD or HCC (7).

The treatment of HCV can also further reduce patient HRQL; IFN-containing regimens are associated with considerable negative side effects, and RBV-containing regimens have a high pill burden and elongated treatment duration, which correspond to reduced treatment adherence and lower HRQL (15, 18). Patients also have to manage with the social stigma associated with CHC, with patients commonly reporting altered behaviours, financial insecurity, internalised shame, and social rejection, irrespective of the method of HCV acquisition or socioeconomic status (19).

In those patients who do not achieve SVR, it is likely that their HRQL is further reduced due to progression of disease and potential anxiety associated with non-response.

Healthcare resource burden

Despite the availability of newer, efficacious treatment options, advanced liver disease, HCC, cirrhosis and liver-related mortality are expected to remain a considerable burden of disease in the UK (11, 19, 20). This is due to slow disease progression, an aging CHC patient population infected more than 20 years ago, lack of prior efficacious therapies, poor adherence to previous treatment regimens and patients unwilling to receive IFN-based therapies (21, 22).

CHC also represents a substantial future burden on healthcare resources (11). However hepatitis C has been identified as the only type of liver disease for which mortality could be avoided through good quality healthcare (23) and significant progress could be made in a relatively short space of time (20).

B.1.3.3. *Clinical pathway of care and current guidelines*

B.1.3.3.1. Clinical care pathway

The current clinical pathway of care takes into account the European Association for the Study of the Liver (EASL) Recommendations on Treatment of Hepatitis C 2016 guidelines (2), UK consensus guidelines 2017 (5) and NICE technology appraisals (TA75, 106, 200, 252, 253, 330, 331, 361, 363, 364, 365, 413 and 430) (24-47).

Treatment efficacy, and hence decisions around the choice of treatments is multifaceted being influenced by HCV GT, the severity of liver disease (absence or presence of cirrhosis, and the stage of cirrhosis) and whether a patient has received treatment for the condition previously (8). There is currently limited evidence to inform treatment decisions for patients who have failed to achieve an SVR with a first-line DAA. The EASL guidelines state that from 2016 onwards, IFN-free regimens should be the preferred treatment option in patients with CHC regardless of treatment history, and specifically in those with compensated or decompensated liver disease, because of their virological efficacy, ease of use and tolerability (5). This was reiterated by the NHS England: Operational Delivery Networks (ODN), who also stated that in areas where treatment is exclusively available in a hospital setting, this is viewed as a barrier for some patients, reducing the numbers receiving curative treatment (48).

Historically patients were poorly treated for CHC, with available NICE-recommended regimens limited to Peg-IFN+RBV alone, or the first-generation protease inhibitors (PIs), boceprevir (BOC) and telaprevir (TVR), both taken in combination with Peg-IFN+RBV (39-43). However, with the emergence of DAA-based regimens there has been a move towards regimens that are generally easier to take and are more tolerable. Multiple new NICE-recommended DAA therapies are now available, including SOF, ledipasvir-sofosbuvir (LDV/SOF), simeprevir (SMV), daclatasvir (DCV), ombitasvir-paritaprevir-ritonavir (OBV/PTV/RTV), dasabuvir (DSV), elbasvir-grazoprevir (GZR/EBR) and SOF/VEL (35-38, 44-47). Current NICE recommendations from technology appraisals for CHC treatments are summarised in Table 3 (patients without cirrhosis) and Table 4 (patients with cirrhosis).

Details on the current treatment options including related NICE guidance, EASL guidelines, UK consensus guidelines 2017 and current unmet need are provided in Section B.1.3.3.2.

Table 3: Summary of NICE technology appraisal recommendations as of August 2017: for patients with CHC without cirrhosis (includes treatment-naïve and treatment-experienced patients)

GT	SOF+R (29, 49)	LDV/ SOF (31, 50)	SOF+ SMV (34)	SOF+DCV (30, 51)	OBV/ PTV/ RTV+DSV (33, 52, 53)	OBV/ PTV/ RTV (33, 53)	SOF+P+R (29, 49)	SMV+P+R (32, 54)	DCV+P+R (30, 51)	BOC+P+R (27, 55)	TVR+P+R (28, 56)	P+R (24-26, 57-59)	GZR/ EBR (47)	SOF/ VEL (46)
GT1a	X	TN: 8w TE: 12w	X	TN: 12w with significant fibrosis only TE: 12w with significant fibrosis only	TN/TE:12w with RBV	X (Not licensed)	TN: 12w TE: 12w	TN: 24w (12w, then P+R 12w) TE: 24w (12w, then P+R 12w, REL) or 48w (12w, then P+R 36 w; PR/NR)	X (Not licensed)	TN: 28w (P+R 4w + B+P+R 24 w) or 48w (P+R 4w + B+P+R 32w + P+R 12 w) TE: 48w (P+R 4w + B+P+R 32w + P+R 12 w) or 48w (P+R 4w + B+P+R 44 w)	TN: 24w (T+P+R 12w + P+R 12w) or 48w (T+P+R 12w + P+R 36w) TE: 24w (T+P+R 12w + P+R 12w) or 48w (T+P+R 12w + P+R 36w)	TN: 48w; 24w with RVR TE: 48w	TN: 12w TE: 12w	TN: 12w TE: 12w
GT1b					TN/TE:12 w								TN: 12w TE: 12w	
GT2	TN: 12w IFN-ineligible only TE: 12w	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	TN/TE: 24w	X (Not licensed)	TN: 12w (only if IFN is not tolerated or IFN not suitable) TE: 12w
GT3	X	X	X (Not licensed)	TN/TE: 12w IFN-ineligible only with significant fibrosis	X (Not licensed)	X (Not licensed)	TN: X TE: 12w	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	TN/TE: 24w	X (Not licensed)	TN: 12w TE: 12w

GT	SOF+R (29, 49)	LDV/ SOF (31, 50)	SOF+ SMV (34)	SOF+DCV (30, 51)	OBV/ PTV/ RTV+DSV (33, 52, 53)	OBV/ PTV/ RTV (33, 53)	SOF+P+R (29, 49)	SMV+P+R (32, 54)	DCV+P+R (30, 51)	BOC+P+R (27, 55)	TVR+P+R (28, 56)	P+R (24-26, 57-59)	GZR/ EBR (47)	SOF/ VEL (46)
GT4	X	TN: 12w + RBV or 24w alone TE: 12w	X	TN: 12w IFN-ineligible with significant fibrosis only TE: 12w with significant fibrosis only	X (Not licensed)	TN/TE: 12w with RBV	X	TN: 24w (12w, then P+R 12w) TE: 24w (12w, then P+R 12w, REL) or 48w (12w, then P+R 36w (PR/NR)	TN: 24w with significant fibrosis only TE: 24w with significant fibrosis only (Both regimens have P+R for 24-48w)	X (Not licensed)	X (Not licensed)	TN: 48w, 24w with RVR TE: 48w	TN: 12w TE: 12w	TN: 12w TE: 12w
GT5 or 6a	X	TN: 8w TE: 12w	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	X	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	TN: 48w TE: 48w	X (Not licensed)	TN: 12w TE: 12w

BOC, boceprevir; DCV; daclatasvir; DSV, dasabuvir; EBR, elbasvir; GT, genotype; GZR, grazoprevir; LDV, ledipasvir; OBV, ombitasvir; P, pegylated interferon; PTV, paritaprevir; R or RBV, ribavirin; REL, relapser; RTV, ritonavir; RVR, rapid virologic response; SMV, simeprevir; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; TVR, telaprevir; VEL, velpatasvir ; VOX, voxilaprevir; w, weeks.
X denotes that the technology is not recommended; X (not licensed) denoted that the technology does not have marketing authorisation for that specific population.

Table 4: Summary of NICE technology appraisal recommendations as of August 2017: for patients with CHC with compensated cirrhosis (includes treatment-naïve and treatment-experienced patients)

GT	SOF+RBV (29, 49)	LDV/SOF (31, 50)	SOF+SMV (34)	SOF+DCV (30, 51)	OBV/PTV/ RTV+DSV (33, 52, 53)	OBV/PTV/ RTV (33, 53)	SOF+P+R (29, 49)	SMV+P+R (32, 54)	DCV+P+R (30, 51)	BOC+P+R (27, 55)	TVR+P+R (28, 56)	SOF+RBV (29, 49)	SOF/VEL (46)
GT1a	X	TN: 12w TE: 12wa	X	TN: 24w +/- RBV IFN-ineligible only TE: 24w +/- RBV IFN-ineligible only	TN/TE: 24w with RBV	X (Not licensed)	TN: 12w TE: 12w	TN: 24w (12w, then P+R 12w) TE: 24w (12w, then P+R 12w, REL) or 48w (12w, then P+R 36w; PR/NR)	X (Not licensed)	TN: 48w (P+R 4w + B+P+R 44w) TE: 48w (P+R 4w + B+P+R 44w)	TN: 48w (T+P+R 12w + P+R 36w) TE: 48w (T+P+R 12w + P+R 36w)	TN: 48w; 24w with RVR TE: 48w	TN: 12w TE: 12w
GT1b					TN/TE: 12w with RBV								
GT2	TN: 12w IFN-ineligible only TE: 12 w	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	TN/TE: 24w	TN: 12w TE: 12w
GT3	TN: 24w IFN-ineligible only TE: 24w IFN-ineligible only	X	X (Not licensed)	TN/TE: 24w with RBV IFN-ineligible only	X (Not licensed)	X (Not licensed)	TN: 12w TE: 12w	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	TN/TE: 24w	TN: 12w with RBV TE: 12w with RBV
GT4	X	TN: 12w TE: 12w[a]	X	TN: 24w +/- RBV IFN-ineligible only TE: 24w +/- RBV	X (Not licensed)	TN/TE: 24w with RBV	TN: 12w TE: 12w	TN: 24w (12w, then P+R 12w) TE: 24w (12w, then P+R	TN: 24w TE: 24w (Both regimens have P+R for 24-48w)	X (Not licensed)	X (Not licensed)	TN: 48w, 24w with RVR TE: 48w	TN: 12w TE: 12w

				IFN-ineligible only				12w, REL) or 48w (12w, then P+R 36w (PR/NR)					
GT5 or 6	X	TN: 12w[b] TE: 12w[a]	X	X (Not licensed)	X (Not licensed)	X (Not licensed)	TN: 12w TE: 12w	X (Not licensed)	X (Not licensed)	X (Not licensed)	X (Not licensed)	TN: 48w TE: 48w	TN: 12w TE: 12w

BOC, boceprevir; DCV; daclatasvir; DSV, dasabuvir; GT, genotype; LDV, ledipasvir; OBV, ombitasvir; P, pegylated interferon; PTV, paritaprevir; R or RBV; ribavirin; REL, relapser; RTV; ritonavir; RVR, rapid virologic response; SOF, sofosbuvir; SMV, simeprevir; TE, treatment-experienced; TN, treatment-naïve; TVR, telaprevir; VEL, velpatasvir; VOX, voxilaprevir; w, weeks.

X denotes that the technology is not recommended; X (not licensed) denoted that the technology does not have marketing authorisation for that specific population.

[a] Recommended only if all the following criteria are met: Child-Pugh class A; platelet count of 75,000/mm^3 or more; no features of portal hypertension; no history of an HCV-associated decompensation episode; not previously treated with an NS5A inhibitor; [b] licensed after TAG, so not appraised, but recommended.

B.1.3.3.2. Relevant NICE guidance, pathways or commissioning guides

Technology appraisals

Recommendations from NICE technology appraisals for each technology appraisal are provided in Table 5.

NICE guidelines

Hepatitis C: Diagnosis and management of hepatitis C (https://www.nice.org.uk/guidance/indevelopment/GID-CGWAVE0666)

In development; this process has been suspended until there is stability in the availability of treatments and the cost to the NHS of the hepatitis C drugs (Status last updated 23rd September 2016).

NICE pathways

Liver conditions NICE pathway (http://pathways.nice.org.uk/pathways/liver-conditions)

Covers the guidance NICE has produced on liver conditions, including resources for all currently available technology appraisals for hepatitis C treatments and the hepatitis C guideline (detailed above).

Hepatitis B and C testing NICE pathway (http://pathways.nice.org.uk/pathways/hepatitis-b-and-c-testing).

Aims to ensure that more people at risk of hepatitis B and C infection are tested.

Public Health Guidance

Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection, December 2012 (https://www.nice.org.uk/guidance/ph43)

This guidance aims to ensure that more people at increased risk of hepatitis B and C are tested, and includes recommendations on raising awareness in the general population, developing knowledge and skills of healthcare professionals and commissioning testing and treatment services.

This guidance does not provide detail on treatments for hepatitis C that are covered by the technology appraisals detailed in Table 5.

NHS England: Operational Delivery Networks (ODN) for Hepatitis C Care in Adults (2016) (https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/hep-c-netwrks-spec.pdf)

This guidance aims to improve access to care for patients with CHC infection who traditionally engage less well with health care services. The guidance suggests the development of a network model to ensure better equity of access for marginalised groups and to encourage outreach and engagement with patients outside of traditional health care settings.

Table 5: NICE technology appraisal guidance in CHC (as of August 2017)

Guidance number/ Issue date	Title	Guidance recommendations (wording as per guidance documents including any reference to other sections in those guidance documents)
TA430/January 2017 (46)	Sofosbuvir-velpatasvir for treating chronic hepatitis C	1.1 Sofosbuvir-velpatasvir is recommended as an option for treating chronic hepatitis C in adults, as specified in table 1 (see TA guidance for further details), only if the company provides the drug with the discount agreed in the simple discount agreement. 1.2 It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need. 1.3 This guidance is not intended to affect the position of patients whose treatment with sofosbuvir-velpatasvir was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.
TA413/October 2016 (47)	Elbasvir-grazoprevir for treating chronic hepatitis C	1.1 Elbasvir-grazoprevir is recommended, within its marketing authorisation, as an option for treating GT1 or 4 chronic hepatitis C in adults, as specified in table 1 (see TA guidance for further details), only if the company provides the drug at the same price or lower than that agreed with the Commercial Medicines Unit. 1.2 It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need.
TA365/November 2015 (38)	Ombitasvir-paritaprevir-ritonavir with or without dasabuvir for treating chronic hepatitis C	1.1 Ombitasvir-paritaprevir-ritonavir with or without dasabuvir is recommended, within its marketing authorisation, as an option for treating GT1 or 4 chronic hepatitis C in adults, as specified in table 1 (see TA guidance document for further details), only if the company provides ombitasvir-paritaprevir-ritonavir and dasabuvir at the same price or lower than that agreed with the Commercial Medicines Unit. 1.2 It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need.
TA364/November 2015 (35)	Daclatasvir for treating chronic hepatitis C	1.1 Daclatasvir is recommended as an option for treating chronic hepatitis C in adults, as specified in table 1 (see TA guidance document for further details), only if the company provides daclatasvir at the same price or lower than that agreed with the Commercial Medicines Unit.

		1.2 It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need. 1.3 People whose treatment with daclatasvir is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.
TA363/November 2015 (36)	Ledipasvir-sofosbuvir for treating chronic hepatitis C	1.1 Ledipasvir-sofosbuvir is recommended as an option for treating chronic hepatitis C in adults, as specified in table 1 (see TA guidance document for further details). 1.2 It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need. 1.3 People whose treatment with ledipasvir-sofosbuvir is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.
TA361/October 2015 (45)	Simeprevir in combination with sofosbuvir for treating GT1 or 4 chronic hepatitis C (terminated appraisal)	In June 2015 Janssen informed NICE that it would not be providing an evidence submission for this appraisal because it does not expect that the combination of simeprevir and sofosbuvir will be used in clinical practice in England because of the other treatments for chronic hepatitis C now available. NICE has therefore terminated this single technology appraisal. Guidance on simeprevir and sofosbuvir may be included in the forthcoming NICE guideline on hepatitis C.
TA331/February 2015 (37)	Simeprevir in combination with peginterferon alfa and ribavirin for treating GTs 1 and 4 chronic hepatitis C	This guidance gives recommendations for simeprevir in combination with peginterferon alfa and ribavirin. Simeprevir also has a marketing authorisation for use in combination with sofosbuvir. Recommendations for simeprevir in combination with sofosbuvir will be developed in separate guidance. 1.1 Simeprevir, in combination with peginterferon alfa and ribavirin, is recommended within its marketing authorisation as an option for treating GT 1 and 4 chronic hepatitis C in adults.
TA330/February 2015 (44)	Sofosbuvir for treating chronic hepatitis C	1.1 Sofosbuvir is recommended as an option for treating chronic hepatitis C in adults, as specified in table 1 (see TA guidance document for further details). 1.2 People currently receiving treatment initiated within the NHS with sofosbuvir that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.
TA253/April 2012 (42)	Boceprevir for the treatment of	1.1 BOC in combination with Peg-IFN alfa and RBV is recommended as an option for the

	GT1 chronic hepatitis C	treatment of GT1 chronic hepatitis C in adults with compensated liver disease: • Who are previously untreated or • In whom previous treatment has failed.
TA252/April 2012 (43)	Telaprevir for the treatment of GT1 chronic hepatitis C	1.1 TVR in combination with Peg-IFN alfa and RBV is recommended as an option for the treatment of GT1 chronic hepatitis C in adults with compensated liver disease: • Who are previously untreated or • In whom previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with RBV has failed, including people whose condition has relapsed, has partially responded or did not respond.
TA200/September 2010 (41)	Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C	1.1 Combination therapy with Peg-IFN alfa (2a or 2b) and RBV is recommended as a treatment option for adults with chronic hepatitis C: • Who have been treated previously with Peg-IFN alfa (2a or 2b) and RBV in combination, or with Peg-IFN alfa monotherapy, and whose condition either did not respond to treatment or responded initially to treatment but subsequently relapsed or • Who are co-infected with HIV 1.2 Shortened courses of combination therapy with Peg-IFN alfa (2a or 2b) and RBV are recommended for the treatment of adults with chronic hepatitis C who: • Have a rapid virological response to treatment at week 4 that is identified by a highly sensitive test and • Are considered suitable for a shortened course of treatment. 1.3 When deciding on the duration of combination therapy, clinicians should take into account the licensed indication of the chosen drug (Peg-IFN alfa-2a or Peg-IFN alfa-2b), the GT of the hepatitis C virus, the viral load at the start of treatment and the response to treatment (as indicated by the viral load).
TA106/August 2006 (40)	Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C Partially updated in TA200 This is an extension of the guidance given in NICE	1.1 Combination therapy, comprising Peg-IFN alfa-2a and RBV or Peg-IFN alfa-2b and RBV, is recommended, within the licensed indications of these drugs, for the treatment of mild chronic hepatitis C. 1.2 Monotherapy with Peg-IFN alfa-2a or Peg-IFN alfa-2b is recommended, within the licensed indications of these drugs, for the treatment of mild chronic hepatitis C for people who are unable to tolerate RBV, or for whom RBV is contraindicated. 1.3 The decision on whether a person with mild chronic hepatitis C should be treated immediately or should wait until the disease has reached a moderate stage ('watchful

	technology appraisal guidance 75	waiting') should be made by the person after fully informed consultation with the responsible clinician. The decision to treat need not depend on a liver biopsy to determine the stage of the disease if treatment is initiated immediately. However, a biopsy may be recommended by the clinician for other reasons or if a strategy of watchful waiting is chosen. 1.4 This recommendation has been updated and replaced by NICE technology appraisal guidance 200 1.5 This recommendation has been updated and replaced by NICE technology appraisal guidance 200 1.6 There is insufficient evidence to recommend combination therapy or monotherapy with Peg-IFN alfa for people who have had a liver transplant.
TA75/January 2004 (24)	Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C Partially updated in TA200 This guidance is a review and extension of Technology Appraisal Guidance No. 14 issued in October 2000	1.1 Combination therapy with Peg-IFN alfa and RBV is recommended within its licensed indications for the treatment of people aged 18 years and over with moderate to severe chronic hepatitis C (CHC), defined as histological evidence of significant scarring (fibrosis) and/or significant necrotic inflammation. 1.2 People with moderate to severe CHC are suitable for treatment if they have: • Not previously been treated with interferon alfa or Peg-IFN alfa, or • Been treated previously with interferon alfa (as monotherapy or in combination therapy), and/or 1.3 People currently being treated with interferon alfa, either as combination therapy or monotherapy, may be switched to the corresponding therapy with Peg-IFN alfa. 1.4 Treatment for the groups identified in Sections 1.1 and 1.2 should be as follows. • People infected with hepatitis C virus (HCV) of GT 2 and/or 3 should be treated for 24 weeks. • For people infected with HCV of GT 1, 4, 5 or 6, initial treatment should be for 12 weeks. Only people showing, at 12 weeks, a reduction in viral load to less than 1% of its level at the start of treatment (at least a 2-log reduction, see Section 4.1.2.5) should continue treatment until 48 weeks. For people in whom viral load at 12 weeks exceeds 1% of its level at the start of treatment, treatment should be discontinued. • People infected with more than one GT that includes one or more of GTs 1, 4, 5, or 6 should be treated as for GT 1. (Recommendation 1.4 still applies for people who are treated with standard courses of combination therapy, but has been replaced by NICE technology appraisal guidance 200

		[TA200] for people who are eligible for shortened courses of combination therapy [as described in recommendation 1.2 of TA200]) 1.5 People satisfying the conditions in Sections 1.1 and 1.2 but for whom RBV is contraindicated or is not tolerated should be treated with Peg-IFN alfa monotherapy. Regardless of GT, individuals should be tested for viral load at 12 weeks, and if the viral load has reduced to less than 1% of its level at the start of treatment, treatment should be continued for a total of 48 weeks. If viral load has not fallen to this extent, treatment should stop at 12 weeks. 1.6 People for whom liver biopsy poses a substantial risk (such as those with haemophilia, or those who have experienced an adverse event after undergoing a previous liver biopsy), and people with symptoms of extrahepatic HCV infection sufficient to impair quality of life, may be treated on clinical grounds without prior histological classification. 1.7 There is insufficient evidence to recommend combination therapy using Peg-IFN alfa or interferon alfa in people who: • This part-recommendation has been updated and replaced by NICE technology appraisal guidance 200 • This part-recommendation has been updated and replaced by NICE technology appraisal guidance 300 • Have had a liver transplantation. Treatment of CHC recurrence after liver transplantation (whether or not the person had been treated with IFN alfa or Peg-IFN alfa therapy at any time before transplantation) should be considered as experimental and carried out only in the context of a clinical trial.

BOC, boceprevir; CHC, chronic hepatitis C; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NHS, National Health Service; NICE, National Institute for Clinical and Health Excellence; IFN, interferon; Peg-IFN, pegylated interferon; RBV, ribavirin; TA, technology appraisal; TVR, telaprevir.

B.1.3.3.3. Clinical guidelines

In addition to the NICE guidance and pathways described in Sections B.1.3.3.1 and B.1.3.3.2, clinical guidelines and national policies of relevance are listed below:

- EASL Recommendations on Treatment of Hepatitis C 2016 (2, 8)
- UK consensus guidelines 2017 - Treatment Recommendations for the management of patients with Chronic HCV Infection (5)

EASL Recommendations on Treatment of Hepatitis C 2016 (2), developed by the European Association for the Study of the Liver, outline treatment recommendations across all HCV GTs. Recommendations by GT are summarised in Table 6. In addition, EASL guidelines also provide the following recommendations:

- Notwithstanding the respective costs of these options, IFN-free regimens are the best options when available in treatment-naïve and treatment-experienced, DAA-naïve patients, with or without compensated because of their virological efficacy, ease of use and tolerability
- Patients with decompensated cirrhosis should be urgently treated with an IFN-free regimen
- Indications for CHC treatment in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection
- The same IFN-free treatment regimens can be used in HIV co-infected patients as in patients without HIV infection, as the virological results of therapy are identical

UK consensus guidelines 2017 (5), are the most recent clinical treatment guidelines and are broadly in line with the EASL guidelines. These guidelines are summarised in Table 7. In addition, UK consensus guidelines also provide the following recommendations:

- The NHS England should consider commissioning pan-genotypic regimens for use in the community for patients who are TN and do not have cirrhosis to avoid the need for genotyping and facilitate rapid access to care
- RBV should be avoided whenever possible
- Eight week regimens without ribavirin are first choice for treatment naïve non-cirrhotic patients treated in community or prison settings regardless of genotype
- Transplantation is not contra-indicated in patients with HCV even in the presence of ‘difficult’ drug resistant mutations
- Drug–drug interactions should continue to be assessed and therapy should take account of potential interactions

Table 6: Summary of 2016 EASL recommendations for CHC

GT	Regimen	Recommendation
GT1	SOF+LDV (8-24 weeks)	IFN-free option 1 • For TN patients with or without compensated cirrhosis for treat 12 weeks • For TN patients without cirrhosis treatment may be shortened to 8 weeks if baseline HCV RNA level <6 million IU/mL • For TE, DAA-naïve patients infected with GT1b with or without compensated cirrhosis treat for 12 weeks without RBV • For TE, DAA-naïve patients infected with GT1a with or without compensated cirrhosis treat for 12 weeks with RBV • For TE, DAA-naïve patients infected with GT1a with or without compensated cirrhosis who have NS5A without ledipasvir RASs treat for 12 weeks without RBV • For TE, DAA-naïve patients infected with GT1a with or without compensated cirrhosis who have NS5A RASs that have high-level resistance to LDV treat for 12 weeks with RBV • For TE, DAA-naïve patients infected with GT1a with contraindications to the use of RBV or with poor tolerance to RBV on treatment treat for 24 weeks without RBV
	SOF+VEL (12 weeks)	IFN-free option 2 • For treatment naïve and treatment experienced patients with or without compensated cirrhosis treat for 12 weeks without RBV
	DSV/OBV/PTV+RTV (8-24 weeks)	IFN-free option 3 • For patients infected with GT1b, with or without compensated cirrhosis, treat for 8 weeks without RBV • For patients infected with subtype 1a without cirrhosis for treat 12 weeks with daily RBV • For patients infected with subtype 1a with compensated cirrhosis treat for 12 weeks with daily RBV

GT	Regimen	Recommendation
	GZR/EBR (12-16 weeks)	IFN-free option 4 • For patients infected with GT1a with or without compensated cirrhosis with an HCV RNA level ≤800,000 IU/ml (5.9 log10 IU/ml) at baseline treat 12 weeks without RBV • For patients infected with GT1a with or without compensated cirrhosis with an HCV RNA level ≤800,000 IU/ml and those with an HCV RNA level >800,000 IU/ml without EBR NS5A RASs at baseline treat for 12 weeks without RBV, if reliable NS5A resistance testing is performed • For TN and TE patients infected with GT1a with or without compensated cirrhosis with an HCV RNA level >800,000 IU/ml (5.9 log10 IU/ml) treat for 16 weeks RBV, if no NS5A resistance testing is performed • For TN and TE patients infected with GT1a with or without compensated cirrhosis treat with RBV for 16 weeks if their HCV RNA level is >800,000 IU/ml and NS5A RASs that confer resistance to EBR, if reliable NS5A resistance testing is performed • For TN and TE patients infected with GT1b with or without compensated cirrhosis for treat 12 weeks without RBV
	SOF+DCV (12-24 weeks)	IFN-free option 5 • For TN patients with or without compensated cirrhosis for 12 weeks • For TE, DAA-naïve patients infected with GT1b with or without compensated cirrhosis treat for 12 weeks • For TE, DAA-naïve patients infected with GT1a with or without compensated cirrhosis treat for 12 weeks and add RBV • For treatment experienced, DAA-naïve patients infected with GT1a with or without compensated cirrhosis without NS5A class RASs detected treat for 12 weeks • Adjust dose of DCV to 30mg in HIV co-infected patients receiving ritonavir- or cobicistat-boosted atazanavir or cobicistat-boosted elvitegravir • Adjust dose of DCV to 90mg in HIV co-infected patients receiving efavirenz • For treatment experienced, DAA-naïve patients infected with GT 1a with or without compensated cirrhosis with NS5A class RASs detected add RBV and treat for 12 weeks • TE, DAA-naïve patients with contraindications to the use of RBV or with poor tolerance to RBV, extend treatment duration to 24 weeks without RBV
GT2	SOF+VEL (12 weeks)	IFN-free option 1

GT	Regimen	Recommendation
		• For TN and TE patients with or without fixed compensated cirrhosis treat for 12 weeks
	SOF+DCV (12 weeks)	IFN-free option 2 • For TN and TE patients with or without compensated cirrhosis treat for 12 weeks
GT3	SOF+VEL (12-24 weeks)	IFN-free option 1 • For TN patients without cirrhosis for treat 12 weeks • For patients without the NS5A RAS Y93H at baseline treat for 12 weeks • For patients with contraindications to the use of RBV or with poor tolerance to RBV treat for 12 weeks • For TE patients without cirrhosis, as well as TN and treatment experienced patients with compensated cirrhosis for 12 weeks with RBV, if no NS5A resistance testing is performed • For treatment experienced patients without cirrhosis, as well as TN and TE patients with compensated cirrhosis, with the NS5A RAS Y93H detectable at baseline for 12 weeks with RBV, if reliable NS5A resistance testing is performed
	SOF+DCV (12 weeks)	IFN-free option 2 • For TN and TE patients without cirrhosis treat for 12 weeks • For TN and TE patients with cirrhosis add RBV and treat for 24 weeks
GT4	LDV/SOF (12-24 weeks)	IFN-free option 1 • For TN patients with or without compensated cirrhosis for treat 12 weeks without RBV • For TE patients with or without compensated cirrhosis add RBV and treat for 12 weeks • For TE patients with or without compensated cirrhosis with contraindications to the use of RBV or with poor tolerance to RBV treat without RBV for 24 weeks
	SOF/VEL (12 weeks)	IFN-free option 2 • For TN and TE patients with or without cirrhosis treat for 12 weeks
	OBV/PTV/RTV+RBV (12-24 weeks)	IFN-free option 3 • For patients with or without compensated cirrhosis treat for 12 weeks
	GZR/EBR (12-16 weeks)	IFN-free option 4 • For TN patients with or without cirrhosis treat for 12 weeks without RBV

GT	Regimen	Recommendation
	SOF+DCV (12 weeks)	IFN-free option 5 • For patients with cirrhosis add RBV • For patients with cirrhosis with contraindications to RBV, extend duration to 24 weeks
	SOF+SMV (12-24 weeks)	IFN-free option 6 • For TN patients with or without cirrhosis treat without RBV treat for 12 weeks • For TE patients with or without compensated cirrhosis treat for 12 weeks with RBV • For TE patients with or without compensated cirrhosis with contraindications to the use of RBV extend treatment to 24 weeks
GT5 or 6	LDV/SOF (12-24 weeks)	IFN-free option 1 • For TN patients with or without compensated cirrhosis treat for 12 weeks without RBV • For TE patients with or without compensated cirrhosis treat with LDV/SOF+RBV for 12 weeks • For TE patients with or without compensated cirrhosis with contraindications to the use of RBV extend treatment to 24 weeks
	SOF/VEL (12 weeks)	IFN-free option 2 • For TN and TE patients with or without compensated cirrhosis treat for 12 weeks without RBV
	SOF+DCV (12-24 weeks)	IFN-free option 3 • For TN patients with or without compensated cirrhosis treat for 12 weeks without RBV • For TE patients with or without compensated cirrhosis treat with SOF+DCV+RBV for 12 weeks • For TE patients with or without compensated cirrhosis with contraindications to the use of RBV extend treatment to 24 weeks

DAA, direct-acting antiviral; DCV; daclatasvir; EBR, elbasvir; EASL; European Association for the Study of the Liver; FDC, fixed dose combination; GT, genotype; GZR, grazoprevir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; IU, international units; LDV, ledipasvir; OBV/PTV/RTV, Ombitasvir/paritaprevir/ritonavir; P, pegylated interferon; PTV, paritaprevir; R or RBV, ribavirin; RAS, resistance-associated substitutions; RNA, ribonucleic acid; RTV, ritonavir; SMV, simeprevir; SOF, sofosbuvir; SVR; sustained virological response; TE, Treatment Experienced; TN; treatment-naïve; VEL, velpatasvir.
Source: EASL recommendations on treatment of Hepatitis C 2016 (60)

Table 7: Summary of UK consensus guidelines 2017 treatment options for CHC

GT	Treatment status	Non-cirrhotic	Cirrhotic
GT1	TN	LDV/SOF (8 weeks) GZR/EBR (12 weeks) SOF/VEL (12 weeks) SOF/VEL/VOX (8 weeks) GLE/PIB (8 weeks) GT1a only: GZR/EBR+RBV (16 weeks) for patients with viral load >800,000 and resistance associated substitutions (16 weeks+RBV is NOT a preferred regimen) GT1a only: OBV/PTV/RTV+DSV+RBV (12 weeks) - should be discarded when GLE/PIB is available GT1b only: OBV/PTV/RTV+DSV (12 weeks) - should be discarded when GLE/PIB is available	LDV/SOF (12 weeks) GZR/EBR (12 weeks) SOF/VEL (12 weeks) SOF/VEL/VOX (12 weeks) GLE/PIB (12 weeks) GT1a only: GZR/EBR+RBV (16 weeks) for patients with viral load >800,000 and resistance associated substitutions (16 weeks+RBV is NOT a preferred regimen) GT1a only: OBV/PTV/RTV+DSV+RBV (12 weeks) - should be discarded when GLE/PIB is available GT1b only: OBV/PTV/RTV+DSV (12 weeks) - should be discarded when GLE/PIB is available
	TE	SOF/LDV (12 weeks)	
	Retreatment of DAA failures[g]	SOF/VEL/VOX (12 weeks) GLE/PIB (12 weeks) no prior NS5A GLE/PIB (16 weeks) prior NS5A. **NB**: GLE/PIB will not be available in this sub-population under its EU license.	
GT2	TN	Strongly recommend that IFN is removed and RBV free regimens are preferred. SOF/VEL (12 weeks) SOF/VEL/VOX (8 weeks) GLE/PIB (8 weeks)	SOF/VEL (12 weeks) SOF/VEL/VOX (12 weeks) GLE/PIB (12 weeks)
	Retreatment of DAA failures[g]	SOF/VEL/VOX (12 weeks) GLE/PIB (16 weeks). **NB**: GLE/PIB will not be available to patients with prior history of NS5A under its EU license.	
GT3	TN	LDV/SOF (12 weeks) SOF/VEL/VOX (8 weeks) GLE/PIB (8 weeks)	LDV/SOF (12 weeks) SOF/VEL/VOX (12 weeks) GLE/PIB (16 weeks)
	Retreatment	SOF/VEL/VOX (12 weeks)	

GT	Treatment status	Non-cirrhotic	Cirrhotic
	of DAA failures[g]		
GT4	TN	GZR/EBR (12 weeks) OBV/PTV/RTV (12 weeks) - should be discarded when GLE/PIB is available SOF/VEL (12 weeks) SOF/VEL/VOX (8 weeks) GLE/PIB (8 weeks)	GZR/EBR (12 or 16 weeks) OBV/PTV/RTV (12 weeks) - should be discarded when GLE/PIB is available SOF/VEL (12 weeks) SOF/VEL/VOX (12 weeks) GLE/PIB (12 weeks)
	Retreatment of DAA failures[g]	SOF/VEL/VOX (12 weeks) GLE/PIB (16 weeks). **NB**: GLE/PIB will not be available to patients with prior history of NS5A under its EU license.	
	All	Given the paucity of data and the availability of better-validated regimens we recommend that the use of LDV/SOF for patients with GT4 HCV infection should be discontinued.	
GT5/6	All	The small number of patients GT5/6 infection in trials reported to date was noted. SOF/VEL (12 weeks) SOF/VEL/VOX (8 weeks) GLE/PIB (8-12 weeks)	SOF/VEL (12 weeks) SOF/VEL/VOX (8 weeks) GLE/PIB (12 weeks)
	Retreatment of DAA failures[g]	SOF/VEL/VOX (12 weeks) GLE/PIB (16 weeks) (note that in patients with both NS5A and NS3 resistance associated variants this regimen is likely to be inadequate). **NB**: GLE/PIB will not be available to patients with prior history of NS5A under its EU license.	
DCC	-	GT1a and GT1b: LDV/SOF+/-RBV (12 weeks) or SOF/VEL+RBV (12 weeks); retreatment requires: SOF/VEL+/-RBV (24 weeks) GT2: SOF/VEL+/-RBV (12 weeks) GT3: SOF/VEL+RBV (12 weeks). Consideration should be given to the use of SOF/VEL for 24 weeks in patients deemed unlikely to respond or intolerant of RBV; retreatment requires: SOF/VEL+/-RBV (24 weeks) GT4 and GT5/6: SOF/VEL+RBV (12 weeks)	
HIV co-infection	-	In general, the same DAA-based treatment regimens used in HCV mono-infection are applicable to co-infected patients with chronic HCV, although consideration of drug-drug interactions between DAAs and antiretrovirals should be taken into account.	

GT	Treatment status	Non-cirrhotic	Cirrhotic
		Where HIV therapy cannot be switched to avoid drug-drug interactions, an appropriate alternate DAA-based regimen is identified.	

DAA, direct-acting antiviral; DCC, decompensated cirrhosis; DCV; daclatasvir; DSV, dasabuvir; EBR, elbasvir; GLE, Glecaprevir; GT, genotype; GZR, grazoprevir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV; ledipasvir; OBV; ombitasvir; Peg-IFN; pegylated interferon; PIB, pibrentasvir; PTV; paritaprevir; RBV; ribavirin; RTV; ritonavir; SMV; simeprevir; SOF, sofosbuvir; TE; treatment-experienced; TN; treatment-naïve; VEL, velpatasvir; VOX, voxilaprevir.
a Consider RBV in patients more likely to have a poor response (e.g. prior null responders); b In patients at low risk of treatment failure RBV may be omitted; c 24 weeks in GT1a prior null responders, otherwise 12 weeks (differs from NICE who recommend 24 weeks for all); treatment can be extended to 24 weeks by the multi-disciplinary team if there are poor response characteristics at baseline (HIV coinfection, post-orthotopic liver transplantation cirrhosis) or on treatment (RBV intolerance, validated viral load kinetic predictor). The majority of patients will be treated for 12 weeks. (Note that NICE recommends 24 weeks); [d] This recommendation is not based on clinical effectiveness but on the assumption of future acquisition costs. SOF+DCV is a cost effective regimen approved by NICE for patients with advanced fibrosis who cannot have IFN; [e] In exceptional circumstances, can consider SOF+DCV+RBV or LDV/SOF 12 weeks (Not NICE approved), in those patients in whom drug-drug interactions with OBV/PTV/RTV+RBV are considered a potential concern; [f] For patients who are at low risk of treatment failure consideration should be given to 12 weeks treatment; [g] Re-treatment for DAA failures requires pre-treatment virological sequencing to identify resistance associated variants whose presence/absence should be used to guide treatment decisions.
Source: UK Consensus Guidelines 2017 (5)

B.1.3.4. *Limitations and unmet need*

The CHC treatment landscape has evolved dramatically to address the limitations associated with early treatment options for CHC, and multiple DAA-based regimens have come to market and achieved positive NICE recommendations. These include various individual drugs or fixed-dose combination therapies which target inhibition of non-structural viral protein NS5A and/or viral NS5B polymerase, including SOF, LDV/SOF, SMV, DCV, OBV/PTV/RTV, DSV, GZR/EBR and SOF/VEL (35-38, 44-47). Cure rates have also increased considerably (up to 100% in certain patient subgroups (61, 62)), which is likely to correspond to fewer patients requiring liver transplants, and fewer deaths due to CHC-related ELSD and HCC. A 2017 Public Health England (PHE) report found that the number of registrations for CHC-related liver transplants fell to an 8-year low of 83 in 2015, from an average of 134 per annum in 2008-2014 (38% reduction) (11). Deaths relating to CHC (ESLD or HCC) have historically increased year-on-year from 187 in 2005 to 387 in 2014 (13), however in 2015, an 8% reduction in CHC-related mortality was reported (11). Although the new DAAs offer improvements in patient outcomes, treatment coverage needs to improve in order to offer all patients with CHC improved health outcomes (1).

The development of resistance to therapy remains an issue, with SMV requiring baseline screening of patients being considered for treatment (63). Many DAAs, including SMV, DCV and OBV/PTV/RTV, and DSV are associated with multiple clinically relevant drug-drug interactions such that they cannot be administered with several commonly used medications, including some antiretroviral drugs (63).

The evolution of the CHC treatment landscape beyond Peg-IFN+RBV and the first generation protease inhibitors (PIs) has seen a move towards improved tolerability, shorter treatment duration, simplified regimens to cut administration burden, and reducing the reliance on Peg-IFN and RBV. The new UK Consensus Guidelines 2017 now recommend that RBV be avoided whenever possible and provide alternative RBV-free treatment options (1). However, there is limited evidence supporting retreatment decisions in those patients who fail to achieve SVR with a first-line DAA.

Unmet needs in CHC

Despite recent advances in treatment options for patients CHC, there still remains substantial unmet need for simple, short duration, RBV-free, highly effective and well tolerated therapies that can be used in a community setting. Groups that are still of particular concern are those for whom high SVR rates are more difficult to achieve:

- DAA-experienced
- GT3 infection (DAA-naïve; with or without compensated cirrhosis)

DAA-experienced patients

A small proportion of patients with CHC do not achieve an SVR when treated with a DAA (64); there is little clinical evidence available to support the retreatment or use of another DAA in treatment-experienced patients, and in particular NS5A-containing regimens. Current guidelines (EASL) acknowledge the limited retreatment options available for this patient population and recommend deferral of treatment, pending availability of data on newer, more suitable, therapy options for these patients. In the UK, 2017 consensus guidelines recognise

DAA-experienced patients as a patient population, with recommendations on retreatment options (5).

By not achieving SVR, DAA-experienced patients are at risk of fibrosis and cirrhosis advancement, continuing risk of HCC and increasing risk of liver and non-liver-related mortality (65-69). The longer a patient remains infected with HCV, the greater the risk of transmitting the infection and perpetuating the burden of disease.

Consequently, there remains a substantial unmet need for novel therapies for patients who have previously failed to respond to available DAA-based regimens, as there is currently no licensed pharmacologic treatment option for the retreatment of these patients.

DAA-naïve patients with GT3 infection

Some genotypes are more difficult to treat than others; of particular consequence is that patients with GT3 infection are at increased risk of disease progression compared with other genotypes, with several studies showing significantly higher rates of fibrosis progression (p=0.007) (70), development of HCC (p=0.003) (71) and all-cause mortality (p=0.01) (68). As GT3 infection is also one of the more prevalent GT in England (3), these patients represent an important target group for treatment. Treatment goals aim to improve SVR rates for patients, especially those with cirrhosis, and shorten duration of therapy (72).

IFN-containing regimens have historically been recommended in GT3 patients (8), however, treatment outcomes for GT3 patients treated with Peg-IFN+RBV are poor, with real-world data in England showing SVR rates of 60% in this population (73). A large number of patients with GT3 CHC therefore remain infected with HCV, with little clinical evidence to support re-treatment as they would be considered to be treatment-experienced. The 2016 EASL guidelines now define patients as DAA-naïve or DAA-experienced, meaning that IFN-experienced patients can be considered eligible for DAA treatment (i.e. they are DAA-naïve).

Although newer DAAs offer both IFN-free treatment and shorter treatment duration, most treatment options for GT3 patients still require RBV in the regimen, resulting in a longer (e.g. 24 weeks) treatment regimen and a higher pill burden; both of which impair adherence and virologic outcomes (74-77). Cirrhosis status is also an influencing factor on treatment adherence and virologic outcomes; patients with F0-F2 stage fibrosis are more likely to adhere to their treatment regimen and more likely to experience SVR compared with patients with F3-F4 fibrosis (78).

Efficacious therapy for these two groups would potentially avoid costly complications associated with liver damage as well as costly retreatment for those who fail to achieve SVR due to non-adherence arising from treatment regimen length and/or pill burden. Timely treatment of these patient groups would also reduce the risk of onward transmission, and therefore helping limit the burden of CHC to patients and the healthcare system in England.

It should also be recognised that the advent of new DAAs there is likely to be a shift in the profile of those requiring CHC treatment. We can expect the number of patients with CHC and cirrhosis to decrease due to NHS England's policy to treat this patient group (79). Consequently, DAA-experineced and DAA-naïve GT3 patients groups are likely to represent the main CHC population in the future.

B.1.3.5. *Sofosbuvir-velpatasvir-voxilaprevir*

The FDC of SOF/VEL/VOX represents the first single tablet regimen (STR) for the treatment of CHC in those patients who have previously failed to achieve SVR with a DAA (DAA-experienced; with or without cirrhosis), as well as an option for DAA-naïve patients with GT3 infection (with or without cirrhosis). SOF/VEL/VOX is a simple, all-oral, once-daily Peg-IFN- and RBV-free treatment option. Clinical trials (see section B.2.6) have demonstrated high cure rates without the need for RBV in both DAA-experienced patients and those who are DAA-naïve with GT3 infection (with or without cirrhosis).

It is anticipated therefore that SOF/VEL/VOX will provide a simple, highly effective and well tolerated treatment option for patients with CHC, irrespective of severity of liver disease or prior treatment experience. SOF/VEL/VOX represents a much-needed option in the sub-populations which are considered the hardest to treat and who have with the highest unmet need.

B.1.4. *Equality considerations*

Not applicable.

B.2. Clinical effectiveness

B.2.1. *Identification and selection of relevant studies*

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2. *List of relevant clinical effectiveness evidence*

The POLARIS trials were conducted to compare the clinical effectiveness of SOF/VEL/VOX versus placebo (POLARIS-1) or SOF/VEL (POLARIS 2-4). All four trials support the application for marketing authorisation and were used in the economic model. A summary of the clinical effectiveness evidence is in Table 8.

Table 8: Clinical effectiveness evidence

Study	POLARIS-1	POLARIS-4	POLARIS-2	POLARIS-3
Study design	Multicentre, randomised, double-blind, placebo-controlled, Phase III	Multicentre, randomised, open-label, active-controlled, Phase III	Multicentre, randomised, open-label, Phase III	
Population	DAA-experienced patients previously treated with an NS5A inhibitor (GT1, GT2, GT3 or GT4, GT5, GT6 or intermediate GT)	DAA-experienced patients not previously treated with an NS5A inhibitor (GT1, GT2, GT3 or GT4, GT5, GT6 or intermediate GT)	DAA-naïve patients (GT1, GT2, GT3 or GT4, GT5 or intermediate GT)	DAA-naïve patients with GT3 CHC and cirrhosis
Intervention(s)	SOF/VEL/VOX for 12 weeks		SOF/VEL/VOX for 8 weeks	
Comparator(s)	Placebo for 12 weeks	SOF/VEL for 12 weeks		
Indicate if trial supports application for marketing authorisation	Yes X / No ; Indicate if trial used in the economic model: Yes X / No	Yes X / No ; Indicate if trial used in the economic model: Yes X / No	Yes X / No ; Indicate if trial used in the economic model: Yes X / No	Yes X / No ; Indicate if trial used in the economic model: Yes X / No
Rationale for use/non-use in the model	NA	NA	NA	NA
Reported outcomes specified in the decision problem	**SVR12**, defined as HCV RNA<LLOQ12 weeks after cessation of treatment, in the FAS in the SOF/VEL/VOX population. The LLOQ was 15 IU/mL			
All other reported outcomes	• Proportion of patients with SVR4 and SVR24 (HCV RNA <LLOQ) at 4 and 24 weeks after EOT • The proportion of patients with HCV RNA<LLOQ on treatment by study visit • HCV RNA absolute values and changes from baseline through EOT • Proportion of patients with virologic failure. On-treatment virologic failure is breakthrough, rebound, or non-response. Relapse, after achieving a response at the end of treatment was also classed as virologic failure • Baseline deep sequencing of the HCV NS3, NS5A, and NS5B genes was performed for all patients. For all patients with virologic failure, deep sequencing was performed at the first time point after virologic failure if the plasma/serum sample was available and HCV RNA was >1000 IU/mL. All data are reported at a 15% assay cut-off			

Study	POLARIS-1	POLARIS-4	POLARIS-2	POLARIS-3
	• To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment • To evaluate the emergence of viral resistance to SOF/VEL/VOX during treatment and after cessation of treatment • HRQL (SF-36, CLDQ-HCV, FACIT-F and WPAI: Hep C)			

CLDQ-HCV, Chronic Liver Disease Questionnaire-Hepatitis C Version; DAA, direct-acting antivirals; EOT, end of treatment; FACT-IF, Fatigue Index; GT, genotype; HCV, hepatitis-c virus; HRQL, health related quality of life; LLOQ, lower limit of quantification; RNA, ribonucleic acid; SF36, SF-36, 36-Item Short-Form Survey; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir; VOX, voxilaprevir; WPAI: Hep C, Work productivity and Activity Impairment: Hepatitis C.

B.2.3. *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1. *Comparative summary of RCT methodology*

Table 9: Comparative summary of methodology

Trial no. (acronym)	GS-US-367-1171 (POLARIS-1) CHC GT1-6	GS-US-367-1170 (POLARIS-4) CHC GT1-6	GS-US-367-1172 (POLARIS-2) CHC GT1-6	GS-US-367-1173 (POLARIS-3) CHC GT3
Study objective	• To determine the efficacy of treatment with SOF/VEL/VOX FDC for 12 weeks as measured by the proportion of patients with SVR12 • To evaluate the safety and tolerability of treatment with SOF/VEL/VOX	• To determine the efficacy of treatment with SOF/VEL/VOX FDC for 12 weeks and SOF/VEL FDC for 12 weeks as measured by the proportion of patients with SVR12 • To evaluate the safety and tolerability of each treatment regimen	• To compare the efficacy of treatment with SOF/VEL/VOX FDC for 8 weeks with that of SOF/VEL FDC for 12 weeks as measured by the proportion of patients SVR12 • To evaluate the safety and tolerability of each treatment regimen	• To determine the efficacy of treatment with SOF/VEL/VOX FDC for 8 weeks and of treatment with SOF/VEL FDC for 12 weeks as measured by the proportion of patients with SVR12 • To evaluate the safety and tolerability of each treatment regimen

Trial no. (acronym)	GS-US-367-1171 (POLARIS-1) CHC GT1-6	GS-US-367-1170 (POLARIS-4) CHC GT1-6	GS-US-367-1172 (POLARIS-2) CHC GT1-6	GS-US-367-1173 (POLARIS-3) CHC GT3
Location	108 sites (United States, Canada, France, Germany United Kingdom, Australia and New Zealand 6 sites (9 patients) in the United Kingdom	101 sites (United States, Canada, France, Germany United Kingdom, Australia and New Zealand 5 sites (12 patients) in the United Kingdom	117 sites (United States, France, Canada, United Kingdom, Australia, Germany, New Zealand 8 sites (47 patients) in the United Kingdom	84 sites (United States, France, Australia, Canada, Germany, United Kingdom and New Zealand 6 sites (15 patients) in the United Kingdom
Design	Multicentre, randomised, double-blind, placebo-controlled, Phase III	Multicentre, randomised, open-label, active-controlled, Phase III	Multicentre, randomised, open-label, Phase III	
Duration of study	Treatment duration: 12 weeks Follow-up: up to 24 weeks	Treatment duration: 12 weeks Follow-up: up to 24 weeks	SOF/VEL/VOX: 8 weeks SOF/VEL: 12 weeks Follow-up: up to 24 weeks	
Method of randomisation	An IWRS was employed to manage patient randomisation and treatment assignment • Patients with GT1 CHC infection were randomised to the SOF/VEL/VOX 12 week or placebo 12 week group. Randomisation was stratified by cirrhosis status (presence or absence of cirrhosis) Patients with GT2-6 or indeterminate CHC	An IWRS was employed to manage patient randomisation and treatment assignment • Patients with GT1, 2, or 3 CHC infection were randomised in a 1:1 ratio into 1 of 2 treatment groups, the SOF/VEL/VOX 12 week or SOF/VEL 12 week group. Randomisation was stratified by: o CHC GT (1, 2, or 3) o Cirrhosis status	An IWRS was employed to manage patient randomisation and treatment assignment • Patients with CHC GT1, 2, 3, or 4 infection were randomised in a 1:1 ratio into 1 of 2 treatment groups (SOF/VEL/VOX for 8 weeks or SOF/VEL for 12 weeks). Randomisation was stratified by: o CHC GT (1, 2, 3 or 4)	An IWRS was employed to manage patient randomisation and treatment assignment. Randomisation was stratified by treatment history: • Treatment-naïve • Treatment-experienced with an IFN-based regimen

Trial no. (acronym)	GS-US-367-1171 (POLARIS-1) CHC GT1-6	GS-US-367-1170 (POLARIS-4) CHC GT1-6	GS-US-367-1172 (POLARIS-2) CHC GT1-6	GS-US-367-1173 (POLARIS-3) CHC GT3
	infection, regardless of cirrhosis status, were enrolled in the SOF/VEL/VOX 12 week group only	(presence or absence) Patients with GT4, 5, or indeterminate (including GT6, due to the inability of the assay to distinguish this GT) CHC infection, regardless of cirrhosis status, were enrolled into the SOF/VEL/VOX 12 week group only	○ Cirrhosis status (presence or absence; not GT3) ○ CHC treatment history ○ Treatment-naïve ○ Treatment-experienced with an IFN-based regimen Patients with GT5 or indeterminate CHC infection (including GT6, due to the inability of the screening assay to distinguish this GT), with or without cirrhosis, were enrolled into the SOF/VEL/VOX 8 week group	
Method of blinding (care provider, patient and outcome assessor)	The study was double-blinded. Study drugs were dispensed to patients in a blinded fashion as directed by the IWRS. In the event of a medical emergency where breaking the blind was required to provide medical care to the patient, the investigator	The study was open-label. All investigators, patients, and trial personnel were aware of the treatment assignments at all points.		

Trial no. (acronym)	GS-US-367-1171 (POLARIS-1) CHC GT1-6	GS-US-367-1170 (POLARIS-4) CHC GT1-6	GS-US-367-1172 (POLARIS-2) CHC GT1-6	GS-US-367-1173 (POLARIS-3) CHC GT3
	may have obtained treatment assignment for that patient. IWRS should have been used as the primary method of breaking the blind. If IWRS could not be accessed, Gilead recommended, but did not require, that the investigator contact the Gilead medical monitor prior to breaking the blind. Treatment assignment should have remained blinded unless it was necessary to determine patient emergency medical care. The rationale for unblinding was required to be clearly explained in source documentation and on the eCRF, along with the date on which the treatment assignment was obtained. The investigator was requested to contact the Gilead medical monitor promptly in case of any treatment unblinding. If a			

Trial no. (acronym)	GS-US-367-1171 (POLARIS-1) CHC GT1-6	GS-US-367-1170 (POLARIS-4) CHC GT1-6	GS-US-367-1172 (POLARIS-2) CHC GT1-6	GS-US-367-1173 (POLARIS-3) CHC GT3
	patient's treatment assignment was disclosed to the investigator, study treatment was discontinued for the patient.			
Intervention(s) (n=) and comparator(s) (n=)	**DAA-experienced patients previously treated with an NS5A inhibitor (GT1, GT2, GT3 or GT4, GT5, GT6 or intermediate GT)** Patients were to be randomised (in a 1:1 ratio) or enrolled to: • **SOF/VEL/VOX for 12 weeks** (n=263): SOF/VEL/VOX FDC (400/100/100 mg) once daily with food • **Placebo for 12 weeks** (n=152): SOF/VEL/VOX placebo tablet once daily with food Approximately 200 patients with GT1 CHC (with a target of at least 30% with cirrhosis) were planned to be randomised in a 1:1 ratio in a double-	**DAA-experienced patients not previously treated with an NS5A inhibitor (GT1, GT2, GT3 or GT4, GT5, GT6 or intermediate GT)** Patients were randomised (1:1 ratio) or enrolled to: • **SOF/VEL/VOX for 12 weeks** (n=182): SOF/VEL/VOX FDC (400/100/100 mg) once daily with food • **SOF/VEL for 12 weeks** (n=151): SOF/VEL (400/100 mg) once daily without regard to food Approximately 350 patients with GT1, 2, or 3 CHC (with a target of at least 30% with cirrhosis) were randomised in a 1:1 ratio into the SOF/VEL/VOX 12 week or	**DAA-naïve patients (GT1, GT2, GT3 or GT4, GT5 or intermediate GT)** Patients were to be randomised 1:1 to: • **SOF/VEL/VOX for 8 weeks** (n=405): SOF/VEL/VOX FDC (400/100/100 mg) once daily with food • **SOF/VEL for 12 weeks** (n=375): SOF/VEL FDC (400/100 mg) once daily with or without food The target enrolments for patients with GT1, 2, 3, 4, 5 or intermediate (including GT6) in the SOF/VEL/VOX treatment group were 200, 50, 75, 50 and 30, respectively Patients with GT5 or indeterminate GT with or without cirrhosis, were	**DAA-naïve patients with GT3 CHC and cirrhosis** Patients were to be randomised 1:1 to: • **SOF/VEL/VOX for 8 weeks** (n=100): SOF/VEL/VOX FDC (400/100/100 mg) once daily with food • **SOF/VEL for 12 weeks** (n=100): SOF/VEL FDC (400/100 mg) once daily without regard to food

Trial no. (acronym)	GS-US-367-1171 (POLARIS-1) CHC GT1-6	GS-US-367-1170 (POLARIS-4) CHC GT1-6	GS-US-367-1172 (POLARIS-2) CHC GT1-6	GS-US-367-1173 (POLARIS-3) CHC GT3
	blind manner into the SOF/VEL/VOX 12 week group or Placebo 12 week group Approximately 150 patients with GT3 (n=100) or 4 (n=50) CHC infection (with a target of at least 30% with cirrhosis) were planned to be enrolled in the SOF/VEL/VOX 12 week group Approximately 30 patients with GT2, 5, or indeterminate with or without cirrhosis were also planned to be enrolled in the SOF/VEL/VOX 12 week group	SOF/VEL 12 week group. The target enrolments for patients with GT1, 2, and 3 CHC were 200, 50, and 100 patients, respectively. The 30 additional patients with GT4, 5, or indeterminate CHC infection, regardless of cirrhosis status, were enrolled in the SOF/VEL/VOX 12 week group only	enrolled into the SOF/VEL/VOX 8 week group	
Permitted and disallowed concomitant medications	Concomitant medications taken within 30 days prior to screening, up to and including 30 days after the last dose of study drug, were recorded. The following were prohibited during the screening period and for a minimum of 28 days prior to the baseline/day 1 visit through the EOT visit: • Hematologic stimulating agents (e.g. ESAs, GCSF, TPO mimetics) • Chronic use of systemic immunosuppressants including, but not limited to: ○ Corticosteroids (prednisone equivalent of >10 mg/day for >2 weeks) ○ Azathioprine ○ Monoclonal antibodies (e.g. infliximab)			

Trial no. (acronym)	GS-US-367-1171 (POLARIS-1) CHC GT1-6	GS-US-367-1170 (POLARIS-4) CHC GT1-6	GS-US-367-1172 (POLARIS-2) CHC GT1-6	GS-US-367-1173 (POLARIS-3) CHC GT3
	• Investigational agents or devices for any indication Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters, e.g. OATP and P-gp) with study drug(s) may have resulted in PK interactions resulting in increases or decreases in exposure of study drug(s). The use of amiodarone was prohibited from 60 days prior to baseline/day 1 through the EOT. Other examples of representative medications which were prohibited or were to be used with caution from 21 days prior to baseline/day 1 through the EOT are listed in the clinical study protocol. Medications for disease conditions excluded from the protocol (e.g. transplantation) were disallowed in the study.			
Assessments performed	• All patients were to have study visits at screening[a], baseline/day 1[b], and on-treatment at the end of week 1, 2, 4, 8 and 12/EOT • Post-treatment visits were to occur at week 4, 12[c] and 24[c] (if applicable) • Screening assessments were to be completed within 28 days (42 days if liver biopsy or for extenuating circumstances with sponsor approval) of the baseline/day 1 visit • Baseline/day 1 assessments were performed prior to dosing • Patients with HCV RNA<LLOQat post-treatment week 12 visit had to complete post-treatment week 24 visit • Patients in the Placebo 12 week group were not required to complete the post-treatment week 12 and 24 visits for the primary study (POLARIS-1 only) **Assessments included:** • Complete physical examination (screening, baseline, on-treatment week 12/EOT, ET) • Body weight (screening, baseline, on-treatment week		• All patients were to have study visits at screening[a], baseline/day 1[b], and on-treatment at the end of week 1, 2, 4, 8 and 12/EOT in the SOF/VEL treatment groups and at the end of week 1, 2, 4 and 8/EOT in the SOF/VEL/VOX treatment groups • Post-treatment visits were to occur at week 4, 12[c] and 24[c] (if applicable) • Screening assessments were to be completed within 28 days (42 days if liver biopsy or for extenuating circumstances with sponsor approval) of the baseline/day 1 visit • Baseline/day 1 assessments were performed prior to dosing • Patients with HCV RNA<LLOQ at post-treatment week 12 visit had to complete post-treatment week 24 visit **Assessments included:** • Complete physical examination (screening, baseline, on-treatment week EOT, and ET) • Body weight (screening, baseline, on-treatment week	

Trial no. (acronym)	GS-US-367-1171 (POLARIS-1) CHC GT1-6	GS-US-367-1170 (POLARIS-4) CHC GT1-6	GS-US-367-1172 (POLARIS-2) CHC GT1-6	GS-US-367-1173 (POLARIS-3) CHC GT3
	12/EOT, ET) • Vital signs (screening, baseline, on-treatment weeks 1, 2, 4, 8 and 12/EOT, ET, post-treatment weeks 4) • 12-lead ECG (screening, baseline, on-treatment weeks 1 and 12/EOT, ET) • Imaging for HCC[d] (screening only) • AEs and concomitant medications (screening, baseline, on-treatment weeks 1, 2, 4, 8 and 12/EOT, ET, post-treatment weeks 4) • HRQL surveys[e] (baseline, on-treatment weeks 4, 12/EOT and ET, post-treatment weeks 4, 12 and 24) • Review of study medication compliance (pill count) on-treatment weeks 1, 2, 4, 8, 12/EOT, ET) • Haematology, Chemistry (screening, baseline, on-treatment weeks 1, 2, 4, 8 and 12/EOT, ET, post-treatment weeks 4) • Coagulation tests (screening, baseline, on-treatment weeks 12/EOT, ET) • HCV RNA (screening, baseline, on-treatment weeks 1, 2, 4, 8 and 12/EOT, ET, post-treatment weeks 4, 12, and 24) • Viral sequencing/phenotyping[g] (baseline, on-treatment weeks 1, 2, 4, 8 and 12/EOT, ET, post-treatment weeks 4, 12, and 24) • Single PK (on-treatment weeks 1, 2, 4, 8, 12/EOT, ET) • Pregnancy testing (screening, baseline, on-treatment weeks 4, 8, 12/EOT, ET, post-treatment week 4)		8/EOT, and ET) • Vital signs (screening, baseline, on-treatment weeks 1, 2, 4, 8 and 12/EOT, ET, and post-treatment week 4) • 12-lead ECG (screening, baseline, on-treatment weeks 1 EOT and ET [SOF/VEL/VOX arm only]) • Imaging for HCC[d] (screening only) • AEs and concomitant medications (screening, baseline, on-treatment weeks 1, 2, 4, 8 and 12/EOT, ET, post-treatment weeks 4) • HRQL surveys (baseline, on-treatment weeks 4 and EOT, ET, post-treatment weeks 4, 12 and 24) • Review of study medication compliance (pill count)f (on-treatment weeks 1, 2, 4, 8, 12/EOT, ET) • Haematology, Chemistry (screening, baseline, on-treatment weeks 1, 2, 4, 8 and 12/EOT, ET, post-treatment weeks 4) • Coagulation tests (screening, baseline, on-treatment weeks 12/EOT, ET) • HCV RNA (screening, baseline, on-treatment weeks 1, 2, 4, 8 and 12/EOT, ET, post-treatment weeks 4, 12, and 24) • Viral sequencing/phenotypingg (baseline, on-treatment weeks 1, 2, 4, 8 and 12/EOT, ET, post-treatment weeks 4, 12, and 24) • Single PK (on-treatment weeks 1, 2, 4, 8, 12/EOT, ET) • Pregnancy testing (screening, baseline, on-treatment	

Trial no. (acronym)	GS-US-367-1171 (POLARIS-1) CHC GT1-6	GS-US-367-1170 (POLARIS-4) CHC GT1-6	GS-US-367-1172 (POLARIS-2) CHC GT1-6	GS-US-367-1173 (POLARIS-3) CHC GT3
	• Urinalysis (screening only) • HCV genotyping[h], IL28B (screening only) • HCV, HIV, HBV testing (screening only) • HbA_{1c} Fibrotest (screening only)		weeks 4, 8, 12/EOT, ET, post-treatment week 4) • Urinalysis (screening only) • HCV genotypingh, IL28B (screening only) • HCV, HIV, HBV testing (screening only) • HbA_{1c} Fibrotest (screening only)	
Primary outcomes (including scoring methods and timings of assessments)	SVR12, defined as HCV RNA<LLOQ12 weeks after cessation of treatment, in the FAS in the SOF/VEL/VOX population. The LLOQ was 15 IU/mL.			
Secondary outcomes	• Proportion of patients with SVR4 and SVR24 (HCV RNA <LLOQ) at 4 and 24 weeks after end of treatment • The proportion of patients with HCV RNA<LLOQ on treatment by study visit • HCV RNA absolute values and changes from baseline through EOT • Proportion of patients with virologic failure. On-treatment virologic failure is breakthrough, rebound, or non-response. Relapse, after achieving a response at the end of treatment was also classed as virologic failure • Baseline deep sequencing of the HCV NS3, NS5A, and NS5B genes was performed for all patients. For all patients with virologic failure, deep sequencing was performed at the first time point after virologic failure if the plasma/serum sample was available and HCV RNA was >1000 IU/mL. All data are reported at a 15% assay cut-off • To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment • To evaluate the emergence of viral resistance to SOF/VEL/VOX during treatment and after cessation of treatment • HRQL (SF-36, CLDQ-HCV, FACIT-F and WPAI: Hep C)			
Pre-planned subgroups	• Age group (<65 years, ≥65 years) • Sex at birth (male, female) • Race (white, non-black, other) • Ethnicity (Hispanic or Latino, non-Hispanic or Latino)			

Trial no. (acronym)	GS-US-367-1171 (POLARIS-1) CHC GT1-6	GS-US-367-1170 (POLARIS-4) CHC GT1-6	GS-US-367-1172 (POLARIS-2) CHC GT1-6	GS-US-367-1173 (POLARIS-3) CHC GT3
	• Region (US, non-US) • Baseline BMI (<30 kg/m2, ≥30 kg/m2) • HCV genotype/subtype by sequencing (POLARIS-1, -2, -4) • Cirrhosis (presence, absence, missing) • IL28B genotype (CC, non-CC [with non-CC further broken down to CT, TT]) • Baseline HCV RNA (<800,000 IU/mL, ≥800,000 IU/mL) • Baseline ALT (≤1.5 x ULN, >1.5 x ULN) • Prior HCV treatment experience (treatment-naïve, treatment-experienced) • Prior HCV treatment (Peg-IFN+RBV, other) for treatment-experienced patients • Number of prior HCV treatment regimens (1, 2 or more) for treatment-experienced patients • Most recent HCV treatment response (non-responder, relapse, other) for treatment-experienced patients • Adherence to study regimen (<80%, ≥80%) • Study treatment status (completed study treatment, discontinued study treatment)			

AE, adverse event; ALT, alanine aminotransferase; BMI, body mass index CHC, chronic hepatitis C; CLDQ, Chronic Liver Disease Questionnaire; DAA direct-acting antiviral; ECG, electrocardiogram; eCRF, electronic case report form; EOT, end of treatment; ESAs, erythropoiesis-stimulating agents; ET, early termination; FACIT-F, Fatigue Index; FAS, full analysis set; FDC, fixed dose combination; GCSF, granulocyte colony stimulating factor; GT, genotype; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQL, Health Related Quality of Life; IFN, interferon; IWRS, interactive web response system; LLOQ, lower limit of quantitation; NS, non-structural protein 5A; OATP, organic anion transporting polypeptide; P-gp, P-glycoprotein; Peg-IFN, pegylated *interferon*; PK, pharmacokinetic; RBV, ribavirin; RNA, ribonucleic acid; SF-36, 36-Item Short-Form Survey; SOF, sofosbuvir; SVR, sustained virologic response; SVRx, sustained virologic response x weeks after cessation of treatment ; TPO, thrombopoietin mimetics; VEL, velpatasvir; VOX, voxilaprevir; WPAI: Hep C, Work productivity and Activity Impairment: Hepatitis C.

[a] Screening assessments were completed within 28 days of the baseline/day 1 visit. The screening window may have been extended to 42 days for patients requiring a liver biopsy or for extenuating circumstances with sponsor approval; [b] Baseline/day 1 assessments were performed prior to dosing; [c] Patients with HCV RNA<LLOQ at the post-treatment week 12 visit were required to complete the post-treatment week 24 visit. Patients identified as participating in Placebo 12 week group were not required to complete the post-treatment week 12 and 24 visits for the primary study; [d] Cirrhotic patients were required to have liver imaging within 6 months of the baseline/day 1 visit to exclude HCC. If cirrhotic patients had liver imaging performed between the baseline/day 1 and post-treatment week 24 visits, as part of standard of care, the data were recorded; [e] If patients completed health-related quality of life surveys at the baseline/day 1 visit, they also completed these surveys at subsequent visits, as applicable; [f] At the end of weeks 6 and 10, patients were contacted to assess study drug adherence; [g] Plasma was collected for possible viral resistance or other virology studies; [h] HCV genotyping was performed by the central laboratory using the Abbott RealTime HCV genotype II assay. Genotype and subtype were subsequently determined by basic local alignment search tool (BLAST) analysis of NS3, NS5A, and NS5B sequences from deep sequencing.

B.2.3.2. *Eligibility criteria*

Summary details of the eligibility criteria for the POLARIS RCTs are presented in Table 10 and full details are presented in Table 11. The POLARIS-1 and POLARIS-4 trials allowed for inclusion of patients who were treatment-experienced. POLARIS-1 and POLARIS-3 trials allowed for inclusion of patients who were treatment-naïve. In POLARIS-1, -2 and -3 approximately 30% of patients with compensated cirrhosis were allowed to be enrolled. In POLARIS-3 all patients had cirrhosis. In POLARIS-1, -4 and -2 patients with HCV GT1-6 or indeterminate were allowed to be enrolled. In POLARIS-3 only patients with HCV GT3 were included.

Table 10: Summary eligibility criteria

Trial no. (acronym)	GS-US-367-1171 (POLARIS-1)	GS-US-367-1170 (POLARIS-4)	GS-US-367-1172 (POLARIS-2)	GS-US-367-1173 (POLARIS-3)
HCV genotype	GT1, GT2, GT4, GT5, GT6 or indeterminate	GT1, GT2, GT4, GT5, GT6 or indeterminate	GT1, GT2, GT4, GT5, GT6 or indeterminate	GT3
Treatment experience	HCV treatment experience with a NS5A inhibitor	HCV treatment experience with a non-NS5A inhibitor	HCV treatment-naïve	
Cirrhosis permitted	Approximately 30% target	Approximately 30% target	Approximately 30% target	Yes, 100%
General inclusion criteria	Males and non-pregnant/non-lactating females; aged ≥18 years; HCV RNA ≥104 IU/mL at screening; confirmed chronic HCV infection (≥6 months) by medical records or liver biopsy; liver imaging with 6 months of baseline in patients with cirrhosis			
General exclusion criteria	Current or prior history of clinically significant illness, GI disorder, difficulty with blood collection, clinical hepatic decompensation, solid organ transplantation, significant pulmonary or cardiac disease, or porphyria, psychiatric instability, malignancy, significant drug allergy; screening/laboratory abnormalities (e.g. ECG); laboratory parameters at screening with ALT >1 x ULN, AST >10 x ULN, bilirubin >1.5 x ULN, platelets <50,000/µL, HbA1c >8.5%, creatinine clearance <50 mL/min, haemoglobin <10 g/dL, albumin <3 g/dL, INR >1.5 x ULN, non-HCV chronic liver disease; infection with HBV or HIV; clinically relevant alcohol or drug abuse; use of systemic immunosuppressive agents; known hypersensitivity to study drugs; use of any prohibited concomitant medication			

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; GI, gastrointestinal; GT, genotype; HbA1c, haemoglobin A1c; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalised ratio; NS, nonstructural protein 5A; SOF, sofosbuvir; SVR, sustained virologic response; RNA, ribonucleic acid; ULN, upper limit of normal; VEL, velpatasvir; VOX, voxilaprevir.

Table 11: Detailed eligibility criteria

Trial no. (acronym)	GS-US-367-1171 (POLARIS-1)	GS-US-367-1170 (POLARIS-4)	GS-US-367-1172 (POLARIS-2)	GS-US-367-1173 (POLARIS-3)
Inclusion criteria				
HCV genotype	GT1, GT2, GT3, GT4, GT5, GT6 or indeterminate	GT1, GT2, GT3, GT4, GT5, GT6 or indeterminate	GT1, GT2, GT3, GT4, GT5, GT6 or indeterminate (GT3 patients with cirrhosis were excluded)	GT3 (non-cirrhotic GT3 patients were excluded)
Treatment experience	HCV treatment-experienced Treatment-experienced with an NS5A inhibitor-containing regimen of at least 4 weeks The most recent treatment was required to have been completed at least 8 weeks prior to screening Patients could not have discontinued the most recent regimen due to either an AE or virologic failure due to noncompliance The patient's medical records were required to include sufficient detail of prior treatment(s) to confirm eligibility	HCV treatment-experienced Treatment-experienced with a non-NS5A inhibitor DAA-containing regimen of at least 4 weeks. Patients who only had DAA exposure to a NS3/4A PI were excluded The most recent treatment was required to have been completed at least 8 weeks prior to screening Patients could not have discontinued the most recent regimen due to either an AE or virologic failure due to noncompliance The patient's medical records were required to include sufficient detail of prior treatment(s) to confirm eligibility	HCV treatment-naïve No prior exposure to any IFN, RBV, or other approved or experimental HCV-specific DAA HCV treatment-experienced IFN-based regimen and no prior exposure to an approved or experimental HCV-specific DAA The most recent treatment must have been completed at least 8 weeks prior to screening Patients must not have discontinued the most recent regimen due to either an AE or virologic failure due to noncompliance	
Cirrhosis determination	Presence of cirrhosis in approximately 30% of patients (POLARIS-1, -2 and -4) and 100% of patients (POLARIS-3). Cirrhosis was defined as any one of the following:			

	• Liver biopsy showing cirrhosis (METAVIR score = 4 or Ishak score ≥5) • FibroTest® score of >0.75 and an AST: APRI of >2 during screening • Transient elastography (Fibroscan®) with a result >12.5 kPa For POLARIS-1, -2 and -4 only: • Absence of cirrhosis was defined as any one of the following, unless the definition of cirrhosis was met: • Liver biopsy within 2 years of screening showing absence of cirrhosis • FibroTest® score of ≤0.48 and APRI of ≤1 during screening • Transient elastography (Fibroscan®) with a result of ≤12.5 kPa within 6 months of baseline/day 1
General inclusion criteria	Willing and able to provide written informed consent Aged ≥18 years BMI ≥18 kg/m^2 HCV RNA ≥104 IU/mL at screening Chronic HCV infection (≥6 months) determined by prior medical history or liver biopsy Females of childbearing potential were required to have a negative serum pregnancy test at screening and a negative urine pregnancy test on baseline/day 1 prior to enrolment Male patients and female patients of childbearing potential who engage in heterosexual intercourse had to agree to use protocol specified method(s) of contraception Lactating females had to agree to discontinue nursing before the study drug was administered General good health, with the exception of chronic HCV infection, as determined by the investigator Able to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments
Exclusion criteria	
General exclusion criteria	Current or prior history of any of the following: Clinically significant illness (other than HCV) or any other major medical disorder that may interfere with patient treatment, assessment or compliance with the clinical study protocol; patients under evaluation for a potentially clinically significant illness (other than HCV) were also excluded GI disorder or post-operative condition that could interfere with absorption of the study drug Difficulty with blood collection and/or poor venous access for the purposes of phlebotomy

	Hepatic decompensation (e.g. clinical ascites, encephalopathy, and/or variceal haemorrhage)
	Solid organ transplantation
	Significant cardiac disease
	Unstable psychiatric condition including hospitalisation, suicide attempt, and/or a period of disability as a result of psychiatric illness within 2 years prior to screening
	Malignancy within 5 years prior to screening, with the exception of specific cancers that have been cured by surgical resection (e.g. basal cell skin cancer). Patients under evaluation for possible malignancy were not eligible
	Significant drug allergy (e.g. anaphylaxis or hepatotoxicity)
	Screening ECG with clinically significant abnormalities
	Laboratory parameters at screening:
	ALT >10 x ULN
	AST >10 x ULN
	Direct bilirubin >1.5 x ULN
	Platelets <50,000/µl
	HbA_{1c} >8.5%
	CLcr <50 mL/min as calculated by the Cockcroft-Gault equation n
	Haemoglobin <10 g/dL
	Albumin <3 g/dL
	INR of prothrombin time >1.5 x ULN unless patient had known haemophilia or was stable on an anticoagulant regimen affecting INR
	Chronic liver disease of a non-HCV aetiology (e.g. hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, cholangitis)
	Infection with HBV or HIV
	Clinically-relevant alcohol or drug abuse within 12 months of screening. A positive drug screen excluded patients unless it was explained by a prescribed medication
	Use of any prohibited concomitant medications described in Table 9
	Known hypersensitivity to the study drug, the metabolites, or formulation excipient

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CLcr, creatinine clearance; DAA, direct acting antiviral; ECG, electrocardiogram; GI, gastrointestinal; GT, genotype; HbA1c, haemoglobin A1c; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; INR, international normalised ratio; NS5A, nonstructural protein 5A; RBV, ribavirin; RNA, ribonucleic acid; ULN, upper limit of normal

B.2.3.3. *Study outcomes*

The relevance of each outcome to the decision problem and their validity in current practice are presented in Table 12.

Table 12: Outcomes investigated in the POLARIS trials

Outcomes and measures	Included in NICE scope	Reliability/validity/current use in clinical practice
Primary outcome		
SVR12	Yes	SVR is the primary aim of treatment in clinical practice SVR12 is the established appropriate endpoint for regulatory approval and is accepted by the EMA and FDA
Secondary outcomes		
SVR4 and SVR24	Yes	Historically, SVR24 has been used as an endpoint for HCV studies to determine efficacy. However, SVR12 has been shown to have high concordance with SVR24 rates, based on clinical trial data of various treatment regimens and durations. SVR12 is now used as standard by regulatory authorities[a]
HCV RNA<LLOQ on treatment	No	The kinetics of circulating HCV RNA during treatment forms part of routine clinical practice with current treatments and is used to monitor and, for some HCV drugs, to guide treatment (referred to as response guided therapy). On-treatment viral kinetics do not inform treatment duration with SOF-based regimens
HCV RNA change from baseline to EOT		
Virologic failure	No	This outcome 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)
Deep sequencing of NS5A and NS5B regions of HCV RNA to detect resistance-associated variants that emerged during treatment	Yes	Deep sequencing refers to the number of times a nucleotide position in the HCV genome is read during the sequencing process. Sequencing accuracy is increased by sequencing individual HCV genomes a large number of times to identify low-frequency mutations. It is accepted by the regulatory authorities as a valid method for characterising low frequency mutations. It is not in use in clinical practice
Other outcomes of interest		

Outcomes and measures	Included in NICE scope	Reliability/validity/current use in clinical practice
ALT normalisation	No	In clinical practice, ALT is an important laboratory test marker for monitoring HCV disease activity. Treatment induced reductions in HCV viral load, and eradication of HCV from the patient, often lead to a normalisation of ALT levels, indicating a reduction in ongoing liver damage
HRQL outcomes	Yes	The following questionnaires were used to assess patients' HRQL: SF-36 CLDQ-HCV FACIT-F WPAI:Hep C All HRQL questionnaires are recognised and validated questionnaires

AE, adverse event; ALT, alanine aminotransferase; CLDQ-HCV, Chronic Liver Disease Questionnaire-Hepatitis C Virus; EMA, European Medicines Agency; EOT, end of treatment; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FDA, Food and Drug Administration; HCV, hepatitis C virus; HRQL, health related quality of life; LDV, ledipasvir; LLOQ, lower limit of quantitation; NS, non-structural; NS (3/4A/5A/5B), nonstructural protein (3/4A/5A/5B); RNA, ribonucleic acid; SF-36, Short Form Health Survey; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir; VOX, voxilaprevir; WPAI: Hep C, Work productivity and Activity Impairment: Hepatitis C.

[a] European Association for Study of Liver (8)

B.2.3.4. *Baseline characteristics and demographics*

Four Phase III trials were included in the clinical trial program for SOF/VEL/VOX. Other than POLARIS-1, the three other POLARIS trials had an active comparator (SOF/VEL). Patient baseline characterises were similar across trials and treatment groups. The majority of patients were male with an average age varying between 52 and 58 years. POLARIS-1 and POLARIS-4 represented a DAA experienced population, whereas the majority of patients in POLARIS-2 and POLARIS-3 were DAA naïve. 46% of patients in POLARIS-1 and POLARIS-4 had cirrhosis, which was greater than the minimum target of 30%, and reflects the enrichment for cirrhosis in the DAA-experienced population. In both POLARIS-1 and POLARIS-4 the majority patients had either HCV GT1 or GT4. Patients in POLARIS-1 failed prior treatment on NS5A+NS5B inhibitors. Patients in the POLARIS-4 trials were primarily treated with an NS5B inhibitor prior to trial initiation. POLARIS-2 and POLARIS-3 mainly comprised of a DAA naïve population. Patient's primarily suffered from HCV GT1 and GT3 and 18.5% of patient were cirrhotic. POLARIS-2 excluded all GT3 patients with cirrhosis, however, POLARIS-3 only considered this sub-group of patients. A comparative summary of patient baseline characteristics is provided Table 13. A detailed summary of patient baseline characteristics of each trial are included in Table 14 to Table 17.

Table 13: Comparative summary of patient baseline characteristics

Characteristic	SOF/VEL/VOX	Placebo	SOF/VEL
POLARIS-1			
Number of patients (N)	263	152	NA
Mean age (range), years	58 (27-84)	59 (29-80)	NA
Male, n (%)	200 (76.0)	121 (79.6)	NA
Mean BMI (range), kg/m^2	28.8 (18.4-66.7)	28.5 (18.0-61.2)	NA
HCV GT/subtype by sequencing			
GT 1, n (%)	150 (57.0)	150 (98.7)	NA
1a	101 (38.4)	117 (77.0)	NA
1b	45 (17.1)	31 (20.4)	NA
1 Other	4 (1.5)	2 (1.3)	NA
GT 2	5 (1.9)	0	NA
GT 3	78 (29.7)	0	NA
GT 4	22 (8.4)	0	NA
GT 5	1 (0.4)	0	NA
GT 6	6 (2.3)	2 (1.3)	NA
Unknown	1 (0.4)	0	NA
Cirrhosis, n (%)			
Yes	121 (46.0)	51 (33.6)	NA
No	142 (54.0)	101 (66.4)	NA
Baseline HCV RNA, log10 IU/mL, mean (SD)	6.3 (0.68)	6.3 (0.63)	NA
Baseline HCV RNA category			
<800,000 IU/mL, n (%)	73 (27.8)	36 (23.7)	NA
≥800,000 IU/mL, n (%)	190 (72.2)	116 (76.3)	NA
Baseline ALT (U/L), mean (SD)	89 (72.0)	74 (84.3)	NA
Baseline ALT category			
≤1.5 x ULN, n (%)	120 (45.6)	93 (61.2)	NA
>1.5 x ULN, n (%)	143 (54.4)	59 (38.8)	NA
Previous HCV treatment experience, n (%)			
Treatment-experienced	263 (100)	152 (100)	NA
DAA experienced	263 (100)	152 (100)	NA
NS5A +/- DAA(s)	262 (99.6)	151 (99.3)	NA
NS5A + NS5B	161 (61.2)	81 (53.3)	NA
NS5A + NS3 +/- NS5B	83 (31.6)	61 (40.1)	NA
NS5A +/- Other(s)	18 (6.8)	9 (5.9)	NA
Other(s)	1 (0.4)	1 (0.7)	NA
Number of Patients Receiving at Least One Concomitant Medication, n (%)	239 (90.9)	138 (90.8)	NA
POLARIS-4			
Number of patients (N)	182	NA	151
Mean age (range), years	57 (24-85)	NA	57 (24-80)
Male, n (%)	143 (78.6)	NA	114 (75.5)

Mean BMI (range), kg/m^2	28.7 (18.0-45.4)	NA	28.5 (17.8-53.3)
HCV GT/subtype by sequencing			
GT 1, n (%)	78 (42.9)	NA	66 (43.7)
1a	54 (29.7)	NA	44 (29.1)
1b	24 (13.2)	NA	22 (14.6)
1 Other	0	NA	0
GT 2	31 (17.0)	NA	33 (21.9)
GT 3	54 (29.7)	NA	52 (34.4)
GT 4	19 (10.4)	NA	0
GT 5	0	NA	0
GT 6	0	NA	0
Unknown	0	NA	0
Cirrhosis, n (%)			
Yes	84 (46.2)	NA	69 (45.7)
No	98 (53.8)	NA	82 (54.3)
Baseline HCV RNA, log10 IU/mL, mean (SD)	6.3 (0.56)	NA	6.3 (0.66)
Baseline HCV RNA category			
<800,000 IU/mL, n (%)	46 (25.3)	NA	38 (25.2)
≥800,000 IU/mL, n (%)	136 (74.7)	NA	113 (74.8)
Baseline ALT (U/L), mean (SD)	84 (65.0)	NA	85 (67.7)
Baseline ALT category			
≤1.5 x ULN, n (%)	88 (48.4)	NA	72 (47.7)
>1.5 x ULN, n (%)	94 (51.6)	NA	79 (52.3)
Previous HCV treatment experience, n (%)			
Treatment-experienced	182 (100)	NA	151 (100)
DAA naïve	0	NA	1 (0.7)
DAA experienced	182 (100)	NA	150 (99.3)
Non-NS5A +/- DAA(s)	182 (100)	NA	150 (99.3)
NS5B only	134 (73.6)	NA	109 (72.2)
NS5B + NS3	46 (25.3)	NA	38 (25.2)
Other(s)	2 (1.1)	NA	3 (2.0)
Number of Patients Receiving at Least One Concomitant Medication, n (%)	153 (84.14)	NA	132 (87.4)
POLARIS-2			
Number of patients (N)	501	NA	440
Mean age (range), years	53 (18-78)	NA	52 (19-82)
Male, n (%)	255 (50.9)	NA	237 (53.9)
Mean BMI (range), kg/m^2	26.9 (16.9-57.3)	NA	27.1 (17.9-54.0)
HCV GT/subtype by sequencing			
GT 1, n (%)	233 (46.5)	NA	232 (52.7)
1a	169 (33.7)	NA	172 (39.1)
1b	63 (12.6)	NA	59 (13.4)

1 Other	1 (0.2)	NA	1 (0.2)
GT 2	63 (12.6)	NA	53 (12.0)
GT 3	92 (18.4)	NA	89 (20.2)
GT 4	63 (12.6)	NA	57 (13.0)
GT 5	18 (3.6)	NA	0
GT 6	30 (6.0)	NA	9 (2.0)
Unknown	2 (0.4)	NA	0
Cirrhosis, n (%)			
Yes	90 (18.0)	NA	84 (19.1)
No	411 (82.0)	NA	356 (80.9)
Baseline HCV RNA, log10 IU/mL, mean (SD)	6.1 (0.75)	NA	6.2 (0.7)
Baseline HCV RNA category			
<800,000 IU/mL, n (%)	155 (30.9)	NA	138 (31.4)
≥800,000 IU/mL, n (%)	346 (69.1)	NA	302 (68.6)
Baseline ALT (U/L), mean (SD)	65 (57.4)	NA	69 (54.2)
Baseline ALT category			
≤1.5 x ULN, n (%)	295 (58.9)	NA	243 (55.2)
>1.5 x ULN, n (%)	206 (41.1)	NA	197 (44.8)
Previous HCV treatment experience, n (%)			
Treatment-naïve	383/501 (76.4)	NA	340/440 (77.3)
Treatment-experienced	118/501 (23.6)	NA	100/440 (22.7)
DAA Naïve			
Peg-IFN+RBV	93/118 (78.8)	NA	81/100 (81.0)
Other	25/118 (21.2)	NA	19/100 (19.0)
Number of Patients Receiving at Least One Concomitant Medication, n (%)	431 (86.0)	NA	361 (82.0)
POLARIS-3			
Number of patients (N)	110	NA	109
Mean age (range), years	54 (25-75)	NA	55 (31-69)
Male, n (%)	74 (67.3)	NA	83 (76.1)
Mean BMI (range), kg/m^2	28.3 (19.6-50.4)	NA	27.8 (17.8-50.4)
HCV GT/subtype by sequencing			
GT 3	110 (100.0)	NA	109 (100.0)
Cirrhosis, n (%)			
Yes	110 (100)	NA	109 (100)
No	0	NA	0
Baseline HCV RNA, log10 IU/mL, mean (SD)	6.0 (0.80)	NA	6.3 (0.63)
Baseline HCV RNA category			
<800,000 IU/mL, n (%)	40 (36.4)	NA	28 (25.7)
≥800,000 IU/mL, n (%)	70 (63.6)	NA	81 (74.3)
Baseline ALT (U/L), mean (SD)	111 (62.2)	NA	132 (74.6)
Baseline ALT category			

≤1.5 x ULN, n (%)	20 (18.2)	NA	20 (18.3)
>1.5 x ULN, n (%)	90 (81.8)	NA	89 (81.7)
Previous HCV treatment experience, n (%)			
Treatment-naïve	75/110 (68.2)	NA	77/109 (70.6)
Treatment-experienced	35/110 (31.8)	NA	32/109 (29.4)
Peg-IFN+RBV	31/35 (88.6)	NA	30/32 (93.8)
Other	4/35 (11.4)		2/32 (6.3)
Number of Patients Receiving at Least One Concomitant Medication, n (%)	153 (84.1)	NA	132 (87.4)

B.2.3.4.1. POLARIS-1

In POLARIS-1, demographics and baseline characteristics were generally balanced across both treatment groups (Table 14). Overall, the majority of patients were male (77.3%) and white (80.7%), with a mean age of 58 years (range: 27-84). Just over half of patients were from the United States (US) (51.3%). In the SOF/VEL/VOX 12 week group, the majority of patients had GT1 HCV infection (57.0%) or GT3 HCV infection (29.7%), and most of the patients (82.1%) had a non-CC IL28B genotype (CT = 62.7%, TT = 19.4%). A greater number of patients with GT1 HCV infection and fewer patients with GT2, 3, 4, 5, 6, and unknown HCV infection were enrolled into the SOF/VEL/VOX 12 week group than planned according to protocol specification. This is likely due to the current GT distribution of patients with ongoing HCV infection who have been exposed to an NS5A inhibitor.

In the SOF/VEL/VOX 12 week group, 121 patients (46.0%) had cirrhosis, which was higher than the minimum target of 30%, and reflects the enrichment for cirrhosis in the DAA-experienced population. In the SOF/VEL/VOX 12 week group, the mean (SD) baseline HCV ribonucleic acid (RNA) was 6.3 (0.68) log10 IU/mL, and most patients had baseline HCV RNA ≥800,000 IU/mL (72.2%). The mean baseline alanine aminotransferase (ALT) value was 89 (72.0) U/L, and 54.4% of patients had baseline ALT values >1.5 x upper limit of normal (ULN).

In the SOF/VEL/VOX 12 week group, 99.6% had been previously treated with an NS5A inhibitor and the most common NS5A inhibitors were ledipasvir (LDV) (50.6%, 133 of 263 patients), daclatasvir (DCV) (26.6%, 70 of 263 patients) and ombitasvir (OMB) (11.4%, 30 of 263 patients): 61.2% of patients had failed prior treatment with an NS5A+NS5B inhibitor (most common regimen was LDV+SOF; 113 patients), 31.6% of patients had failed prior treatment with an NS5A+NS3 inhibitor with or without an NS5B inhibitor, and 6.8% of patients had failed prior treatment with an NS5A inhibitor without other DAAs. One patient (0.4%) had failed prior single treatment with an NS5B inhibitor (SOF).

Table 14: POLARIS-1: Characteristics of participants (SAS)

Characteristic	SOF/VEL/VOX N=263	Placebo N=152
Mean age (range), years	58 (27-84)	59 (29-80)
Male, n (%)	200 (76.0)	121 (79.6)

Characteristic	SOF/VEL/VOX N=263	Placebo N=152
Mean BMI (range), kg/m2	28.8 (18.4-66.7)	28.5 (18.0-61.2)
Race, n (%)		
White	211 (80.2)	124 (81.6)
Black	38 (14.4)	22 (14.5)
Asian	8 (3.0)	6 (3.9)
Native Hawaiian or Pacific Islander	3 (1.1)	0
Not disclosed	1 (0.4)	0
American Indian or Alaska Native	1 (0.4)	0
Other	1 (0.4)	0
HCV GT/subtype by sequencing		
GT 1, n (%)	150 (57.0)	150 (98.7)
1a	101 (38.4)	117 (77.0)
1b	45 (17.1)	31 (20.4)
1 Other	4 (1.5)	2 (1.3)
GT 2	5 (1.9)	0
GT 3	78 (29.7)	0
GT 4	22 (8.4)	0
GT 5	1 (0.4)	0
GT 6	6 (2.3)	2 (1.3)
Unknown	1 (0.4)	0
Cirrhosis, n (%)		
Yes	121 (46.0)	51 (33.6)
No	142 (54.0)	101 (66.4)
IL28B genotype, n (%)		
CC	47 (17.9)	27 (17.8)
Non-CC	216 (82.1)	125 (82.2)
CT	165 (62.7)	93 (61.2)
TT	51 (19.4)	32 (21.1)
Baseline HCV RNA, log10 IU/mL, mean (SD)	6.3 (0.68)	6.3 (0.63)
Baseline HCV RNA category		
<800,000 IU/mL, n (%)	73 (27.8)	36 (23.7)
≥800,000 IU/mL, n (%)	190 (72.2)	116 (76.3)
Baseline ALT (U/L), mean (SD)	89 (72.0)	74 (84.3)
Baseline ALT category		
≤1.5 x ULN, n (%)	120 (45.6)	93 (61.2)
>1.5 x ULN, n (%)	143 (54.4)	59 (38.8)

Characteristic	SOF/VEL/VOX N=263	Placebo N=152
Previous HCV treatment experience, n (%)		
Treatment-experienced	263 (100)	152 (100)
DAA experienced	263 (100)	152 (100)
NS5A +/- DAA(s)	262 (99.6)	151 (99.3)
NS5A + NS5B	161 (61.2)	81 (53.3)
NS5A + NS3 +/- NS5B	83 (31.6)	61 (40.1)
NS5A +/- Other(s)	18 (6.8)	9 (5.9)
Other(s)	1 (0.4)	1 (0.7)
Estimated GFR (mL/min), mean (SD)	119.2 (35.7)	113.1 (33.6)

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), nonstructural protein (3/4A/5A/5B); RNA, ribonucleic acid; SOF, sofosbuvir; SD, standard deviation; ULN, upper limit of normal; VEL, velpatasvir; VOX, voxilaprevir.

B.2.3.4.2. POLARIS-4

In POLARIS-4, demographics and baseline characteristics were generally balanced across both treatment groups (Table 15). Overall, the majority of patients were male (77.2%), white (87.4%), and non-Hispanic/Latino (91.9%). The mean age was 57 years (range: 24-85).

Most patients had GT1 (43.2% [1a, 29.4%; 1b, 13.8%]) or GT3 (31.8%) HCV infection. Patients with GT4 HCV infection (5.7%) were enrolled into the SOF/VEL/VOX 12 week group according to the clinical study protocol specification. No patients with GT5 or GT6 HCV infection were enrolled into this study. Most patients (81.4%) had a non-CC IL28B genotype.

Overall, the mean (SD) baseline HCV RNA value was 6.3 (0.61) log10 IU/mL and most patients had HCV RNA ≥800,000 IU/mL (74.8%). Overall, 45.9% of patients had cirrhosis, which was higher than the minimum enrolment target of 30% and reflects the enrichment of cirrhosis in the DAA-experienced patient population. The mean (SD) baseline ALT value was 84 (66.1) U/L, and 48.0% of patients had baseline ALT values ≤1.5 x ULN. The mean (SD) baseline eGFR using the Cockcroft-Gault equation was 123.5 (37.13) mL/min.

Most patients (73.0%) had been previously treated with a NS5B inhibitor only; 25.2% of patients had been previously treated with a combination of a NS5B inhibitor and NS3 inhibitor.

Table 15: POLARIS-4: Characteristics of participants (SAS)

Characteristic	SOF/VEL/VOX 12 weeks N=182	SOF/VEL 12 weeks N=151
Mean age (range), years	57 (24-85)	57 (24-80)
Male, n (%)	143 (78.6)	114 (75.5)
Mean BMI (range), kg/m^2	28.7 (18.0-45.4)	28.5 (17.8-53.3)
Race, n (%)		

White	160 (87.9)	131 (86.8)
Black	16 (8.8)	13 (8.6)
Asian	2 (1.1)	4 (2.6)
Other	2 (1.1)	4 (2.6)
American Indian or Alaska Native	2 (1.1)	0
Native Hawaiian or Pacific Islander	0	2 (1.3)
HCV GT/subtype by sequencing		
GT 1, n (%)	78 (42.9)	66 (43.7)
1a	54 (29.7)	44 (29.1)
1b	24 (13.2)	22 (14.6)
GT 2	31 (17.0)	33 (21.9)
GT 3	54 (29.7)	52 (34.4)
GT 4	19 (10.4)	0
Cirrhosis, n (%)		
Yes	84 (46.2)	69 (45.7)
No	98 (53.8)	82 (54.3)
IL28B genotype, n (%)		
CC	33 (18.1)	29 (19.2)
Non-CC	149 (81.9)	122 (80.8)
CT	107 (58.8)	95 (62.9)
TT	42 (23.1)	27 (17.9)
Baseline HCV RNA, log10 IU/mL, mean (SD)	6.3 (0.56)	6.3 (0.66)
Baseline HCV RNA category		
<800,000 IU/mL, n (%)	46 (25.3)	38 (25.2)
≥800,000 IU/mL, n (%)	136 (74.7)	113 (74.8)
Baseline ALT (U/L), mean (SD)	84 (65.0)	85 (67.7)
Baseline ALT category		
≤1.5 x ULN, n (%)	88 (48.4)	72 (47.7)
>1.5 x ULN, n (%)	94 (51.6)	79 (52.3)
Previous HCV treatment experience, n (%)		
Treatment-experienced	182 (100)	151 (100)
DAA naïve	0	1 (0.7)
DAA experienced	182 (100)	150 (99.3)
Non-NS5A +/- DAA(s)	182 (100)	150 (99.3)
NS5B only	134 (73.6)	109 (72.2)
NS5B + NS3	46 (25.3)	38 (25.2)
Other(s)	2 (1.1)	3 (2.0)
Estimated GFR (mL/min), mean (SD)	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), nonstructural protein (3/4A/5A/5B); RNA, ribonucleic acid; SOF, sofosbuvir; SD, standard deviation; ULN, upper limit of normal; VEL, velpatasvir; VOX, voxilaprevir.

B.2.3.4.3. POLARIS-2

In POLARIS-2, demographics and baseline characteristics were generally balanced across both treatment groups (Table 16). Overall, the majority of patients were male (52.3%) and white (80.3%), with a mean age of 52 years (range: 18-82). The majority of patients were from the US (58.7%).

The majority of patients had GT1 (49.4% [1a = 36.2%, 1b = 13.0%, 1 other = 0.2%] or GT3 (19.2%) HCV infection; 12.3% of patients had GT2, 12.8% had GT4, 1.9% had GT5, and 4.1% had GT6. Two patients (0.2%), both in the SOF/VEL/VOX 8 week group, had unknown HCV genotype. All of the patients with GT5 HCV infection and most of the patients with GT6 HCV infection were enrolled in the SOF/VEL/VOX 8 week group, in accordance with the protocol enrolment specifications; 9 patients with GT6 HCV infection were enrolled in the SOF/VEL 12 week group due to the inability of the screening assay to determine HCV GT6. Most of the patients (67.9%) had a non-CC IL28B genotype (CT = 52.9%, TT = 15.0%). Overall, 18.5% of patients had cirrhosis. Patients with GT3 HCV infection and cirrhosis were excluded from this study. These patients became eligible for participation in another study (Study GS-US-367-1173; POLARIS-3).

Table 16: POLARIS-2: Characteristics of participants (SAS)

Characteristic	**SOF/VEL/VOX N=501**	**SOF/VEL N=440**
Mean age (range), years	53 (18-78)	52 (19-82)
Male, n (%)	255 (50.9)	237 (53.9)
Mean BMI (range), kg/m^2	26.9 (16.9-57.3)	27.1 (17.9-54.0)
Race, n (%)		
White	391 (78.0)	365 (83.0)
Black	48 (9.6)	47 (10.7)
Asian	51 (10.2)	22 (5.0)
Other	5 (1.0)	2 (0.5)
American Indian or Alaska Native	3 (0.6)	2 (0.5)
Native Hawaiian or Pacific Islander	3 (0.6)	2 (0.5)
HCV GT/subtype by sequencing		
GT 1, n (%)	233 (46.5)	232 (52.7)
1a	169 (33.7)	172 (39.1)
1b	63 (12.6)	59 (13.4)
1 Other	1 (0.2)	1 (0.2)
GT 2	63 (12.6)	53 (12.0)
GT 3	92 (18.4)	89 (20.2)
GT 4	63 (12.6)	57 (13.0)
GT 5	18 (3.6)	0
GT 6	30 (6.0)	9 (2.0)
Unknown	2 (0.4)	0
Cirrhosis, n (%)		
Yes	90 (18.0)	84 (19.1)
No	411 (82.0)	356 (80.9)
IL28B genotype, n (%)		
CC	166 (33.1)	136 (30.9)
Non-CC	335 (66.9)	304 (69.1)

CT	253 (50.5)	245 (55.7)
TT	82 (16.4)	59 (13.4)
Baseline HCV RNA, log10 IU/mL, mean (SD)	6.1 (0.75)	6.2 (0.7)
Baseline HCV RNA category		
<800,000 IU/mL, n (%)	155 (30.9)	138 (31.4)
≥800,000 IU/mL, n (%)	346 (69.1)	302 (68.6)
Baseline ALT (U/L), mean (SD)	65 (57.4)	69 (54.2)
Baseline ALT category		
≤1.5 x ULN, n (%)	295 (58.9)	243 (55.2)
>1.5 x ULN, n (%)	206 (41.1)	197 (44.8)
Type of previous HCV treatment, n/total (%)		
Treatment-naïve	383/501 (76.4)	340/440 (77.3)
Treatment-experienced	118/501 (23.6)	100/440 (22.7)
DAA Naïve		
Peg-IFN+RBV	93/118 (78.8)	81/100 (81.0)
Other	25/118 (21.2)	19/100 (19.0)
Estimated GFR (mL/min), mean (SD)	111.2 (34.4)	111.5 (33.8)

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; Peg-IFN, pegylated interferon; ribonucleic acid; RNA, ribonucleic acid; SOF, sofosbuvir; SD, standard deviation; ULN, upper limit of normal; VEL, velpatasvir; VOX, voxilaprevir.

B.2.3.4.4. POLARIS-3

In POLARIS-3, demographics and baseline characteristics were generally balanced across both treatment groups (Table 17). Overall, the majority of patients were male (71.7% and white (90%), with a mean age of 55 years (range: 25-75). All patients had GT3 CHC infection. The majority of patients (57.5%) had non-CC IL28B genotype (CT = 46.1%, TT = 11.4%). 100% had cirrhosis at screening. Overall, 30.6% (67 of 219 patients) of patients had prior treatment with an IFN-based regimen; the majority of these patients (91.0%; 61 of 67 patients) had failed prior treatment with Peg-IFN+RBV.

Table 17: POLARIS-3: Characteristics of participants (SAS)

Characteristic	**SOF/VEL/VOX N=110**	**SOF/VEL N=109**
Mean age (range), years	54 (25-75)	55 (31-69)
Male, n (%)	74 (67.3)	83 (76.1)
Mean BMI (range), kg/m^2	28.3 (19.6-50.4)	27.8 (17.8-50.4)
Race, n (%)		
White	100 (90.9)	97 (89.0)
Black	0	1 (0.9)
Asian	8 (7.3)	9 (8.3)
American Indian or Alaska Native	1 (0.9)	1 (0.9)
Black or African American	0	1 (0.9)
Native Hawaiian or Pacific Islander	0	1 (0.9)
Other	1 (0.9)	0

HCV Genotype by Sequencing		
GT3	110 (100.0)	109 (100.0)
Cirrhosis, n (%)		
Yes	110 (100)	109 (100)
No	0	0
IL28B genotype, n (%)		
CC	41 (37.3)	52 (47.7)
Non-CC	69 (62.7)	57 (52.3)
CT	57 (51.7)	44 (40.4)
TT	12 (10.9)	13 (11.9)
Baseline HCV RNA, log10 IU/mL, mean (SD)	6.0 (0.80)	6.3 (0.63)
Baseline HCV RNA category		
<800,000 IU/mL, n (%)	40 (36.4)	28 (25.7)
≥800,000 IU/mL, n (%)	70 (63.6)	81 (74.3)
Baseline ALT (U/L), mean (SD)	111 (62.2)	132 (74.6)
Baseline ALT category		
≤1.5 x ULN, n (%)	20 (18.2)	20 (18.3)
>1.5 x ULN, n (%)	90 (81.8)	89 (81.7)
Type of previous HCV treatment, n/total (%)		
Treatment-naïve	75/110 (68.2)	77/109 (70.6)
Treatment-experienced	35/110 (31.8)	32/109 (29.4)
Peg-IFN+RBV	31/35 (88.6)	30/32 (93.8)
Other	4/35 (11.4)	2/32 (6.3)
Estimated GFR (mL/min), mean (SD)	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; Peg-IFN, pegylated interferon; ribonucleic acid; RNA, ribonucleic acid; SOF, sofosbuvir; SD, standard deviation; ULN, upper limit of normal; VEL, velpatasvir; VOX, voxilaprevir.

B.2.4. *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

Analysis sets

The main analysis sets in the POLARIS RCTs are defined below.

Full analysis set (FAS): All patients who were randomised or enrolled into the study and received at least 1 dose of study drug. Patients were grouped within the FAS by the treatment group to which they were randomised or enrolled. The FAS was the primary analysis set for efficacy analyses.

Safety analysis set (SAS): Patients who were randomised into the study and received at least 1 dose of study drug. Patients were grouped by the treatment group to which they were randomised. The SAS was the primary analysis set for safety analyses.

A summary of statistical analyses completed for each of the POLARIS trials is presented in Table 18.

Table 18: Summary of statistical analyses

Trial no. (acronym)	Hypothesis objective	Statistical analysis of primary endpoint	Statistical analysis of secondary efficacy endpoints	Sample size, power calculation	Data management, patient withdrawals
GS-US-367-1171 (POLARIS-1) CHC GT1-6	The primary efficacy hypothesis was that the rate of SVR12 among patients receiving SOF/VEL/VOX would be superior to the pre-specified SVR of 85%	• The SVR12 rate in the SOF/VEL/VOX 12 week group was compared with the performance goal of 85% using a 2-sided exact 1-sample binomial test at the 0.05 significance level • A 2-sided 1-sample exact binomial test was used to test the statistical hypothesis. The point estimate and the 2-sided 95% exact CI for SVR12 rate based on the Clopper-Pearson method was provided for the SOF/VEL/VOX 12 week group • The point estimate and the 2-sided 95% exact CI for SVR4 rate based on Clopper-Pearson method was provided for the Placebo 12 week group	• Proportion of patients with SVR4 and SVR24: SVR4 and SVR24 results were summarised. ○ In POLARIS-1 the SOF/VEL/VOX 12 week group was further broken down by HCV GT (1 [1a, 1b, or 1 other], 2, 3, 4, 5, 6 and other) for patients with both observed SVR12 and observed SVR24 data ○ In POLARIS-4 a concordance table between SVR12 and SVR24 by HCV GT (1 [1a, 1b, or 1 other], 2, 3, 4, 5, 6 and other) and overall for each treatment group is provided for patients with both observed SVR12 and observed SVR24 data ○ In POLARIS-2 a concordance table between SVR12 and SVR24 by HCV GT (1 [1a, 1b], 2, 3, 4, 5, 6 and other) and overall for each treatment group is provided for patients with both observed SVR12 and observed SVR24	A sample size of 280 patients in the SOF/VEL/VOX week 12 group provided >90% power to detect an improvement in SVR12 rate from the performance goal of 85% to 95% using a 2-sided exact 1-sample binomial test at the 0.05 significance level	• Values for missing data were not imputed for any outcomes except HCV RNA and post-treatment HRQL data • For categorical HCV RNA data, if a data point was missing, and was preceded and followed by values that were a success (<LLOQ TND and/or <LLOQ detected) then the missing data point was termed a bracketed success; otherwise the data point was termed a bracketed failure (≥LLOQ detected), otherwise, the data point was termed a bracketed failure (i.e. ≥LLOQ detected) • Missing on-treatment HCV RNA data was imputed up to the time of the last dose (for on-treatment displays). If the study day associated with the last dose date of any study drug was greater than or equal to the lower
GS-US-367-1170 (POLARIS-4) CHC GT1-6	The primary efficacy hypothesis was that the rate of SVR12 among patients receiving SOF/VEL/VOX and SOF/VEL would be superior to the pre-specified SVR of 85%	• The SVR12 rate for the SOF/VEL/VOX 12 week and SOF/VEL 12 week groups were compared with the performance goal of 85% using a 2-sided exact 1-sample binomial test at the 0.025 significance level • A 2-sided 1-sample binomial test was used to test the statistical hypotheses. The 2-sided 95% exact CI based on the Clopper-Pearson method was determined for the SVR12 rate for each treatment group		A sample size of 205 patients in the SOF/VEL/VOX 12 week group and 175 patients in SOF/VEL 12 week group provided >90% power to detect an improvement in SVR12 rate from 85% to 95% using a 2-sided exact 1-sample binomial test at the 0.025 significance level	

Trial no. (acronym)	Hypothesis objective	Statistical analysis of primary endpoint	Statistical analysis of secondary efficacy endpoints	Sample size, power calculation	Data management, patient withdrawals
GS-US-367-1172 (POLARIS-2) CHC GT1-6	The primary efficacy endpoint was SVR12 among patients receiving SOF/VEL/OX would be non-inferior to that among patients receiving SOF/VEL	• Non-inferiority was demonstrated (i.e. non-inferiority null hypothesis was rejected) if the lower bound of the 2-sided 95% CI for the difference in SVR12 rates was >−5.0% • If non-inferiority was demonstrated, the p-value associated with the test of superiority of SOF/VEL/VOX for 8 weeks versus SOF/VEL for 12 weeks was calculated, using the CMH test statistic for stratified proportions. If the Mantel-Fleiss criterion was not met, the exact CMH test was used. Superiority was demonstrated if the 2-sided p-value was <0.05 • Point estimates and 2-sided 95% exact CIs for SVR12 based on the Clopper-Pearson method were provided for each treatment group	data • Proportion of patients with HCV RNA<LLOQ by study visit: Two-sided 95% exact CI based on the Clopper-Pearson method are provided for the percentage of patients with HCV RNA<LLOQ at each visit by treatment group. 'HCV RNA <LLOQ' was split into 2 categories: <LLOQ TND (for patients with target not detected) and <LLOQ detected (for patients with <LLOQ) ○ In POLARIS-1 the SOF/VEL/VOX 12 week group was further broken down by HCV GT(1 [1a, 1b, or 1 other], 2, 3, 4, 5, 6 and other) ○ In POLARIS-4 treatment groups were further broken down by HCV GT (1 [1a, 1b, or 1 other], 2, 3, 4, 5, 6 and other) ○ In POLARIS-2 treatment groups were further broken down by HCV GT (1 [1a, 1b], 2, 3, 4, 5, 6, and other) • HCV RNA absolute values and change from baseline: Summary statistics are presented by visit through to EOT. Imputation rules (described further in "data management, patient	A total sample size of 780, including 405 in the SOF/VEL/VOX 8 week group and 375 patient in SOF/VEL 12 week group, patients was calculated to provide >95% power to establish non-inferiority of SVR12 between the 2 groups, on the basis of an SVR rate of 97%, using a 1-sided test at significant level of 0.025	bound of a visit window and the value at the visit was missing, the value was imputed • If the study day associated with the last dose date was less than the lower bound of a visit window, the on-treatment value at that visit remained missing • If HCV RNA data were missed and were not bracketed, the missing data point was termed a failure (≥LLOQ detected), except for SVR24 which was imputed according to SVR12 status, due to the high correlation between SVR12 and SVR24 • For continuous HCV RNA efficacy data, missing values in a visit window which were bracketed by values that were a success (<LLOQ TND or <LLOQ detected) were set to LLOQ - 1 IU/m. No other imputations were performed for continuous data • For HRQL data, missing data at on-treatment visits and
GS-US-367-1173 (POLARIS-3) CHC GT 3	The primary efficacy endpoint of SVR12 among patients receiving SOF/VEL/VOX and SOF/VEL was compared to the pre-specified SVR of 83%	• The SVR12 rate in each of the 2 treatment groups was compared to the performance goal of 83% using a 2-sided exact 1-sample binomial test following a sequential testing procedure • If and only if the primary test for SVR12 rate in the SOF/VEL/VOX 8 week group comparing with 83% was statistically significant at the 0.05 significance level, the SVR12 rate in the SOF/VEL 12 week group was compared with 83% at the 0.05 significance level • The 2-sided 95% CI exact based		A total sample size of 200, including 100 in the SOF/VEL/VOX 8 week group and 100 patient in SOF/VEL 12 week group, patients was calculated to provide >80% power to detect an improvement in SVR12 rate from 83% to 93% using a 2-sided exact 1-sample binomial test at a significance level of 0.05	

Trial no. (acronym)	Hypothesis objective	Statistical analysis of primary endpoint	Statistical analysis of secondary efficacy endpoints	Sample size, power calculation	Data management, patient withdrawals
		on Clopper-Pearson method was provided for the SVR12 rate within each treatment group and subgroup	withdrawals" later in this table) were used to assign HCV RNA values for missing values at a visit that was preceded and followed by <LLOQ TND and/or <LLOQ detected. Otherwise, a missing = excluded analysis was performed ○ In POLARIS-1 the SOF/VEL/VOX 12 week group was further broken down by HCV GT (1 [1a, 1b, or 1 other], 2, 3, 4, 5, 6 and other) ○ In POLARIS-4 treatment groups were further broken down by HCV GT (1 [1a, 1b, or 1 other], 2, 3, 4, 5, 6 and other) ○ In POLARIS-2 treatment groups were further broken down by HCV GT (1 [1a, 1b], 2, 3, 4, 5, 6 and other) • Virologic failure: Patients who did not achieve SVR12 and did not meet criteria for virologic failure were categorised as 'other': virologic failure (breakthrough, rebound, and nonresponse) and relapse were defined as follows: ○ On treatment virological failure: ▪ Breakthrough: HCV RNA ≥LLOQ after having previously had		post-treatment week 4 and week 12 visit were not imputed. The last post-treatment observation carried forward was used for imputation of missing data at the post-treatment week 24 visit

Trial no. (acronym)	Hypothesis objective	Statistical analysis of primary endpoint	Statistical analysis of secondary efficacy endpoints	Sample size, power calculation	Data management, patient withdrawals
			HCV RNA<LLOQ, while on treatment, confirmed with 2 consecutive values (the second confirmation value could have been post-treatment) or last available on-treatment measurement with no subsequent follow-up values ▪ Rebound: 1 log_{10} IU/mL increase in HCV RNA from baseline while on treatment, confirmed with 2 consecutive values (the second confirmation value could have been post-treatment), or last available on-treatment measurement with no subsequent follow-up values ▪ Nonresponse: HCV RNA persistently ≥LLOQ through 8 weeks of treatment ○ Relapse: ▪ HCV RNA ≥LLOQ during the post-treatment period having achieved HCV RNA<LLOQ at EOT, confirmed with 2 consecutive values or the last available post-treatment measurement		

Trial no. (acronym)	Hypothesis objective	Statistical analysis of primary endpoint	Statistical analysis of secondary efficacy endpoints	Sample size, power calculation	Data management, patient withdrawals
			▪ In POLARIS-1 the SOF/VEL/VOX group was further broken down by HCV GT (1 [1a, 1b, or 1 other], 2, 3, 4, 5, 6 and other) ▪ In POLARIS-4 treatment groups were further broken down by HCV GT (1 [1a, 1b, or 1 other], 2, 3, 4, 5, 6 and other) ▪ In POLARIS-2 treatment groups were further broken down by HCV GT (1 [1a, 1b], 2, 3, 4, 5, 6 and other) ▪ Virologic resistance analysis: Results for the HCV drug resistance-associated variants at baseline, during study drug dosing, and after study drug dosing were reported. Results for HCV drug resistance substitutions through post-treatment week 12 were summarised HRQL: for all HRQL tools, transformed scale scores (0 to 100) and changes from baseline were calculated. Wilcoxon signed rank test was used to explore within treatment group changes in status from		

Trial no. (acronym)	Hypothesis objective	Statistical analysis of primary endpoint	Statistical analysis of secondary efficacy endpoints	Sample size, power calculation	Data management, patient withdrawals
			baseline to each of the time points, and from EOT to post treatment time points. A Wilcoxon rank sum test was used to explore differences between treatment groups in change in status from baseline to each of the post treatment time points. A plot of mean±SD of change from baseline in summary scores was also presented. P-values should be interpreted with caution as multiple endpoints are being tested, and the study was not powered to test these exploratory endpoints		

CHC, chronic hepatitis C; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; EOT, end of treatment; FAS, full analysis set; GT, genotype; HCV, hepatitis C virus; HRQL, health-related quality of life; IU, international unit; LLOQ, lower limit of quantitation; RNA, ribonucleic acid; SD, standard deviation; SOF, sofosbuvir; SVR, sustained virologic response; TND, target not detected; VEL, velpatasvir; VOX, voxilaprevir.

B.2.5. *Quality assessment of the relevant clinical effectiveness evidence*

Table 19: Quality assessment of the relevant clinical effectiveness evidence

	GS-US-367-1171 (POLARIS-1) CHC GT1-6	**GS-US-367-1170 (POLARIS-4) CHC GT1-6**	**GS-US-367-1172 (POLARIS-2) CHC GT1-6**	**GS-US-367-1173 (POLARIS-3) CHC GT3**
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	No	No	No
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes

B.2.6. *Clinical effectiveness results of the relevant trials*

B.2.6.1. *POLARIS-1*

B.2.6.1.1. Primary efficacy results: SVR12

The primary efficacy endpoint was SVR12, defined as HCV RNA<LLOQ 12 weeks after discontinuation of the study drug, in the SOF/VEL/VOX 12 week group in the FAS. The primary efficacy endpoint analysis for SVR12 was conducted after all patients in the SOF/VEL/VOX 12 week group completed the post-treatment week 12 visit or prematurely discontinued from the study, and after all patients in the Placebo 12 week group completed the post-treatment week 4 visit or prematurely discontinued from the study. Primary efficacy results for POLARIS-1 are presented in Table 20.

The proportion of patients who achieved SVR12 following treatment with SOF/VEL/VOX for 12 weeks was 96.2% (253 of 263; 95% CI: 93.1 to 98.2).

The SOF/VEL/VOX 12 week group met the primary endpoint of an SVR12 rate that was statistically superior relative to the pre-specified SVR12 performance goal of 85% (p<0.001). No patients in the Placebo 12 week group (0 of 152) achieved SVR4.

Table 20: POLARIS-1: Proportion of patients who achieve SVR12 in the SOF/VEL/VOX 12 week group (FAS)

	SOF/VEL/VOX 12 weeks N=263
At week 12 (SVR12), n/N (%)	253/263 (96.2)
95% CI	93.1 to 98.2
p-value (compared with 85%)	<0.001

CI, confidence interval; LLOQ, lower limit of quantitation; SOF, sofosbuvir; SVR, sustained virologic response; TND, target not detected; VEL, velpatasvir; VOX, voxilaprevir.
A missing SVR12 value is imputed as a success if it is bracketed by values that are termed successes (i.e. '<LLOQ TND' or '<LLOQ detected'), otherwise, the missing SVR12 value is imputed as a failure. The exact 95% CI for the proportion within treatment group is based on the Clopper-Pearson method. The p-value is obtained from the 2-sided exact 1-sample binomial test for the superiority over the performance goal of 85%.

B.2.6.1.2. Secondary efficacy outcomes

Proportion of patients with SVR at 4 and 24 weeks

Overall, SVR4 results (Table 21) were the same as the SVR12 results for patients in the SOF/VEL/VOX 12 week group, with the exception of 4 patients (3 who relapsed and 1 who withdrew consent). SVR24 results are currently not available.

Table 21: POLARIS-1: SVR at post-treatment follow-up in the SOF/VEL/VOX 12 week group (FAS)

	SOF/VEL/VOX 12 weeks N=263	Placebo 12 weeks N=152
Post-treatment, n/N (%)		
SVR4	257/263 (97.7)	0/152
95% CI	95.1 to 99.2	0.0 to 2.4
SVR12	253/263 (96.2)	0/152
95% CI	93.1 to 98.2	0.0 to 2.4
SVR24[a]	-	-

CI, confidence interval; LLOQ, lower limit of quantitation; SOF, sofosbuvir; SVR, sustained virologic response; TND, target not detected; VEL, velpatasvir; VOX, voxilaprevir.
A missing SVR value is imputed as a success if it is bracketed by values that are termed successes (i.e. '<LLOQ TND' or '<LLOQ detected'), otherwise, the missing SVR value is imputed as a failure. The exact 95% CI for the proportion within treatment group is based on the Clopper-Pearson method.
[a] SVR24 data for POLARIS-1 will not be available until 2018.

Proportion of patients with HCV RNA<LLOQ on treatment

Potent and rapid suppression of HCV RNA while on treatment was observed in all patients across all HCV genotypes in patients who received SOF/VEL/VOX for 12 weeks. At week 1, 15.6% of patients in the SOF/VEL/VOX 12 week group had HCV RNA<LLOQ. At weeks 2 and 4, 56.7% and 92.7% of patients had HCV RNA<LLOQ, respectively. Early viral response had no impact on SVR12 rates. Nineteen patients in the SOF/VEL/VOX 12 week group had HCV RNA>LLOQ at week 4 and all achieved SVR12. Table 22 summarises the proportion of patients with HCV RNA<LLOQ on treatment at weeks 2, 4, 6, and 8.

Table 22: POLARIS-1: Proportion of patients with HCV RNA<LLOQ (15 IU/mL) while on treatment by visit (FAS)

	SOF/VEL/VOX 12 weeks N=263	Placebo 12 weeks N=152
Baseline, n/N (%)		
<LLOQ	0/263	0/152
Week 1		
<LLOQ	41/263 (15.6)	0/152
95% CI	11.4 to 20.5	0.0 to 2.4
<LLOQ detected	38/263 (14.4)	0/152
<LLOQ TND	3/263 (1.1)	0/152
Week 2		
<LLOQ	149/263 (56.7)	0/150
95% CI	50.4 to 62.7	0.0 to 2.4
<LLOQ detected	93/263 (35.4)	0/150
<LLOQ TND	56/263 (21.3)	0/150

Week 4		
<LLOQ	243/262 (92.7)	0/150
95% CI	88.9 to 95.6	0.0 to 2.4
<LLOQ detected	76/262 (29.0)	0/150
<LLOQ TND	167/262 (63.7)	0/150
Week 8		
<LLOQ	262/262 (100.0)	0/150
95% CI	98.6 to 100.0	0.0 to 2.4
<LLOQ detected	5/262 (1.9)	0/150
<LLOQ TND	257/262 (98.1)	0/150
Week 12		
<LLOQ	260/261 (99.6)	0/149
95% CI	97.9 to 100.0	0.0 to 2.4
<LLOQ detected	0/261	0/149
<LLOQ TND	260/261 (99.6)	0/149

CI, confidence interval; LLOQ, lower limit of quantitation; SOF, sofosbuvir; TND, target not detected; VEL, velpatasvir; VOX, voxilaprevir.
LLOQ=15 IU/mL. Missing values for on-treatment visits are imputed up to the time of last dose (if the study day associated with the last dose date is greater than or equal to the lower bound of a visit window, the missing value at the visit will be imputed, otherwise, the value will be excluded); Missing values bracketed by values of '<LLOQ TND' will be set to '<LLOQ TND'; bracketed by '<LLOQ detected', or '<LLOQ TND' and '<LLOQ detected' will be set to '<LLOQ detected'; otherwise, the missing values will be set as '≥LLOQ'. The exact 95% CI for the proportion within treatment group and genotype is based on the Clopper-Pearson method.

HCV change from baseline

HCV RNA levels (log10 IU/mL) declined rapidly in the SOF/VEL/VOX 12 week group with a mean (SD) log10 IU/mL value of 2.06 (0.674) log10 IU/mL, and a change from baseline of−4.20 (0.733) log10 IU/mL after a week of treatment. The decreases in HCV RNA were maintained from weeks 2 to 12 (EOT), with mean HCV RNA levels ranging from 1.15 to 1.45 log10 IU/mL and mean changes from baseline ranging from −5.11 to −4.81 log10IU/mL. No notable decreases or changes from baseline in HCV RNA levels were observed in the Placebo 12 week group.

Proportion of patients with virologic failure

A total of 10 of 263 patients (3.8%) in the SOF/VEL/VOX 12 week group did not achieve SVR12. Of these, 1 patient had on-treatment virologic failure (breakthrough) and 6 patients relapsed. Three additional patients did not achieve SVR12 but did not meet virologic failure criteria (categorised as “Other” in Table 23).

Three patients had relapse determined at post-treatment week 4; all had GT3 HCV infection and cirrhosis. Three patients (HCV GT1a, GT3, or GT4, all with cirrhosis) achieved SVR4, but had relapse determined at the post-treatment week 12 visit. Three additional patients did not achieve SVR12 (2 patients withdrew consent, 1 patient was lost to follow-up).

Table 23: POLARIS-1: Virologic outcomes for patients in the SOF/VEL/VOX 12 week group (FAS)

	SOF/VEL/VOX 12 weeks N=263
SVR12, n/N (%)	253/263 (96.2)
Overall virologic failure	7/263 (2.7)
Relapse	6/261 (2.3)
Completed study treatment	6/260 (2.3)
Discontinued study treatment	0/1
On-treatment virologic failure	1/263 (0.4)
Other	3/263 (1.1)

SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir; VOX, voxilaprevir.
Relapse = confirmed HCV RNA ≥LLOQ during the post-treatment period having achieved HCV RNA<LLOQat last on-treatment visit. 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).
Other = patient who did not achieve SVR12 and did not meet virologic failure criteria.

Development of resistance

Virologic resistance analysis is presented for patients in the SOF/VEL/VOX 12 week group only and does not include patients who were randomised to the Placebo 12 week group. In the SOF/VEL/VOX 12 week group, 78.8% of patients had baseline NS3 and/or NS5A resistance-associated variants (RAVs). NS5A RAVs were the most common RAVs in patients across genotypes, observed in 75.4% of patients. The presence of baseline RAVs did not impact the SVR12 rate in the SOF/VEL/VOX 12 week group, with an SVR12 rate of 97.1% for patients with RAVs, compared with an SVR12 rate of 97.7% for patients without RAVs.

In the SOF/VEL/VOX 12 week group the NS3, NS5A, and NS5B genes were successfully sequenced at baseline for all of the 7 patients who did not achieve SVR12, and at virologic failure for 6 of these patients. Assay failure occurred for the NS5B gene for 1 patient at relapse. Sequencing for both NS3 and NS5A genes is ongoing for 1 patient, with no data currently available.

B.2.6.1.3. Other outcomes of interest

ALT normalisation

Coincident with suppression of viral replication, the SOF/VEL/VOX 12 week group had a decrease from baseline in median ALT for the duration of the treatment period and at the post-treatment week 4 visit (median change -40 U/L). No relevant changes in ALT were observed in the Placebo 12 week group.

HRQL

Four HRQL questionnaires were used, SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C, to assess the effect of treatment on patient-reported outcomes. At the time of post-treatment questionnaire completion, patients were unaware of their response status.

Overall, results from the SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C questionnaires indicated that quality of life (QOL) parameters improved during treatment with SOF/VEL/VOX for 12 weeks in patients with chronic HCV infection. The mean scores for most scales continued to improve from EOT to post-treatment weeks 4 and 12 (

Table **24**). These results should be interpreted with caution, as multiple endpoints were tested and the study was not powered to test these exploratory endpoints.

Table 24: POLARIS-1: Summary of HRQL outcomes (FAS)

Instrument	BL Mean (SD)	EOT Mean (SD)	PT week 4 Mean (SD)	PT week 12 Mean (SD)	BL Mean (SD)	EOT Mean (SD)	PT week 4 Mean (SD)	PT week 12 Mean (SD)
	SOF/VEL/VOX 12 weeks				**Placebo 12 weeks**			
SF-36, Physical component	49.6 (9.03)	50.0 (8.50) p=0.26[a] p=0.73[b]	50.5 (8.68) p=0.019[a] p=0.27[b] p=0.31[c]	50.7 (8.72) p<0.003[a] p=0.12[c]	48.0 (9.55)	48.6 (8.50) p=0.22[a]	48.5 (9.48) P=0.63[a] P=0.48[b]	N/A
SF-36, Mental component	49.2 (10.26)	49.4 (10.46) p=0.51[a] p=0.094[b]	50.2 (10.32) p=0.079[a] p=0.055[b] p=0.061[c]	51.2 (9.78) p<0.001[a] p<0.001[b]	49.9 (10.12)	48.8 (10.40) p=0.11[a]	48.9 (10.66) p=0.26[a] p=0.92[b]	N/A
CLDQ-HCV	5.3 (1.10)	5.5 (1.11) p<0.001[a] p=0.008[b]	5.6 (1.05) p<0.001[a] p=0.002[b] p=0.002[c]	5.7 (1.02) p<0.001[a] p<0.001[b]	5.2 (1.19)	5.2 (1.20) p=0.86[a]	5.2 (1.22) p=0.36[a] p=1.00[b]	N/A
FACIT-F Trial Outcome Index	82.6 (20.60)	82.6 (20.82) p=0.73[a] p=0.98[b]	84.8 (20.37) p=0.009[a] p=0.001[b] p=0.077[c]	86.5 (19.50) p<0.001[a] p<0.001[b]	80.0 (22.30)	79.6 (21.82) p=0.77[a]	80.3 22.53 p=0.90[a] p=0.71[b]	N/A
FACIT-F Total score	121.4 (26.40)	122.4 (27.10) p=0.17[a] p=0.39[b]	125.4 (26.65) p<0.001[a] p=0.001[b] p=0.014[c]	127.8 (26.11) p<0.001[a] p<0.001[b]	118.7 (28.52)	117.9 (28.59) p=0.89[a]	118.5 (29.29) p=0.86[a] p=0.45[b]	N/A
WPAI, percentage of overall work impairment due to CHC	11.9 (21.35)	14.4 (23.55) p=0.25[a] p=0.13[b]	13.6 (22.44) p=0.33[a] p=0.99[b] p=0.80[c]	11.8 (22.15) p=0.86[a] p=0.30[b]	18.8 (27.54)	14.9 (24.61) p=0.13[a]	17.0 (26.28) p=0.81[a] p=0.026[b]	N/A

WPAI, percentage of activity impairment due to CHC	18.3 (26.29)	16.5 (24.22) p=0.14[a] p=0.23[b]	15.4 (23.24) p=0.075[a] p=0.47[c] p=0.13[b]	12.6 (22.55) p<0.001[a] p=0.004[c]	20.7 (28.25)	19.5 (25.65) p=0.90[a]	20.6 (26.74) p=0.75[a] p=0.33[b]	N/A

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; RBV, ribavirin; SD, standard deviation; SF-36, Short Form Health Survey; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir; WPAI, Work productivity and Activity Impairment.
[a] p-value for change from baseline to time point;[b] p-value for between treatment difference for change from baseline;[c] p-value for change from EOT to time point.

Conclusion (POLARIS-1)

- The SOF/VEL/VOX 12 week group met the primary endpoint of an SVR12 rate that was statistically superior relative to the pre-specified performance goal of 85% (p<0.001). The SVR12 rate in the SOF/VEL/VOX 12 week group was 96.2% (253 of 263 patients; 95% CI: 93.1 to 98.2).
- A total of 10 of 263 patients (3.8%) in the SOF/VEL/VOX 12 week group did not achieve SVR12.
- Three patients had relapse determined at post-treatment week 4; all had GT3 HCV infection and cirrhosis. Three patients (HCV GT1a, GT3, or GT4, all with cirrhosis) achieved SVR4, but had relapse determined at the post-treatment week 12 visit. Three additional patients did not achieve SVR12 (2 patients withdrew consent, 1 patient was lost to follow-up).
- HCV RNA levels (log10 IU/mL) declined rapidly with similar decreases in HCV RNA observed across all HCV genotypes in the SOF/VEL/VOX 12 week group. Consistent with the rapid and sustained decline in HCV RNA, 92.7% of patients in the SOF/VEL/VOX 12 week group had HCV RNA<LLOQ at week 4. Time to virologic suppression was not associated with overall treatment outcome, or in any GT.
- In the SOF/VEL/VOX 12 week group, 78.8% of patients had baseline NS3 and/or NS5A RAVs NS5A RAVs were the most common RAVs in patients across genotypes, observed in 75.4% of patients. The presence of baseline RAVs did not impact the SVR12 rate in the SOF/VEL/VOX 12 week group, with an SVR12 rate of 97.1% for patients with RAVs, compared with 97.7% for patients without RAVs.
- Of the 7 patients with virologic failure, only 1 patient developed treatment-emergent RAVs L31M and Y93H; this patient, with GT1a CHC, experienced virologic breakthrough at the end of treatment and had pharmacokinetic (PK) data consistent with nonadherence. No NS3, NS5A and NS5B RAVs emerged in any of the 6 patients who relapsed with data available.
- Overall, results from the SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C questionnaires indicated that QOL parameters improved during treatment with SOF/VEL/VOX for 12 weeks in patients with chronic HCV infection. The mean scores for most scales continued to improve from EOT to post-treatment weeks 4 and 12. These results should be interpreted with caution, as multiple endpoints were tested and the study was not powered to test these exploratory endpoints.

B.2.6.2. *POLARIS-4*

B.2.6.2.1. Primary efficacy results: SVR12

The primary efficacy endpoint was SVR12, defined as HCV RNA<LLOQ 12 weeks after discontinuation of the study drug, in the SOF/VEL/VOX 12 week group in the FAS. The primary efficacy endpoint analysis for SVR12 was conducted after all patients completed the post-treatment week 12 visit or prematurely discontinued from the study. Primary efficacy results for POLARIS-4 are presented in Table 25.

The proportion of patients who achieved SVR12 following treatment with SOF/VEL/VOX for 12 weeks was 97.8% (95% CI: 94.5% to 99.4%). The proportion of patients who achieved SVR12 following treatment with SOF/VEL for 12 weeks was 90.1% (95% CI: 84.1% to 94.3%).

The SOF/VEL/VOX 12 week group met the primary endpoint with a significantly higher SVR12 rate of 97.8% compared with the performance goal of 85% at the significance level of 0.025 (p<0.001). The SOF/VEL 12 week group did not meet the primary efficacy endpoint with a SVR12 rate of 90.1% compared with the performance goal of 85% at the significance level of 0.025 (p=0.092).

Table 25: POLARIS-4: Proportion of patients who achieve SVR12 (FAS)

	SOF/VEL/VOX 12 weeks N=182	**SOF/VEL 12 weeks N=151**
SVR12[a], n/N (%)	178/182 (97.8%)	136/151 (90.1)
95% CI	94.5% to 99.4%	84.1 to 94.3
p-value (compared with 85%)	<0.001	0.092

CI, confidence interval; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir; VOX, voxilaprevir.
A missing SVR12 value is imputed as a success if it is bracketed by values that are termed successes (i.e. '<LLOQ TND' or '<LLOQ detected'); otherwise, the missing SVR12 value is imputed as a failure. The exact 95% CI for the proportion within treatment group is based on the Clopper-Pearson method. The p-value is obtained from the 2-sided exact 1-sample binomial test for the superiority over the performance goal of 85%.
[a] The SVR4 and SVR12 rates for the SOF/VEL/VOX 12 week group reported in the interim analysis were updated in the final analysis due to achievement of SVR24 by 1 subject who had missed the post-treatment week 4 and 12 visits at the time of the interim analysis.

B.2.6.2.2. Secondary efficacy outcomes

Proportion of patients with SVR at 4 and 24 weeks

The secondary efficacy endpoint of SVR4 and SVR24, defined as HCV RNA<LLOQ 4 and 24 weeks after discontinuation of therapy are summarised below.

Table 26 presents the proportion of patients with SVR4 and SVR12. Overall, the SVR4 results were similar to the SVR12 results. Most relapses occurred by the post-treatment week 4 visit. In the SOF/VEL/VOX 12 week group, the only relapse occurred by post-treatment week 4. In the SOF/VEL 12 week group, 12 of 14 relapses occurred by post-treatment week 4, and 2 of 14 relapses occurred between post-treatment weeks 4 and 12. The SVR12 and SVR24 rates were the same for both treatment groups as no patients relapsed between post-treatment week 12 and post-treatment week 24.

Table 26: POLARIS-4: SVR at post-treatment follow-up (FAS)

	SOF/VEL/VOX 12 weeks N=182	SOF/VEL 12 weeks N=151
SVR4, n/N (%)	179/182 (98.4)	138/151 (91.4)
95% CI	95.3 to 99.7	85.7 to 95.3
SVR12	178/182 (97.8)	136/151 (90.1)
95% CI	94.5 to 99.4	84.1 to 94.3
SVR24	178/182 (97.8)	136/151 (90.1)
95% CI	94.5 to 99.4	84.1 to 94.3

CI, confidence interval; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir; VOX, voxilaprevir.
A missing SVR value is imputed as a success if it is bracketed by values that are termed successes (i.e. '<LLOQ TND' or '<LLOQ detected'); otherwise, the missing SVR value is imputed as a failure. TND = target not detected.
The exact 95% CI for the proportion within treatment group is based on the Clopper-Pearson method

Proportion of patients with HCV RNA<LLOQ on treatment

A summary of the proportion of patients with HCV RNA<LLOQ on treatment by analysis visit is presented in Table 27.

Potent and rapid suppression of HCV RNA while on treatment was observed in both treatment groups. At week 1, 15.9% of patients in the SOF/VEL/VOX 12 week group and 17.2% of patients in the SOF/VEL 12 week group had HCV RNA<LLOQ. At week 2, 62.6% of patients in the SOF/VEL/VOX 12 week group and 56.3% of patients in the SOF/VEL 12 week group had HCV RNA<LLOQ. At week 4, 88.5% of patients in the SOF/VEL/VOX 12 week group and 90.7% of patients in the SOF/VEL 12 week group had HCV RNA<LLOQ.

Early viral response had no impact on SVR12 rates in either study arm. All 35 patients who had HCV RNA>LLOQ at week 4, regardless of treatment arm, achieved SVR12.

Table 27: POLARIS-4: Proportion of patients with HCV RNA<LLOQ (15 IU/mL) while on treatment by visit (FAS)

	SOF/VEL/VOX 12 weeks N=182	SOF/VEL 12 weeks N=151
Baseline, n/N (%)		
<LLOQ	0/182	0/151
Week 1		
<LLOQ	29/182 (15.9)	26/151 (17.2)
95% CI	10.9 to 22.1	11.6 to 24.2
<LLOQ detected	25/182 (13.7)	22/151 (14.6)
<LLOQ TND	4/182 (2.2)	4/151 (2.6)
Week 2		
<LLOQ	114/182 (62.6)	85/151 (56.3)
95% CI	55.2 to 69.7	48.0 to 64.3

<LLOQ detected	83/182 (45.6)	61/151 (40.4)
<LLOQ TND	31/182 (17.0)	24/151 (15.9)
Week 4		
<LLOQ	161/182 (88.5)	137/151 (90.7)
95% CI	82.9 to 92.7	84.9 to 94.8
<LLOQ detected	46/182 (25.3)	47/151 (31.1)
<LLOQ TND	115/182 (63.2)	90/151 (59.6)
Week 8		
<LLOQ	182/182 (100.0)	149/151 (98.7)
95% CI	98.0 to 100.0	95.3 to 99.8
<LLOQ detected	6/182 (3.3)	4/151 (2.6)
<LLOQ TND	176/182 (96.7)	145/151 (96.0)
Week 12		
<LLOQ	180/182 (98.9)	149/150 (99.3)
95% CI	96.1 to 99.9	96.3 to 100.0
<LLOQ detected	0/182	1/150 (0.7)
<LLOQ TND	180/182 (98.9)	148/150 (98.7)

CI, confidence interval; LLOQ, lower limit of quantitation; SOF, sofosbuvir; SVR, sustained virologic response; TND, target not detected; VEL, velpatasvir; VOX, voxilaprevir.
LLOQ=15 IU/mL. Missing values for on-treatment visits are imputed up to the time of last dose (if the study day associated with the last dose date is greater than or equal to the lower bound of a visit window, the missing value at the visit will be imputed, otherwise, the value will be excluded). Missing values bracketed by values of '<LLOQ TND' will be set to '<LLOQ TND'; bracketed by '<LLOQ detected', or '<LLOQ TND' and '<LLOQ detected' will be set to '<LLOQ detected'; otherwise, the missing values will be set as '≥LLOQ'. The exact 95% CI for the proportion within treatment group and genotype is based on the Clopper-Pearson method.

HCV change from baseline

HCV RNA levels (log10 IU/mL) declined rapidly, with similar decreases in HCV RNA observed in both treatment groups. After a week of treatment, the mean (SD) change from baseline in HCV RNA levels was -4.29 (0.627) log10 IU/mL in the SOF/VEL/VOX 12 week group and -4.17 (0.651) log10 IU/mL in the SOF/VEL 12 week group. The decreases in HCV RNA were maintained from weeks 2 through 12. Mean HCV RNA levels at week 12 were 1.15 and 1.17 log10 IU/mL for the SOF/VEL/VOX 12 week and SOF/VEL 12 week groups, respectively. At week 12 mean change from baseline were -5.17 and -5.09 log10 IU/mL for the SOF/VEL/VOX 12 week and SOF/VEL 12 week groups, respectively.

Proportion of patients with virologic failure

In the SOF/VEL/VOX 12 week group, 4 of 182 patients (2.2%) did not achieve SVR12. Of these, no patients had on-treatment virologic failure, 1 patient relapsed and 3 patients were categorised as “Other”. Patients were categorised as “Other” if they did not achieve SVR12 and did not meet criteria for virologic failure: 1 patient died and 2 patients missed their post-treatment week 12 visit.

In the SOF/VEL 12 week group, 15 of 151 patients (9.9%) did not achieve SVR12: 1 patient had on-treatment virologic failure and 14 patients relapsed (Table 23). Of the 14 patients who relapsed following SOF/VEL treatment for 12 weeks, 8 patients had GT3 HCV infection, and 7 of these patients also had cirrhosis. The remaining 6 patients who relapsed had GT1 HCV infection (3 patients with GT1a with cirrhosis, 2 patients with GT1a without cirrhosis, and 1 patient with GT1b without cirrhosis who completed only 56 days of study treatment).

Table 28: POLARIS-4: Virologic outcomes (FAS)

	SOF/VEL/VOX 12 weeks N=182	SOF/VEL 12 weeks N=151
SVR12, n/N (%)	178/182 (97.8)	136/151 (90.1)
Overall virologic failure	1/182 (0.5)	15/151 (9.9)
Relapse	1/182 (0.5)	14/150 (9.3)
Completed study treatment	1/182 (0.5)	13/149 (8.7)
Discontinued study treatment	0/0	1/1 (100.0)
On-treatment virologic failure	0/182	1/151 (0.7)
Other	3/182 (1.6)	0/151

SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir; VOX, voxilaprevir.
Relapse = confirmed HCV RNA ≥LLOQ during the post-treatment period having achieved HCV RNA<LLOQat last on-treatment visit. 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). Other = patient who did not achieve SVR12 and did not meet virologic failure criteria.

Development of resistance

The presence of baseline RAVs did not impact the SVR12 rates of the SOF/VEL/VOX 12 week or SOF/VEL 12 week group overall or by HCV genotype. In the SOF/VEL/VOX 12 week group, the SVR12 rates were 100.0% and 98.8% in patients with and without baseline NS3 and/or NS5A RAVs, respectively. In the SOF/VEL 12 week group, the SVR12 rates were 90.0% and 89.3% in patients with and without baseline NS3 and/or NS5A RAVs, respectively. For the single patient who relapsed in the SOF/VEL/VOX 12 week group, no NS3, NS5A, or NS5B NI RAVs were detected at baseline or at time of relapse.

In the SOF/VEL 12 week group, 15 patients had a virologic failure: 1 patient had on-treatment virologic failure and 14 patients relapsed. The patient with on-treatment virologic failure developed treatment-emergent NS5A RAV Y93H and NS5B RAV S282T. Ten of 14 patients who relapsed had the NS5A RAV Y93H or Y93C emerge. No NS5B NI RAVs were observed in any patients who relapsed.

B.2.6.2.3. Other outcomes of interest

ALT Normalisation

Coincident with decreases in HCV RNA, decreases from baseline in median ALT values were observed in both treatment groups for the duration of treatment and at the post-treatment week 4 visit. Median changes from baseline to post-treatment week 4 ranged from −40 to −38 U/L across both treatment groups.

HRQL

Four HRQL questionnaires were used, SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C, to assess the effect of treatment on patient-reported outcomes. At the time of post-treatment questionnaire completion, patients were unaware of their response status.

Overall, results from the SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C questionnaires indicated that no on-treatment decrements in QoL were observed in the SOF/VEL/VOX 12 week or SOF/VEL 12 week group. The mean scores for most scales continued to improve from EOT to post-treatment weeks 4 and 12 (

Table **29**). These results should be interpreted with caution, as multiple endpoints were tested and the study was not sufficiently powered to test these exploratory endpoints.

Table 29: POLARIS-4: Summary of HRQL outcomes (FAS)

Instrument	BL Mean (SD)	EOT Mean (SD)	PT week 12 Mean (SD)	BL Mean (SD)	EOT Mean (SD)	PT week 12 Mean (SD)
	SOF/VEL/VOX 12 weeks			**SOF/VEL 12 weeks**		
SF-36, Physical component	48.4 (9.03)	49.0 (8.51) p=0.12[a] p=0.91[b]	49.8 (9.01) p=0.006[a] p=0.010[c] p=0.99[b]	48.4 (9.17)	49.1 (8.46) 0.18[a]	49.9 (8.74) p=0.002[a] p=0.13[c]
SF-36, Mental component	47.8 (11.15)	48.9 (10.54) p=0.14[a] p=0.12[b]	50.6 (10.06) p<0.001[a] p<0.001[c] p=0.73[b]	48.3 (10.23)	47.9 (10.55) 0.40[a]	50.1 (10.34) p=0.005[a] p<0.001[c]
CLDQ-HCV	5.1 (1.12)	5.4 (1.04) p<0.001[a] p=0.31[b]	5.6 (1.00) p<0.001[a] p<0.001[c] p=0.97[b]	5.1 (1.16)	5.3 (1.04) p<0.001[a]	5.6 (1.07) P<0.001[a] p<0.001[c]
FACIT-F Trial Outcome Index	77.9 (21.96)	79.8 (21.37) p=0.22[a] p=0.67[b]	84.5 (20.30) p<0.001[a] p<0.001[c] p=0.98[b]	78.9 (20.79)	80.2 (19.97) p=0.55[a]	84.8 (19.18) p<0.001[a] p<0.001[b]
FACIT-F Total score	116.2 (27.99)	119.9 (27.07) p=0.034[a] p=0.44[b]	124.7 (26.92) p<0.001[a] p<0.001[c] p=0.94[b]	117.7 (26.75)	119.7 (25.64) p=0.42[a]	125.3 (26.12) p<0.001[a] p<0.001[b]
WPAI, percentage of overall work impairment due to CHC	17.0 (24.61)	16.9 (24.27) p=0.71[a] p=0.40[b]	14.2 (25.94) p=0.041[a] p=0.17[c] p=0.68[b]	15.2 (21.83)	18.2 (22.54) p=0.12[a]	9.4 (17.21) p=0.004[a] p<0.001[b]
WPAI,	21.6	19.2	12.5	23.2	20.7	13.8

percentage of activity impairment due to CHC	(25.01)	(25.22) p=0.048[a] p=0.43[b]	(22.74) p<0.001[a] p=0.001[c] p=0.87[b]	(27.12)	(25.04) p=0.43 [a]	(22.13) p<0.001[a] p<0.001[b]

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; RBV, ribavirin; SD, standard deviation; SF-36, Short Form Health Survey; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir; WPAI: Hep C, Work productivity and Activity Impairment: Hepatitis C.
[a] p-value for change from baseline to time point;[b] p-value for between treatment difference for change from baseline; [c] p-value for change from EOT to time point

Conclusion (POLARIS-4)

- The SOF/VEL/VOX 12 week group met the primary endpoint as the SVR12 rate for the SOF/VEL/VOX 12 week group was statistically superior relative to the pre-specified SVR12 performance goal of 85% at the significance level of 0.025 ($p<0.001$). The SVR12 rate for the SOF/VEL 12 week group was not statistically superior relative to the pre-specified SVR12 performance goal of 85% at the significance level of 0.025. SVR12 rates were:
  - SOF/VEL/VOX 12 week group: 97.8% (95% CI: 94.5 to 99.4%) of patients (178 of 182) achieved SVR12.
  - SOF/VEL 12 week group: 90.1% (95% CI: 84.1 to 94.3) of patients (136 of 151) achieved SVR12.
  - The SVR12 and SVR24 rates were the same for both treatment groups, and no patients relapsed between post-treatment week 12 and post-treatment week 24.
- In the SOF/VEL/VOX 12 week group, 4 of 182 patients (2.2%) did not achieve SVR12. Of these, 1 patient relapsed and 3 patients were categorised as "Other". Patients were categorised as "Other" because they did not have post-treatment week 12 assessments due to death (1 patient) or missed post-treatment week 12 visit (2 patients). Only 1 patient in the SOF/VEL/VOX 12 week group experienced virologic failure, precluding any meaningful subgroup analysis.
- In the SOF/VEL 12 week group, 15 of 151 patients (9.9%) did not achieve SVR12. Of these, 1 patient had on-treatment virologic failure (breakthrough) at week 8 and 14 patients relapsed. Of the 14 patients who relapsed following SOF/VEL treatment for 12 weeks, 8 patients had GT3 HCV infection, and 7 of these patients also had cirrhosis. The remaining 6 patients who relapsed had GT1 HCV infection (3 patients with GT1a with cirrhosis, 2 patients with GT1a without cirrhosis, and 1 patient with GT1b without cirrhosis who completed only 56 days of study treatment).
- HCV RNA levels (log10 IU/mL) declined rapidly with similar decreases in HCV RNA observed across all HCV genotypes in both treatment groups. Consistent with the rapid and sustained decline in HCV RNA, 88.5% of patients in the SOF/VEL/VOX 12 week group and 90.7% of patients in the SOF/VEL 12 week group had HCV RNA<LLOQ at week 4.
- The presence of baseline RAVs did not impact the SVR12 rates of the SOF/VEL/VOX 12 week or SOF/VEL 12 week groups overall or by HCV genotype. In the SOF/VEL/VOX 12 week group, the SVR12 rates were 100.0% and 98.8% in patients with and without baseline NS3 and/or NS5A RAVs, respectively. In the SOF/VEL 12 week group, the SVR12 rates were 90.0% and 89.3% in patients with and without baseline NS3 and/or NS5A RAVs, respectively.
- For the 1 patient who relapsed in the SOF/VEL/VOX 12 week group, no NS3, NS5A, or NS5B NI RAVs were detected at baseline or at the time of relapse. In the SOF/VEL 12 week group, 15 patients had a virologic failure: 1 patient had on-treatment virologic failure and 14 patients relapsed. The patient with on-treatment virologic failure developed treatment-emergent NS5A Y93H and NS5B S282T. Ten of 14 patients who relapsed had the NS5A RAV Y93H or Y93C emerge. No NS5B NI RAVs were observed in any patients who relapsed.

B.2.6.3. *POLARIS-2*

B.2.6.3.1. Primary efficacy results: SVR12

The primary efficacy endpoint was SVR12, defined as HCV RNA<LLOQ 12 weeks after discontinuation of all study drugs for the FAS. The primary efficacy endpoint analysis was conducted after all patients had completed the post-treatment week 12 visit or had prematurely discontinued from the study. Primary efficacy results for POLARIS-2 are presented in Table 30.

The SVR12 rate for the SOF/VEL/VOX 8 week group did not demonstrate non-inferiority to the SVR12 rate for the SOF/VEL 12 week group. The difference (95% CI) in the stratum-adjusted Mantel-Haenszel proportions was −3.2% (−6.0% to −0.4%), the lower bound of which was not greater than the pre-specified non-inferiority margin of −5%.

Table 30 presents the proportion of patients who achieved SVR12 following 8 weeks of treatment with SOF/VEL/VOX or 12 weeks treatment with SOF/VEL.

Table 30: POLARIS-2: Proportion of patients who achieved SVR12 (FAS)

	SOF/VEL/VOX 8 weeks N=501	**SOF/VEL 12 weeks N=440**
SVR12[a], n/N (%)	477/501 (95.2)	432/440 (98.2)
95% CI	93.0 to 96.9	96.4 to 99.2

CI, confidence interval; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir; VOX, voxilaprevir.
A missing SVR12 value is imputed as a success if it is bracketed by values that are termed successes (i.e. '<LLOQ TND' or '<LLOQ detected'); otherwise, it is imputed as a failure. The exact 95% CI for the proportion within treatment group is based on Clopper-Pearson method. Difference in proportions between treatment groups and associated 95% CI are calculated based on stratum-adjusted. Mantel-Haenszel proportions. The stratum is determined by HCV GT (1, 2, 3, 4, other), cirrhosis status (yes, no) and prior HCV treatment history (TN, TE). GT other patients are combined into one stratum. Any other stratum with ≤1 patient in either treatment group is combined with its adjacent stratum (i.e. GT3/yes/TN with GT3/no/TN; GT2/yes/TE with GT2/yes/TN). CMH test for superiority of SOF/VEL/VOX over SOF/VEL is not performed as non-inferiority is not demonstrated.
[a] SVR12 rate for SOF/VEL/VOX 8 week group changed from interim analysis and was updated in the SVR24 analysis due to achievement of SVR24 by 1 subject who had missed the posttreatment visits at the time of the interim analysis. In the final analysis, 1 subject in each treatment group who had achieved SVR12 did not achieve SVR24.

B.2.6.3.2. Secondary efficacy outcomes

Proportion of patients with SVR at 4 and 24 weeks

Overall, the SVR4 and SVR24 results were similar to the SVR12 results for each treatment group. In the final analysis, 1 patient in each treatment group who had achieved SVR12 did not achieve SVR24. The majority of relapses had occurred by post-treatment week 4. In the SOF/VEL/VOX 8 week group, 16 of 21 relapses occurred by post-treatment week 4, and 5 of 21 relapses occurred between post-treatment weeks 4 and 12. In the SOF/VEL 12 week group, 2 of 3 relapses occurred by post-treatment week 4, and 1 of 3 relapses occurred between post-treatment weeks 4 and 12. Table 31 presents SVR at post-treatment weeks 4 and 12 by treatment group for the FAS.

Table 31: POLARIS-2: Proportion of patients who achieved SVR4 and SVR24 post-treatment (FAS)

	Total (All GTs)

	SOF/VEL/VOX N=501	SOF/VEL N=440
SVR4, n/N (%)	483/501 (96.4)	435/440 (98.9)
95% CI	94.4 to 97.9	97.4 to 99.6
SVR24	476/501 (95.0)	431/440 (98.0)
95% CI	92.7 to 96.7	96.2 to 99.1

CI, confidence interval; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir; VOX, voxilaprevir. A missing SVR value is imputed as a success if it is bracketed by values that are termed successes (i.e. '<LLOQ TND' or'<LLOQ detected'); otherwise, the missing SVR value is imputed as a failure. The exact 95% CI for the proportion within treatment group is based on the Clopper-Pearson method.

Proportion of patients with HCV RNA<LLOQ on treatment

A summary of the proportion of patients with HCV RNA<LLOQ on treatment at weeks 1, 2, 4, 8 and 12 is presented in Table 32. There was a potent and rapid suppression of HCV RNA while on treatment observed in both treatment groups. At week 1, 24.8% of patients in the SOF/VEL/VOX 8 week group and 22.7% of patients in the SOF/VEL 12 week group had HCV RNA<LLOQ. At treatment week 2, >60% of patients in each treatment group had HCV RNA<LLOQ. At week 4, >90% of patients in each treatment group had HCV RNA<LLOQ. At the EOT visit, 99.2% of patients in the SOF/VEL/VOX 8 week group (week 8) and 99.8% of patients in the SOF/VEL 12 week group (week 12) had HCV RNA<LLOQ.

Table 32: POLARIS-2: Proportion of patients with HCV RNA<LLOQ (15 IU/mL) while on treatment by visit (FAS)

	Total (All GTs)	
	SOF/VEL/VOX N=501	**SOF/VEL N=440**
Baseline, n/N (%)		
<LLOQ	0/501	0/440
95% CI	0.0 to 0.7	0.0 to 0.8
Week 1		
<LLOQ	124/501 (24.8)	100/440 (22.7)
95% CI	21.0 to 28.8	18.9 to 26.9
<LLOQ detected	91/501 (18.2)	77/440 (17.5)
<LLOQTND	33/501 (6.6)	23/440 (5.2)
Week 2		
<LLOQ	300/501 (65.9)	269/439 (61.3)
95% CI	61.5 to 70.0	56.5 to 65.9
<LLOQ detected	193/501 (38.5)	154/439 (35.1)
<LLOQTND	137/501 (27.3)	115/439 (26.2)
Week 4		
<LLOQ	463/501 (92.4)	404/439 (92.0)
95% CI	89.7 to 94.6	89.1 to 94.4
<LLOQ detected	124/501 (24.8)	116/439 (26.4)
<LLOQTND	339/501 (67.7)	288/439 (65.6)
Week 8		
<LLOQ	496/500 (99.2)	438/439 (99.8)
95% CI	98.0 to 99.8	98.7 to 100.0
<LLOQ detected	16/500 (3.2)	14/439 (3.2)
<LLOQTND	480/500 (96.0)	424/439 (96.6)
Week 12		
<LLOQ	N/A	438/439 (99.8)
95% CI	N/A	98.7 to 100.0
<LLOQ detected	N/A	0/439
<LLOQTND	N/A	438/439 (99.8)

CI, confidence interval; LLOQ, lower limit of quantitation; SOF, sofosbuvir; SVR, sustained virologic response; TND, target not detected; VEL, velpatasvir; VOX, voxilaprevir.
LLOQ=15 IU/mL. Missing values for on-treatment visits are imputed up to the time of last dose (if the study day associated with the last dose date is greater than or equal to the lower bound of a visit window, the missing value at the visit will be imputed; otherwise, the value will be excluded). Missing values bracketed by values of '<LLOQ TND' will be set to '<LLOQ TND'; bracketed by '<LLOQ detected', or '<LLOQ TND' and '<LLOQ detected' will be set to '<LLOQ detected'; otherwise, the missing values will be set as '≥LLOQ'. The exact 95% CI for the proportion within treatment group is based on the Clopper-Pearson method.

HCV change from baseline

HCV RNA levels (log10 IU/mL) declined rapidly with similar decreases in HCV RNA observed in both treatment groups and across genotypes. After a week of treatment, the overall mean (SD)

change from baseline in HCV RNA levels was −4.23 (0.689) log10 IU/mL in the SOF/VEL/VOX 8 week group and −4.24 (0.679) log10 IU/mL in the SOF/VEL 12 week group. The decreases in HCV RNA were maintained from weeks 2 through the EOT, with mean HCV RNA levels ranging from 1.15 to 1.41 log10 IU/mL and mean changes from baseline ranging from −5.03 to −4.75 log10 IU/mL across treatment groups.

Proportion of patients with virologic failure

Among the 501 patients who received SOF/VEL/VOX, 21 (4.2%) relapsed after the end of treatment, and 4 patients were categorised as “Other” (i.e. did not achieve SVR12 and did not meet virologic failure criteria). Among the 440 patients who received SOF/VEL, 8 (1.8%) did not achieve SVR12: 3 (0.7%) had had virologic failure on-treatment and 5 were categorised as “Other”. Table 33 presents virologic outcomes by treatment group for patients in POLARIS 2 (FAS).

Table 33: POLARIS-2: Virologic outcomes (FAS)

	SOF/VEL/VOX N=501	**SOF/VEL N=440**
SVR12, n/N (%)	476/501 (95.0)	432/440 (98.2)
Overall virological failure	21/501 (4.2)	3/440 (0.7)
Relapse	21/498 (4.2)	3/439 (0.7)
Completed study treatment	21/498 (4.2)	3/437 (0.7)
Discontinued study treatment	0/1	0/2
On-treatment virologic failure	0/501	0/440
Other	4/501 (0.8)	5/440 (1.1)

HCV, hepatitis C virus; LLOQ, lower limit of quantitation; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir; VOX, voxilaprevir.
Relapse = confirmed HCV RNA ≥LLOQ during the post-treatment period having achieved HCV RNA<LLOQat last on-treatment visit. 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). Other = patient who did not achieve SVR12 and did not meet virologic failure criteria.

Development of resistance

Baseline deep sequencing of the HCV NS3, NS5A, and NS5B genes was performed for all patients. For all patients with virologic failure, deep sequencing was performed at the first time point after virologic failure if the plasma/serum sample was available and HCV RNA was >1,000 IU/mL RAV were defined as the specific substitutions that either confer a reduced susceptibility to drugs of the given class with a >2.5-fold change in half-maximal effective concentration (EC50) compared with a genotype-specific reference in a replicon model or that commonly emerge in patients with virologic failure at the time of relapse.

In the SOF/VEL/VOX 8 week group, 50.3% (250 of 497 patients) had NS3 and/or NS5A RAVs at baseline. The SVR12 rate was 93.6% (234 of 250 patients) for patients with baseline RAVs and 97.8% (223/228 patients) for patients without baseline RAVs Nineteen patients in the SOF/VEL/VOX 8 week group did not have sequence determined for both genes; the SVR12 rate for these patients was 100% (19 of 19 patients). One of the 21 patients (4.8%) who relapsed in the SOF/VEL/VOX 8 week group had treatment-emergent NS5A RAVs Q30R and L31M; this patient did not have treatment-emergent NS3 or NS5B NI RAVs The other patient who relapsed did not have available sequencing data at relapse. None of the other 19 patients

(90.5%) who relapsed and had sequencing data available had detectable NS3, NS5A, or NS5B NI treatment-emergent RAVs at relapse.

The presence of baseline RAVs did not impact the SVR12 rate for the SOF/VEL 12 week group; 99.5% (217 of 218 patients) of the patients with RAVs and 99.0% (206 of 208 patients) of the patients without RAVs achieved SVR12.

B.2.6.3.3. Other outcomes of interest

ALT normalisation

Coincident with decreases in HCV RNA, decreases from baseline in median ALT values were observed in both treatment groups for the duration of treatment and at the post-treatment week 4 visit. During treatment, median changes from baseline ranged from −24 to −34 U/L, with no notable differences between the groups.

HRQL

Four HRQL questionnaires were used, SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C, to assess the effect of treatment on patient-reported outcomes. At the time of post-treatment questionnaire completion, patients were unaware of their response status.

Overall, results from the SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C questionnaires indicated that QOL parameters improved during treatment with SOF/VEL/VOX and SOF/VEL for patients with chronic HCV infection. The mean scores for most scales continued to improve from EOT to post-treatment weeks 4 and 12 (Table 34). These HRQL results should be interpreted with caution, as multiple endpoints were tested and the study was not sufficiently powered to test these exploratory endpoints.

Table 34: POLARIS-2: Summary of HRQL outcomes (FAS)

Instrument	BL Mean (SD)	EOT Mean (SD)	PT week 12 Mean (SD)	BL Mean (SD)	EOT Mean (SD)	PT week 12 Mean (SD)
	SOF/VEL/VOX, N=501			SOF/VEL, N=440		
SF-36, Physical component	48.7 (9.95)	50.2 (9.61) p<0.001[a] p=0.64[b]	50.8 (9.62) p<0.001[a] p=0.006[c] p=0.10[b]	49.8 (9.74)	51.5 (8.62) p<0.001[a]	52.6 (8.40) p<0.001[a] p<0.001[c]
SF-36, Mental component	47.2 (11.19)	49.4 (10.91) p<0.001[a] p=0.079[b]	50.1 (10.91) p<0.001[a] p=0.054[c] p=0.28[b]	47.7 (11.48)	50.3 (10.61) p<0.001[a]	52.0 (10.10) p<0.001[a] p<0.001[c]
CLDQ-HCV	5.0 (1.29)	5.6 (1.11) p<0.001[a] p=0.34[b]	5.7 (1.10) p<0.001[a] p<0.001[c] p=0.52[b]	5.2 (1.23)	5.7 (1.08) p<0.001[a]	5.9 (0.97) p<0.001[a] p<0.001[c]
FACIT-F Trial Outcome Index	77.2 (23.33)	82.6 (22.25) p<0.001[a] P=0.65[b]	85.4 (21.57) p<0.001[a] p<0.001[c] p=0.16[b]	80.0 (22.69)	85.8 (21.31) p<0.001[a]	89.8 (19.79) p<0.001[a] p<0.001[c]
FACIT-F Total score	115.8 (30.13)	124.2 (28.58) p<0.001[a] p=0.89[b]	127.2 (28.82) p<0.001[a] p<0.001[c] p=0.18[b]	119.0 (29.37)	127.7 (27.58) p<0.001[a]	132.8 (26.61) p<0.001[a] p<0.001[c]
WPAI, percentage of overall work impairment due to CHC	15.6 (25.29)	11.9 (21.91) p=0.042[a] p=0.88[b]	9.0 (20.31) p<0.001[a] p=0.023[c] p=0.71[b]	12.8 (21.62)	10.3 (21.42) p=0.13[a]	5.0 (13.88) p<0.001[a] p<0.001[c]
WPAI, percentage of activity impairment due to CHC	23.0 (29.03)	16.6 (24.44) p<0.001[a] p=0.98[b]	10.7 (21.03) p<0.001[a] p<0.001[c] p=0.27[b]	19.3 (27.22)	13.7 (26.67) p<0.001[a]	9.2 (19.44) p<0.001[a] p<0.001[c]

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; RBV, ribavirin; SD, standard deviation; SF-36, Short Form Health Survey; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir; WPAI: Hep C, Work productivity and Activity Impairment: Hepatitis C.
[a] p-value for change from baseline to time point; [b] p-value for between treatment difference for change from baseline; [c] p-value for change from EOT to time point
Note: For SF-36, CLDQ-HCV, and FACIT-F total score: a higher value indicates better quality of life outcome. For WPAI, percentage of overall work impairment and WPAI, percentage of activity impairment: a lower value indicated better quality of life.

Conclusion (POLARIS-2)

- POLARIS 2 did not meet its primary endpoint as the SVR 12 rate for SOF/VEL/VOX did not demonstrate non-inferiority to the SOF/VEL group resulting in an SVR12 of 95.2% (95% CI: 93.0, 96.9; p<0.001) compared with 98.2% (95% CI: 96.4, 99.2%)
- SVR12 rates with SOF/VEL/VOX 8 weeks were consistently high (>91%) irrespective of presence or absence of cirrhosis, or prior treatment experience:
  - Without cirrhosis: 96.1% SOF/VEL/VOX versus 98.0% SOF/VEL
  - With cirrhosis: 91.1% SOF/VEL/VOX versus 98.8% SOF/VEL
  - Treatment-naïve: 95.8% SOF/VEL/VOX versus 97.6% SOF/VEL
  - Treatment-experienced: 93.2% SOF/VEL/VOX versus 100% SOF/VEL
- SVR24 results were similar to the SVR12 results for each treatment group. Patients in the SOF/VEL/VOX 8 week group achieved an SVR24 rate of 95% compared with 98% in the SOF/VEL group.
- Of 501 patients treated with SOF/VEL/VOX, 21 (4.2%) patients experienced virologic failure, all as a result of relapse following completion of treatment. By comparison, 3 of 440 (0.7%) patients treated with SOF/VEL had a relapse following completion of treatment.
- HCV RNA levels (log10 IU/mL) declined rapidly with similar decreases in HCV RNA observed in both treatment groups and across genotypes. After 1 week of treatment, the mean change from baseline in HCV RNA levels was −4.23 log10 IU/mL in the SOF/VEL/VOX 8 week group and −4.24 log10 IU/mL in the SOF/VEL 12 week group. Consistent with the rapid and sustained decline in HCV RNA, >90% of patients in each treatment group had HCV RNA <LLOQ by treatment week 4.
- In the SOF/VEL/VOX 8 week group, 50.3% (250 of 497 patients) had NS3 and/or NS5A RAVs at baseline. One of the 21 patients (4.8%) who relapsed in the SOF/VEL/VOX 8 week group had treatment-emergent NS5A RAVs None of the other 19 patients (90.5%) who relapsed and had sequencing data available had detectable NS3, NS5A, or NS5B NI treatment-emergent RAVs at relapse. One of the patients who relapsed did not have available sequencing data at relapse. The very small number of patients who relapsed on SOF/VEL treatment mean that conclusions cannot be drawn on any potential association between NS5A resistance and virologic outcome.
- HRQL was assessed using the SF-36, CLDQ-HCV, FACIT-F and WPAI: Hep C questionnaires. Patients treated with SOF/VEL/VOX showed improvements in HRQL measures while on treatment. Mean scores of most scales improved from the end of treatment to post-treatment weeks 4 and 12.

B.2.6.4. *POLARIS-3*

B.2.6.4.1. Primary efficacy results: SVR12

The primary efficacy endpoint was SVR12, defined as HCV RNA<LLOQ 12 weeks after discontinuation of the study drug for the FAS. The primary efficacy endpoint analysis for this was conducted after all patients who completed the post-treatment week 12 visit or prematurely

discontinued from the study. Primary efficacy results for POLARIS-3 are presented in Table 35. The SOF/VEL/VOX 8 week group and the SOF/VEL 12 week group met their primary endpoints of SVR12 rates that were statistically superior relative to the prespecified SVR12 performance goal of 83% (p<0.001 for both groups). In the SOF/VEL/VOX 8 week group, the SVR12 (95% CI) rate was 96.4% (91.0% to 99.0%); in the SOF/VEL 12 week group, the SVR12 (95% CI) rate was 96.3% (90.9% to 99.0%). The SVR12 rates in both treatment groups were high and very similar, with a slightly higher rate observed in the SOF/VEL/VOX treatment group. This difference did not reach statistical significance.

Table 35 below presents proportion of patients who achieved SVR12 following 8 weeks of treatment with SOF/VEL/VOX or 12 weeks of treatment with SOF/VEL.

Table 35: POLARIS-3: Proportion of patients who achieved SVR12 (FAS)

	SOF/VEL/VOX **8 weeks** **N=110**	**SOF/VEL** **12 weeks** **N=109**
SVR12, n/N (%)	106/110 (96.4)	105/109 (96.3)
95% CI	91.0 to 99.0	90.9 to 99.0
p-value (compared with 83%)	<0.001	<0.001

CI, confidence interval; LLOQ, lower limit of quantitation; SOF, sofosbuvir; SVR, sustained virologic response; TND, target not detected; VEL, velpatasvir; VOX, voxilaprevir.
A missing SVR12 value is imputed as a success if it is bracketed by values that are termed successes (i.e. '<LLOQ TND' or '<LLOQ detected'); Otherwise, the missing SVR12 value is imputed as a failure. The exact 95% CI for the proportion within treatment group is based on the Clopper-Pearson method. The p-value is obtained from the 2-sided exact 1-sample binomial test for the superiority over the performance goal of 83%. The SVR12 rate in SOF/VEL will be tested at the 0.05 significance level if and only if the SVR12 rate in SOF/VEL/VOX is significant at 0.05.

B.2.6.4.2. Secondary efficacy outcomes

Proportion of patients with SVR at 4 and 24 weeks

Overall, the SVR4 results were similar to the SVR12 results for each treatment group: In the SOF/VEL/VOX 8 week treatment arm SVR4 was 97.3% and SVR12 was 96.4%. A similar trend was observed in the SOF/VEL treatment arm; SVR4 was 97.2% and SVR12 was 96.3%. The difference between SVR rates at post-treatment weeks 4 and 12 was because 1 patient in the SOF/VEL/VOX 8 week group died and 1 patient in the SOF/VEL 12 week group failed to return for the SVR12 visit (Table 36). The SVR12 and SVR24 rates were the same for both treatment groups.

Table 36: POLARIS-3: Proportion of patients who achieved SVR4 and SVR24 post-treatment (FAS)

	Total (All Genotypes)	
	SOF/VEL/VOX **N=110**	**SOF/VEL** **N=109**
SVR4, n/N (%)	107/110 (97.3)	106/109 (97.2)
95% CI	92.2 to 99.4	92.2 to 99.4

	Total (All Genotypes)	
	SOF/VEL/VOX N=110	**SOF/VEL N=109**
SVR24	106/110 (96.4)	105/109 (96.3)
95% CI	91.0 to 99.0	90.9 to 99.0

CI, confidence interval; LLOQ, lower limit of quantitation; SOF, sofosbuvir; SVR, sustained virologic response; TND, target not detected; VEL, velpatasvir; VOX, voxilaprevir.
SVRx is sustained virologic response (HCV RNA<LLOQ) x weeks after stopping study treatment.
A missing SVR value is imputed as a success if it is bracketed by values that are termed successes (i.e. '<LLOQ TND' or'<LLOQ detected'); otherwise, the missing SVR value is imputed as a failure. TND = target not detected.
The exact 95% CI for the proportion within treatment group is based on the Clopper-Pearson method.

Proportion of patients with HCV RNA<LLOQ on treatment

A summary of the proportion of patients with HCV RNA<LLOQ on treatment at weeks 1, 2, 4, 8 and 12 is presented in Table 37. There was a potent and rapid suppression of HCV RNA while on treatment observed in both treatment groups. At week 1, 17.3% of patients in the SOF/VEL/VOX 8 week group and 10.1% of patients in the SOF/VEL 12 week group had HCV RNA<LLOQ. At treatment week 2, >50% of patients in each treatment group had HCV RNA<LLOQ. At week 4, >85% of patients in each treatment group had HCV RNA<LLOQ. At week 8 >97% of patients in each treatment group had HCV RNA<LLOQ. At week 12, all (100%) patients in the SOF/VEL 12 week group had HCV RNA<LLOQ.

Table 37: POLARIS-3: Proportion of patients with HCV RNA<LLOQ while on treatment by visit (FAS)

	Total (All GTs)	
	SOF/VEL/VOX N=110	**SOF/VEL N=109**
Baseline, n/N (%)		
<LLOQ	0/110	0/109
95% CI	0.0 to 3.3	0.0 to 3.3
Week 1		
<LLOQ	19/110 (17.3)	11/109 (10.1)
95% CI	10.7 to 25.7	5.1 to 17.3
<LLOQ detected	15/110 (13.6)	10/109 (9.2)
<LLOQTND	4/110 (3.6)	1/109 (0.9)
Week 2		
<LLOQ	62/100 (56.4)	55/108 (50.9)
95% CI	46.6 to 65.8	41.1 to 60.7
<LLOQ detected	49/110 (44.5)	46/108 (42.6)
<LLOQTND	13/110 (11.8)	9/108 (8.3)
Week 4		
<LLOQ	96/110 (87.3)	92/108 (85.2)
95% CI	79.6 to 92.9	77.1 to 91.3
<LLOQ detected	32/110 (29.1)	45/108 (41.7)
<LLOQTND	64/110 (58.2)	47/108 (43.5)
Week 8		
<LLOQ	107/110 (97.3)	107/108 (99.1)
95% CI	92.2 to 99.4	94.9 to 100.0
<LLOQ detected	6/110 (5.5)	10/108 (9.3)
<LLOQTND	101/110 (91.8)	97/108 (89.8)
Week 12		
<LLOQ	N/A	107/107 (100.0)
95% CI	N/A	96.6 to 100.0
<LLOQ detected	N/A	0/107
<LLOQTND	N/A	107/107 (100.0)

CI, confidence interval; LLOQ, lower limit of quantitation; SOF, sofosbuvir; SVR, sustained virologic response; TND, target not detected; VEL, velpatasvir; VOX, voxilaprevir.
Missing values for on-treatment visits are imputed up to the time of last dose (if the study day associated with the last dose date is greater than or equal to the lower bound of a visit window, the missing value at the visit will be imputed; otherwise, the value will be excluded).
Missing values bracketed by values of '<LLOQ TND' will be set to '<LLOQ TND'; bracketed by '<LLOQ detected', or '<LLOQ TND' and '<LLOQ detected' will be set to '<LLOQ detected'; otherwise, the missing values will be set as '≥LLOQ'. TND = target not detected.
The exact 95% CI for the proportion within treatment group is based on the Clopper-Pearson method.

HCV change from baseline

HCV RNA levels (log10 IU/mL) declined rapidly with similar decreases in HCV RNA observed in both treatment groups. After 1 week of treatment, the overall mean (SD) change from baseline in HCV RNA levels 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 decreases in HCV RNA were maintained from weeks 2 through the EOT, with mean HCV RNA levels ranging from 1.15 to 1.54 log10 IU/mL, and mean changes from baseline ranging from −5.14 to −4.60 log10 IU/mL across treatment groups.

Proportion of patients with virologic failure

In the SOF/VEL/VOX 8 week group, 4 of 110 patients (3.6%) did not achieve SVR12. Of these, 2 patients (1.9%) relapsed and 2 patients (1.8%) were categorised as “other” because they did not achieve SVR12, but also did not meet the criteria for virologic failure. In the SOF/VEL 12 week group, 4 of 109 patients (3.7%) did not achieve SVR12. Of these, 1 patient (0.9%) had on-treatment virologic failure, 1 patient (0.9%) relapsed, and 2 patients (1.8%) were similarly categorised as “other”. Table 38 presents virologic outcomes by treatment group for patients in the FAS.

Table 38: POLARIS-3: Virologic outcomes (FAS)

	Total (All Genotypes)	
	SOF/VEL/VOX N=110	**SOF/VEL N=109**
SVR12, n/N (%)	106/110 (96.4)	105/109 (96.3)
Overall virological failure	2/110 (1.8)	2/109 (1.8)
Relapse	2/108 (1.9)	1/107 (0.9)
Completed study treatment	2/108 (1.9)	1/107 (0.9)
Discontinued study treatment	0/0	0/0
On-treatment virological failure	0/110	1/109 (0.9)
Other	2/110 (1.8)	2/109 (1.8)

HCV, hepatitis C virus; LLOQ, lower limit of quantitation; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir; VOX, voxilaprevir.
Relapse = confirmed HCV RNA ≥LLOQ during the post-treatment period having achieved HCV RNA<LLOQat last on-treatment visit. 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). Other = patient who did not achieve SVR12 and did not meet virologic failure criteria.

Development of resistance

Baseline deep sequencing of the HCV NS3, NS5A, and NS5B genes was performed for all patients. For all patients with virologic failure, deep sequencing was performed at the first time point after virologic failure if the plasma/serum sample was available and HCV RNA was >1,000 IU/mL. RAV were defined as the specific substitutions that either confer a reduced susceptibility to drugs of the given class with a >2.5-fold change in half-maximal effective concentration (EC50) compared with a genotype-specific reference in a replicon model or that commonly emerge in patients with virologic failure at the time of relapse.

Baseline RAVs had no impact on virologic outcome in either treatment group; all patients with baseline NS3 and/or NS5A RAVs achieved SVR12.

In the SOF/VEL/VOX 8 week group, 2 (1.8%) patients experienced virologic failure. No NS3 or NS5A RAVs were detected in these patients 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. In the SOF/VEL 12 week group, 2 (1.8%) patients experienced virologic failure. Both patients with virologic failure had the NS5A RAV Y93H emerge. No other RAVs were detected at baseline or at virologic failure in these patients.

B.2.6.4.3. Other outcomes of interest

ALT Normalisation

Coincident with decreases in HCV RNA, decreases from baseline in median ALT values were observed in both treatment groups for the duration of treatment and at the post-treatment week 4 visit. Median changes from baseline ranged from −41 to −106 U/L for both treatment groups, with no notable differences between the groups.

HRQL

Four HRQL questionnaires were used, SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C, to assess the effect of treatment on patient-reported outcomes. At the time of post-treatment questionnaire completion, patients were unaware of their response status.

Overall, results from the SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C questionnaires indicated that QOL parameters improved during treatment with SOF/VEL/VOX and SOF/VEL for patients with chronic HCV infection. The mean scores for most scales continued to improve from EOT to post-treatment weeks 4 and 12 (Table 39). These results should be interpreted with caution, as multiple endpoints were tested and the study was not powered to test these exploratory endpoints.

Table 39: POLARIS-3: Summary of HRQL outcomes (FAS)

Instrument	BL Mean (SD)	EOT Mean (SD)	PT week 12 Mean (SD)	BL Mean (SD)	EOT Mean (SD)	PT week 12 Mean (SD)
	SOF/VEL/VOX, N=110			SOF/VEL, N=109		
SF-36, Physical component	43.9 (10.64)	45.6 (10.01) p=0.025[a] p=0.89[b]	46.7 (10.17) p=0.002[a] p=0.10[c] p=0.90[b]	47.1 (9.22)	48.8 (8.80) p=0.058[a]	49.5 (9.70) p=0.001[a] p=0.14[c]
SF-36, Mental component	45.2 (11.76)	48.3 (11.13) p<0.001[a] p=0.20[b]	48.7 (10.53) p=0.002[a] p=0.90[c] p=0.96[b]	46.2 (10.86)	47.9 (11.77) p=0.093[a]	49.5 (10.77) p=0.001[a] p=0.17[c]
CLDQ-HCV	4.5 (1.28)	5.2 (1.19) p<0.001[a] p=0.42[b]	5.3 (1.17) p<0.001[a] p=0.33[c] p=0.69[b]	4.8 (1.17)	5.4 (1.10) p<0.001[a]	5.5 (1.11) p<0.001[a] p=0.092[c]
FACIT-F Trial Outcome Index	66.1 (24.46)	75.7 (24.89) p<0.001[a] p=0.15[b]	77.5 (22.95) p<0.001[a] p=0.40[c] p=0.67[b]	73.9 (21.66)	79.5 (23.14) p=0.002[a]	83.4 (21.95) p<0.001[a] p=0.032[c]
FACIT-F Total score	101.1 (30.75)	114.6 (31.99) p<0.001[a] p=0.16[b]	116.6 (29.98) p<0.001[a] p=0.45[c] p=0.65[b]	110.8 (27.61)	119.7 (29.24) p<0.001[a]	124.0 (27.82) p<0.001[a] p=0.045[c]
WPAI, percentage of overall work impairment due to CHC	19.1 (27.95)	17.8 (25.92) p=0.64[a] p=0.87[b]	19.2 (29.38) p=0.99[a] p=0.85[c] p=0.068[b]	21.2 (26.21)	16.1 (25.97) p=0.27[a]	11.9 (20.18) p=0.039[a] p=0.70[c]
WPAI, percentage of activity impairment due to CHC	33.8 (32.61)	22.7 (29.09) p<0.001[a] p=0.23[b]	21.6 (29.22) p=0.002[a] p=0.51[c] p=0.58[b]	27.1 (27.95)	22.8 (26.52) p=0.027[a]	15.3 (23.72) p<0.001[a] p=0.004[c]

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; RBV, ribavirin; SD, standard deviation; SF-36, Short Form Health Survey; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir; WPAI: Hep C, Work productivity and Activity Impairment: Hepatitis C.
Note: For SF-36, CLDQ-HCV, and FACIT-F total score: a higher value indicates better quality of life outcome. For WPAI, percentage of overall work impairment and WPAI, percentage of activity impairment: a lower value indicated better quality of life.
[a] p-value for change from baseline to time point; [b] p-value for between treatment difference for change from baseline; [c] p-value for change from EOT to time point

Conclusion (POLARIS-3)

- The primary efficacy endpoint was SVR12, defined as HCV RNA<LLOQ12 weeks after discontinuation of the study drug for the FAS. SOF/VEL/VOX FDC administered orally daily for 8 weeks and SOF/VEL FDC administered orally daily for 12 weeks to treatment-naïve patients with HCV GT3.
- The SVR12 rates for the SOF/VEL/VOX 8 week and SOF/VEL 12 week groups were both statistically superior relative to the pre-specified SVR12 performance goal of 83% ($p<0.001$ for both groups). SVR 12 rates were similar between treatment arms: in the SOF/VEL/VOX 8 group were 96.4% (95% CI: 91.0 to 99.0) and SOF/VEL 12 week were 96.3% (95% CI: 90.9 to 99.0).
- The SVR12 and SVR24 rates were the same for both treatment groups.
- Of 110 patients treated with SOF/VEL/VOX, 4 patients experienced virologic failure, 2 of which had relapse determined at post-treatment week 4. Both patients had GT3a CHC; 1 patient was treatment-naïve and the other patient was treatment-experienced (Peg-IFN+RBV). One patient who achieved SVR4 died during the post-treatment period, and 1 patient who completed the study treatment and achieved HCV RNA<LLOQ withdrew consent and had no post-treatment data. Four of 109 patients in the SOF/VEL group did not achieve SVR12.
- HCV RNA levels (log10 IU/mL) declined rapidly with similar decreases in HCV RNA observed in both treatment groups. After 1 week of treatment, the mean change from baseline in HCV RNA levels was −4.06 log10 IU/mL in the SOF/VEL/VOX 8 week group and −4.09 log10 IU/mL in the SOF/VEL 12 week group. Consistent with the rapid and sustained decline in HCV RNA, >85% of patients in each treatment group had HCV RNA <LLOQ at treatment week 4 and >97% of patients in each treatment group had HCV RNA <LLOQ at treatment week 8. At week 12, all (100%) patients in the SOF/VEL 12 week group had HCV RNA <LLOQ.
- Baseline RAVs had no impact on virologic outcome in either treatment group; all patients with baseline NS3 and/or NS5A RAVs achieved SVR12.
- HRQL was assessed using the SF-36, CLDQ-HCV, FACIT-F and WPAI: Hep C questionnaires. Patients treated with SOF/VEL/VOX showed improvements in HRQL measures while on treatment. Mean scores of most scales improved from the end of treatment to post-treatment weeks 4 and 12.

B.2.7. *Subgroup analysis*

Across the POLARIS RCTs pre-planned sub-group analyses were performed on SVR12 rates for randomisation stratification factors and other prognostic baseline characteristics. Point estimates and 2-sided 95% exact CIs (based on the Clopper-Pearson method) were determined for SVR12 rates for treatment groups for each of the following subgroups across all 4 trials:

- Age group (<65 years, ≥65 years)
- Sex at birth (male, female)
- Race (white, non-black, other)
- Ethnicity (Hispanic or Latino, non-Hispanic or Latino)
- Region (US, non-US)
- Baseline BMI (<30 kg/m^2, ≥30 kg/m^2)
- HCV genotype/subtype by sequencing (POLARIS-1, -2, -4)
- Cirrhosis (presence, absence, missing)
- IL28B genotype (CC, non-CC [with non-CC further broken down to CT, TT])
- Baseline HCV RNA (<800,000 IU/mL, ≥800,000 IU/mL)
- Baseline ALT (≤1.5 x ULN, >1.5 x ULN)
- Prior HCV treatment experience (treatment-naïve, treatment-experienced)
- Prior HCV treatment (Peg-IFN+RBV, other) for treatment-experienced patients
- Number of prior HCV treatment regimens (1, 2 or more) for treatment-experienced patients
- Most recent HCV treatment response (non-responder, relapse, other) for treatment-experienced patients
- Adherence to study regimen (<80%, ≥80%)
- Study treatment status (completed study treatment, discontinued study treatment)

A summary of the results for the subgroups are in Appendix E.

B.2.8. *Meta-analysis*

DAA-experience patients

No meta-analysis was required in patients with prior DAA treatment experience, as the economic analysis compared SOF/VEL/VOX with no treatment and the clinical trial (POLARIS-1) provided this head-to-head comparison. Full clinical study results for POLARIS-1 are in Section B.2.6.1.

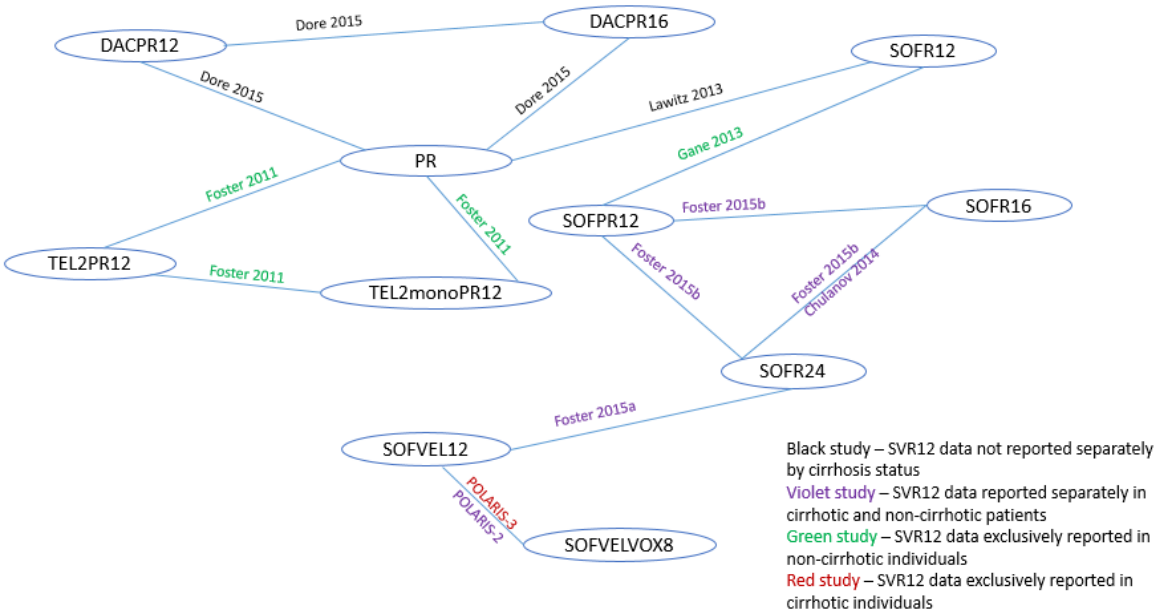
DAA-naïve patient, GT3 infection

A network meta-analysis (NMA) was explored in the SOF/VEL submission, specifically for treatment-naïve patients with GT3 infection. This NMA was deemed inappropriate for use in the economic analysis.

Based on the clinical systematic literature review conducted for the SOF/VEL/VOX submission (see Appendices for further details) the feasibility of conducting an NMA in DAA-naïve patients with GT3 infection was explored. Since the systematic literature review for SOF/VEL was conducted, the only new evidence identified for consideration was the SVR data for DAA-naïve patients with GT3 infection and compensated cirrhosis from the POLARIS-3 trial, and the SVR data for DAA-naïve patients with GT3 infection who are non-cirrhotic from the POLARIS-2 trial.

In order to create the network in DAA-naïve patients (Figure 2) literature reporting SVR outcomes for treatment-naïve patients and treatment-experienced patients (pre-treated with IFN-based regimen) were considered (identified via the systematic literature review described in the Appendics). As the comparator was defined as Peg-IFN2a+RBV, which was consistent with the previous submission in SOF/VEL, the network could only be created if considering patients who are non-cirrhotic and cirrhotic together. Clinical experts agreed that patient METAVIR score was a significant treatment effect modifier and that the requirement to pool data from cirrhotic and non-cirrhotic patients was likely to give rise to heterogeneity that could obscure the true treatment effect of comparator treatments compared with Peg-IFN+RBV. This would be especially true when considering Peg-IFN+RBV in non-cirrhotic patients, which is known to perform quite differently compared with efficacy in cirrhotic patients (see Section B.3.2.2.2. Furthermore, the trials considered in the potential network inconsistent reported the proportion of patients with cirrhosis. In those trials where the information was included, it was clear that the proportion of patients with cirrhosis varied significantly.

Figure 2. Proposed network for DAA-naïve patients with GT3 infection (cirrhotic and non-cirrhotic)



DAC, daclatasvir; PR; pegylated interferon + ribavirin; TEL, telaprevir; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir; VOX, voxilaprevir.

In addition, it is necessary to use the Phase II ELECTRON trial (Gane 2013) to create the network, which compared SOF+RBV 12 weeks with SOF+Peg-IFN4/8/12+RBV. In the ELECTRON trial, the efficacy of both relevant randomised arms i.e. SOF+RBV 12 weeks and SOF+Peg-IFN+RBV 12 weeks, were found to be 100% (80). The finding of an SVR of 100% with SOF+RBV 12 weeks in treatment-naïve patients with GT3 infection in ELECTRON lacks clinical credibility as it has not been replicated in other studies within the SOF development programme. For example, in the Phase III FISSION trial, the SVR rate of SOF+RBV 12 weeks in treatment-naive patients with GT3 infection was 56% (81). The results from ELECTRON can therefore be assumed to be an outlier and an implausible result. This has been discussed and validated by external clinical expert opinion as part of the SOF/VEL submission previously accepted by NICE.

In summary, given the heterogeneity introduced in the network from pooling data from cirrhotic and non-cirrhotic patients and the requirement to include results from the ELECTRON trial, it is not appropriate to use the NMA to inform the economic model. This finding is consistent with the conclusions drawn for the SOF/VEL submission. This decision is appropriate in the context of the NICE scope, which requires economic model analyses to be stratified by treatment history and cirrhosis status, for each genotype. Therefore, an alternative approach to performing economic model comparisons, in which SVR rates from the most appropriate individual trials were used in the model, was deemed to be the most appropriate and transparent approach to take from both a methodological and a clinical perspective (see Section B.2 for SVR data for SOF/VEL/VOX and SOF/VEL and the Appendices for SVR data identified via the systematic literature review). This is consistent with the approach used in the SOF/VEL submission, and previously accepted by NICE.

B.2.9. *Indirect and mixed treatment comparisons*

Not applicable.

B.2.10. *Indirect and mixed treatment comparisons*

Not applicable.

B.2.10.1. *Uncertainties in the indirect and mixed treatment comparisons*

Not applicable.

B.2.11. *Adverse reactions*

Safety evidence for SOF/VEL/VOX in support of this technology appraisal is drawn from the four POLARIS trials (POLARIS-1, -2, -3 and -4), the methodologies for which have been described previously in Section B.2.3.

B.2.11.1. *POLARIS-1*

The majority of patients experienced at least 1 adverse event (AE), including [redacted] of patients in the SOF/VEL/VOX 12 week group and 70.4% of patients in the Placebo 12 week group; [redacted] and 41.4% of patients, respectively, had an AE that was assessed as related to study drug (Table 40).

AE severity

Most AEs reported in the study were mild or moderate in severity (Grade 1/Grade 2). Grade 3 (severe) or 4 (life-threatening) AEs were reported for [redacted] of patients ([redacted]) in the SOF/VEL/VOX 12 week group and 2.6% of patients (4 of 152) in the Placebo 12 week group. Most Grade 3 and 4 AEs were considered to be unrelated to study drug. [redacted] in the SOF/VEL/VOX 12 week had Grade 3 AEs of dizziness and headache that were assessed as not serious but related to study drug. [redacted] in the SOF/VEL/VOX 12 week group had a Grade 4 AE of seizure in addition to Grade 3 AEs of cerebral haemorrhage and neurological neglect syndrome; the seizure was reported as serious and not related to study drug. One patient in the Placebo 12 week group had a Grade 4 AE of ventricular fibrillation that was assessed as serious but not related to study drug.

Treatment-related AEs

A higher proportion of patients in the SOF/VEL/VOX 12 week group ([redacted]) compared with the Placebo 12 week group (41.4%; 63 patients) had AEs that were assessed as related to study drug. The 4 most commonly reported treatment-related AEs were headache, fatigue, diarrhoea, and nausea.

SAEs and deaths

A total of [redacted] in the SOF/VEL/VOX 12 week group and 7 patients (4.6%) in the Placebo 12 week group had SAEs. No trends in SAEs were observed, and no SAE was reported in more than 1 patient. All SAEs were considered to be unrelated to study drug.

No deaths were reported during this study.

Discontinuations

[redacted], [redacted] in the SOF/VEL/VOX 12 week group and 3 in the Placebo 12 week group, had AEs that led to discontinuation of study drug.

Other AEs

Most laboratory abnormalities were Grade 1 or Grade 2 in severity. The incidence of Grade 3 and 4 hematologic laboratory abnormalities was similar for both treatment groups; there were no clinically meaningful hematologic abnormalities. Patients in the SOF/VEL/VOX 12 week group had Grade 3 or 4 chemistry abnormalities of elevated AST (Grade 3, [redacted]; [redacted]), elevated creatinine kinase (Grade 3, [redacted]; [redacted]: Grade 4, [redacted]), elevated serum glucose (Grade 3, [redacted]), elevated lipase (Grade 3, [redacted]Grade 4, [redacted]), and elevated total bilirubin (Grade 3, [redacted]). In the SOF/VEL/VOX 12 week group, all Grade 3 or 4 creatinine kinase elevations were isolated events and were attributed by the investigators to exercise, all Grade 3 or 4 lipase elevations were asymptomatic and generally transient with no cases of clinical pancreatitis, and Grade 3 or 4 serum glucose elevations occurred in patients with a medical history of diabetes. The most commonly observed Grade 3 or 4 laboratory abnormalities observed in placebo treated patients were elevated AST (Grade 3, [redacted]), consistent with untreated HCV infection, and elevated serum glucose (Grade 3, [redacted]) that mostly occurred in patients with a medical history of diabetes.

No notable changes from baseline in vital signs were observed during the study. No patients had clinically significant ECG abnormalities.

Table 40: POLARIS-1: adverse events summary (SAS)

Adverse events, n (%)	SOF/VEL/VOX 12 weeks (N=263)	Placebo 12 weeks (N=152)
Number of patients experiencing any		
AE	[redacted]	107 (70.4)
Grade 3 or above AE	[redacted]	4 (2.6)
Treatment related AE	[redacted]	63 (41.4)
Grade 3 or above treatment related AE	[redacted]	0
Serious AE	[redacted]	7 (4.6)
Treatment related SAE	[redacted]	0
AE leading to premature discontinuation of the study drug	[redacted]	3 (2.0)
Adverse Event Leading to Interruption of the Study Drug	[redacted]	1 (0.7)
All Deaths	[redacted]	0
AE in ≥5% of patients		
Headache	[redacted]	26 (17.1)
Fatigue	[redacted]	30 (19.7)

Adverse events, n (%)	SOF/VEL/VOX 12 weeks (N=263)	Placebo 12 weeks (N=152)
Diarrhoea	[redacted]	19 (12.5)
Nausea	[redacted]	12 (7.9)
Asthenia	[redacted]	9 (5.9)
Insomnia	[redacted]	8 (5.3)
Dizziness	[redacted]	14 (9.2)
Back pain	[redacted]	8 (5.3)
Arthralgia	[redacted]	8 (5.3)
Treatment related AE in ≥5% of patients		
Headache	[redacted]	21 (13.8)
Fatigue	[redacted]	23 (15.1)
Diarrhoea	[redacted]	14 (9.2)
Nausea	[redacted]	10 (6.6)
Asthenia	[redacted]	6 (3.9)
Insomnia	[redacted]	5 (3.3)

AE, adverse event; CI, confidence interval; SAE, serious adverse event.
Common AEs were those that occurred in ≥5% of patients in any treatment group.

B.2.11.2. *POLARIS-4*

The majority of patients experienced at least 1 AE, including 76.9% of patients in the SOF/VEL/VOX 12 week group and 73.5% of patients in the SOF/VEL 12 week group. Of these patients, 58.2% and 51.0% experienced an AE that was considered related to study drug in the SOF/VEL/VOX 12 week and SOF/VEL 12 week groups, respectively (Table 41).

The most commonly reported AEs (>10% in either treatment group) were headache ([redacted]), fatigue ([redacted]), diarrhoea ([redacted]) and nausea ([redacted]) in the SOF/VEL/VOX 12 week group, and headache and fatigue (28.5%; 43 patients each) and nausea (7.9%; 12 patients) in the SOF/VEL 12 week group.

The type and incidence of common AEs were similar for the 2 treatment groups, with the exception of diarrhoea, which were reported for [redacted] patients in the SOF/VEL/VOX 12 week group compared with the SOF/VEL 12 week group. All of the AEs of diarrhoea were assessed as Grade 1 or 2 in severity. In the SOF/VEL/VOX 12 week group, [redacted] experienced diarrhoea, and, for most of these patients, AEs of diarrhoea ([redacted]) were Grade 1.

AE severity

Most AEs reported in the study were mild or moderate in severity (Grade 1/Grade 2). A total of 4 patients ([redacted] in each treatment group) experienced a Grade 3 or 4 AE. No Grade 3 or 4 AE was reported in more than 1 patient, and all Grade 3 or 4 AEs were considered to be unrelated to study drug.

[redacted] in the SOF/VEL/VOX 12 week group experienced a Grade 4 AE of illicit drug overdose, which was considered serious, and had an outcome of death. The remaining AEs

were Grade 3 (congestive cardiac failure, [redacted] in the SOF/VEL/VOX 12 week group and cerebrovascular accident and lumbar spinal stenosis, 1 patient each in SOF/VEL 12 weeks) and resolved. All of these AEs were considered serious. The Grade 3 AE of congestive heart failure led to interruption of the study drug.

Treatment-related AEs

A higher proportion of patients in the SOF/VEL/VOX 12 week group ([redacted]) compared with the Placebo 12 week group (51.0%; 77 patients) had AEs that were assessed as related to study drug. The most commonly reported treatment-related AEs were the same as the most commonly reported AEs overall (headache, fatigue, diarrhoea, and nausea). Similar trends were observed for the SOF/VEL/VOX 12 week and SOF/VEL 12 week groups, with the exception that treatment-related AEs of nausea and diarrhoea were more common in the SOF/VEL/VOX 12 week group compared with the SOF/VEL 12 week group.

SAEs and deaths

A total of [redacted] in the SOF/VEL/VOX 12 week group and 4 patients (2.6%) in the SOF/VEL 12 week group had SAEs. No trends in SAEs were observed, and no SAE was reported for greater than 1 patient. All SAEs were considered to be unrelated to study drug.

[redacted] in the SOF/VEL/VOX 12 week group died of an illicit drug overdose 2 days after the last dose of study drug. The preliminary toxicology report indicated the presence of heroin and fentanyl. The AE of overdose was considered Grade 4, serious, but not related to study drug.

Discontinuations

[redacted] in the SOF/VEL 12 week group experienced an AE of headache that led to the premature discontinuation of study drug on day 56. This event was considered Grade 2, related to study drug, and resolved following study drug discontinuation.

Other AEs

Most laboratory abnormalities were Grade 1 or 2 in severity. The most common Grade 3 haematology laboratory abnormality was decreased platelet count in the SOF/VEL/VOX 12 week and SOF/VEL 12 week groups ([redacted] and 1.3%, respectively). No Grade 3 haematology laboratory abnormalities were associated with clinical symptoms or reported as AEs. No Grade 4 haematology laboratory abnormalities were observed.

The most common Grade 3 chemistry laboratory abnormality was increased serum glucose in the SOF/VEL/VOX 12 week and SOF/VEL 12 week groups ([redacted] and 2.0%, respectively). All of the patients with Grade 3 increased serum glucose had a history of diabetes. Four patients had a Grade 3 or 4 laboratory abnormality of increased lipase. These abnormalities were asymptomatic, with no cases of clinical pancreatitis.

No patients reported pregnancies. Across treatment groups, there were no notable changes in vital sign measurements. No patients in either treatment group had a treatment-emergent clinically significant abnormal 12-lead ECG.

Table 41: POLARIS-4 adverse events summary (SAS)

Adverse events, n (%)	SOF/VEL/VOX 12 weeks (N=182)	SOF/VEL 12 weeks (N=151)
Number of patients experiencing any		
Adverse event	[redacted]	111 (73.5)
Grade 3 or above AE	[redacted]	2 (1.3)
Treatment related AE	[redacted]	77 (51.0)
Grade 3 or above treatment related AE	[redacted]	0
Serious AE	[redacted]	4 (2.6)
Treatment related SAE	[redacted]	0
AE leading to premature discontinuation of the study drug	[redacted]	1 (0.7)
Adverse Event Leading to Interruption of the Study Drug	[redacted]	0
All Deaths	[redacted]	0
AE in ≥5% of patients		
Headache	[redacted]	43 (28.5)
Fatigue	[redacted]	43 (28.5)
Diarrhoea	[redacted]	7 (4.6)
Nausea	[redacted]	12 (7.9)
Back pain	[redacted]	8 (5.3)
Asthenia	[redacted]	9 (6.0)
Insomnia	[redacted]	3 (2.0)
Abdominal pain	[redacted]	9 (6.0)
Irritability	[redacted]	8 (5.3)
Treatment related AE in ≥5% of patients		
Headache	[redacted]	34 (22.5)
Fatigue	[redacted]	34 (22.5)
Diarrhoea	[redacted]	4 (2.6)
Nausea	[redacted]	5 (3.3)
Asthenia	[redacted]	9 (6.0)
Irritability	[redacted]	8 (5.3)

AE, adverse event; CI, confidence interval; SAE, serious adverse event.
Common AEs were those that occurred in ≥5% of patients in any treatment group.

B.2.11.3. *POLARIS-2*

The majority of patients experienced at least 1 AE, including [redacted] of patients in the SOF/VEL/VOX 8 week group and 68.9% of patients in the SOF/VEL 12 week group (Table 42).

The most commonly reported AEs (>10% in either treatment group) were headache ([redacted]), fatigue ([redacted]), diarrhoea ([redacted]) and nausea

([redacted]) in the SOF/VEL/VOX 8 week group, and headache (22.5%; 99 patients), fatigue (20.5%; 90 patients), nausea (9.1%; 40 patients) and diarrhoea (7.3%; 32 patients) in the SOF/VEL 12 week group.

The type and incidence of common AEs were similar for the 2 treatment groups, with the exception of diarrhoea and nausea, which were reported for [redacted] patients in the SOF/VEL/VOX 8 week group compared with the SOF/VEL 12 week group. In most cases these AEs were Grade 1 (diarrhoea: [redacted], [redacted]; nausea: [redacted], [redacted]).

AE severity

Most AEs reported in the study were mild or moderate in severity (Grade 1/Grade 2). A total of [redacted] patients ([redacted]) in the SOF/VEL/VOX 8 week group and [redacted]([redacted]) in the SOF/VEL 12 week group had a Grade 3 AE. Two Grade 4 (life-threatening) AEs were reported for 1 patient (0.2%) in the SOF/VEL 12 week group who attempted suicide by a motor vehicle accident (not attributed to study drug). None of the other Grade 3 or 4 AEs were reported in more than 1 patient.

Treatment-related AEs

A [redacted]percentage of patients in the SOF/VEL/VOX 8 weeks group experienced treatment-related AEs ([redacted]) compared with the SOF/VEL 12 week group (41.4%). The most common treatment-related AEs were fatigue, headache, insomnia, nausea and diarrhoea.

SAEs and deaths

A total of [redacted] ([redacted]) patients in the SOF/VEL/VOX 8 week group and [redacted] ([redacted]) patients in the SOF/VEL 12 week group had SAEs. No trends in SAEs were observed, and no SAE were reported in more than 1 patient. All SAEs were considered to be unrelated to study drug.

In the SOF/VEL 12 week group, 1 patient had an SAE that led to discontinuation of study drug on study day 81, and 1 patient had an SAE (severe depression) that led to interruption of SOF/VEL dosing. No patients died during the study.

Discontinuations

Two patients (both in the SOF/VEL 12 week group) had AEs that led to discontinuation of study drug. Both events were considered to be unrelated to the study drug.

Other AEs

Most laboratory abnormalities were Grade 1 (35.7%; 336 of 940 patients) or 2 (14.8%; 139 of 940 patients). The most common Grade 3 haematology laboratory abnormality was decreased platelet count in the SOF/VEL/VOX 8 week group ([redacted]) and decreased lymphocytes, neutrophils and platelets SOF/VEL 12 week groups (all at 0.5%).

In general, Grade 3 decreases in lymphocytes and neutrophils were either isolated events or intermittent and transient, and none were reported as AEs. The only reported Grade 4 abnormality was decreased lymphocytes (0.2%; 1 patient in the SOF/VEL 12 week group). The most common Grade 3 chemistry laboratory abnormality was increased serum glucose in the SOF/VEL/VOX 8 week and SOF/VEL 12 week group ([redacted]and 0.7%, respectively). All of the patients with Grade 3 increased serum glucose had a history of diabetes. [redacted] ([redacted]) in the SOF/VEL/VOX 8 week group and 3 patients (0.7%) in the SOF/VEL 12 week

group had a Grade 3 or 4 laboratory abnormality of increased lipase. These abnormalities were asymptomatic, with no cases of clinical pancreatitis.

[redacted] in the SOF/VEL/VOX 8 week group became pregnant during the study. Across treatment groups, there were no notable changes from baseline in vital sign measurements. One patient in the SOF/VEL 12 week group had an ECG with atrial flutter considered clinically significant at the week 12 visit.

Table 42: POLARIS-2 adverse events summary (SAS)

Adverse events, n (%)	SOF/VEL/VOX 8 weeks (N=501)	SOF/VEL 12 weeks (N=440)
Number of patients experiencing any		
AE	[redacted]	303 (68.9)
Grade 3 or above AE	[redacted]	6 (1.4)
Treatment-related AE	[redacted]	182 (41.4)
Grade 3 or above treatment related AE	[redacted]	0
Serious AE	[redacted]	7 (1.6)
Treatment-related serious AE	[redacted]	0
AE leading to premature discontinuation of the study drug	[redacted]	2 (0.5)
AE leading to interruption of the study drug	[redacted]	2 (0.5)
All deaths	[redacted]	0
AE in ≥5% of patients		
Headache	[redacted]	99 (22.5)
Fatigue	[redacted]	90 (20.5)
Diarrhoea	[redacted]	32 (7.3)
Nausea	[redacted]	40 (9.1)
Asthenia	[redacted]	27 (6.1)
Insomnia	[redacted]	21 (4.8)
Arthralgia	[redacted]	24 (5.5)
Treatment related AE in ≥5% of patients		
Headache	[redacted]	76 (17.3)
Fatigue	[redacted]	57 (13.0)
Diarrhoea	[redacted]	16 (3.6)
Nausea	[redacted]	32 (7.3)

AE, adverse event; CI, confidence interval; SAE, serious adverse event.
Common AEs were those that occurred in ≥5% of patients in any treatment group.

B.2.11.4. *POLARIS-3*

The majority of patients experienced at least 1 AE, including [redacted] of patients in the SOF/VEL/VOX 8 week group and 74.3% of patients in the SOF/VEL 12 week group (Table 43).

The most commonly reported AEs (>10% in either treatment group) were fatigue ([redacted]), headache ([redacted]), nausea ([redacted]) and diarrhoea ([redacted]) in the SOF/VEL/VOX 8 week group, and headache (29.4%; 32 patients), fatigue (28.4%; 31 patients), nausea (9.2%; 10 patients) and diarrhoea (4.6%; 5 patients) in the SOF/VEL 12 week group.

The type and incidence of common AEs were [redacted] for the 2 treatment groups, with the [redacted] of diarrhoea and nausea, which were reported [redacted] patients in the SOF/VEL/VOX 8 week group compared with the SOF/VEL 12 week group. In most cases these AEs were Grade 1 (diarrhoea: [redacted]; nausea: [redacted]).

AE severity

Most AEs reported in the study were Grade 1 (mild) or 2 (moderate) in severity. Grade 3 AEs (severe) occurred in [redacted] ([redacted]) in the SOF/VEL/VOX 8 week group and in 4 patients (3.7%) in the SOF/VEL 12 week group. Two patients, both in the SOF/VEL 12 week group had Grade 3 AEs that were assessed as related to study drug (headache and hypertensive. No Grade 4 (life-threatening) AEs were reported.

Treatment-related AEs

A [redacted] percentage of patients in the SOF/VEL/VOX 8 week group experienced treatment-related AEs ([redacted]) compared with the SOF/VEL 12 week group (46.8%; 51 patients). The most common treatment-related AEs were headache, fatigue, nausea and diarrhoea.

SAEs and deaths

A total of [redacted] ([redacted] patients in the SOF/VEL/VOX 8 week group and 3 (2.8%) patients in the SOF/VEL 12 week group had SAEs. No trends in SAEs were observed, and no SAE were reported in more than 1 patient. All SAEs were considered to be unrelated to the study drug.

There were was [redacted] non-treatment-related death reported, occurring in the SOF/VEL/VOX 8 week group, on post-treatment day 78. The death was due to hypertension.

Discontinuations

One patient in the SOF/VEL 12 week group discontinued the study drug on day 6 due to a SAE (Grade 2 pelvic fracture). The SAE was considered to be unrelated to the study drug.

Other AEs

Most laboratory abnormalities were Grade 1 (36.7%, 80 of 218 patients) or 2 (24.3%, 53 of 218 patients). The most common Grade 3 laboratory abnormality was decreased lymphocytes in the SOF/VEL/VOX 8 week group ([redacted]) compared to none in SOF/VEL 12 week group.

Grade 3 decreases in haemoglobin, lymphocytes, and neutrophils were either isolated events or intermittent and transient and none were assessed as AEs. The only reported Grade 4 abnormality was decreased lymphocytes ([redacted]; [redacted] in each treatment group). The most common Grade 3 chemistry laboratory abnormality was increased serum glucose

in the SOF/VEL/VOX 8 week and SOF/VEL 12 week groups ([redacted] and 2.8%, respectively). All of the patients with Grade 3 increased serum glucose had a history of diabetes. [redacted] in the SOF/VEL/VOX 8 week group and one patient (0.9%) in the SOF/VEL 12 week group had a Grade 3 laboratory abnormality of increased lipase. These abnormalities were asymptomatic, with no cases of clinical pancreatitis. [redacted] Grade 4 chemistry laboratory abnormality was reported for creatinine kinase in the SOF/VEL/VOX 8 week group.

No patients reported pregnancies. Across treatment groups, there were no notable changes from baseline in vital sign measurements. No patients in either treatment group had a treatment-emergent clinically significant abnormal 12-lead ECG.

Table 43: POLARIS-3: adverse events summary (SAS)

Adverse events, n (%)	SOF/VEL/VOX 8 weeks (N=110)	SOF/VEL 12 weeks (N=109)
Number of patients experiencing any		
AE	[redacted]	81 (74.3)
Grade 3 or above AE	[redacted]	4 (3.7)
Treatment-related AE	[redacted]	51 (46.8)
Grade 3 or above treatment related AE	[redacted]	2 (1.8)
Serious AE	[redacted]	3 (2.8)
Treatment-related serious AE	[redacted]	0
AE leading to premature discontinuation of the study drug	[redacted]	1 (0.9)
AE leading to interruption of the study drug	[redacted]	0
All deaths	[redacted]	0
AE in ≥5% of patients		
Fatigue	[redacted]	31 (28.4)
Headache	[redacted]	32 (29.4)
Nausea	[redacted]	10 (9.2)
Diarrhoea	[redacted]	5 (4.6)
Abdominal pain	[redacted]	5 (4.6)
Insomnia	[redacted]	5 (4.6)
Abdominal pain upper	[redacted]	7 (6.4)
Muscle spasms	[redacted]	2 (1.8)
Vomiting	[redacted]	1 (0.9)
Back pain	[redacted]	6 (5.5)
Myalgia	[redacted]	6 (5.5)
Treatment related AE in ≥5% of patients		
Headache	[redacted]	24 (22.0)
Fatigue	[redacted]	15 (13.8)
Diarrhoea	[redacted]	3 (2.8)
Nausea	[redacted]	7 (6.4)

AE, adverse event; CI, confidence interval; SAE, serious adverse event.
Common AEs were those that occurred in ≥5% of patients in any treatment group.

B.2.12. *Ongoing studies*

There are currently no ongoing studies involving SOF/VEL/VOX.

B.2.13. *Innovation*

DAA-experienced patients

SOF/VEL/VOX is the only pan-genotypic STR available for the treatment of DAA-experienced patients, regardless of cirrhosis status. Clinical trial evidence indicates that SOF/VEL/VOX can offer high cure rates among this difficult to treat group. This treatment therefore represents an important advance on previous treatments in that it offers the realistic prospect of CHC cure to the small number of patients who do not achieve SVR after initial treatment with a DAA-containing regimen (including NS5A-containing regimens).

There is currently no licensed and reimbursed pharmacologic treatment option for the retreatment of DAA-experienced patients, and limited guidance available to inform retreatment decisions. By not achieving SVR, DAA-experienced patients are at risk of fibrosis and cirrhosis advancement, continuing risk of HCC and increasing risk of liver and non-liver-related mortality (65-69). The longer a patient remains infected with HCV, the greater the risk of transmitting the infection and perpetuating the burden of disease. This is especially true for patients who inject drugs, where preventing transmission in these populations through curing the HCV infection is a cost-effective approach (67, 82-84).

SOF/VEL/VOX can therefore address a substantial current unmet need, should it be recommended in this patient population.

DAA-naïve patients with GT3 infection

As a patient population, GT3 represents a large (44% (3)) and difficult to treat group. Patients with GT3 infection are at a greater risk of disease progression (70) and worsening liver disease compared with other GTs (68). Moreover, this patient population have typically worse virologic response to DAA therapy (i.e. fewer achieve SVR), particularly in those who have advanced liver disease (i.e. are cirrhotic patients).Higher pill burden and longer duration of RBV treatment are both associated with poor adherence and virologic outcomes (74-77). The presence of cirrhosis is also associated with worse adherence and virology outcomes (78).

SOF/VEL/VOX has demonstrated high cure rates in both non-cirrhotic and cirrhotic DAA-naïve GT3 patients, with SVRs of >95% after 8 weeks of treatment compared with 12 weeks of treatment with SOF/VEL. It therefore represents the first 8 week therapeutic option for the treatment of CHC in all DAA-naïve GT3 patients, including those who have previously failed on an IFN therapy, regardless of cirrhosis status.

SOF/VEL/VOX can therefore address a substantial current unmet need, should it be recommended in this patient population.

Overall

The EMA adopted an accelerated regulatory process for SOF/VEL/VOX, a designation only granted to those medicines of major public health interest. In addition, SOF/VEL/VOX fulfils a number of criteria identified by the Kennedy Report as constituting innovation (85):

- SOF/VEL/VOX offers a STR for all patients with CHC who are DAA-experienced, regardless of cirrhosis status, and as an 8 week option for patients with GT3 infection, who are DAA-naïve, regardless of cirrhosis status. Therefore, SOF/VEL/VOX has the potential to significantly and substantially improve the care of patients with CHC.
- By providing a cure for the majority of patients in these subgroups, treatment with SOF/VEL/VOX has the potential to reduce HCV related-liver disease and associated mortality. This meets a need important to the NHS, as evidenced by the recent NHS Outcomes Framework reflecting the government commitment to reduce mortality due to liver disease in people under 75 years of age (86).

In 2016, NHS England set an annual treatment target for CHC of 10,000 patients, increasing to 15,000 per year by 2020 (11). SOF/VEL/VOX represents a simple and effective therapeutic regimen to help achieve the treatment target in England.

B.2.14. *Interpretation of clinical effectiveness and safety evidence*

B.2.14.1. *Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology*

Key efficacy data supporting the use of SOF/VEL/VOX for patients with CHC infection of any genotype (GT1-6) are summarised in Section B.2.6 and described below, with GT-specific summaries provided in **Error! Reference source not found.**.

DAA-experienced

Very high cure rates (SVR) of 90-100% can be achieved in adult patients with CHC GT1-6 infection with SOF/VEL/VOX administered as an STR once daily for 8 or 12 weeks (depending on treatment experience). In POLARIS-1 and -4, the SOF/VEL/VOX group met the primary endpoint of an SVR rate that was statistically significant to the pre-specified goal of 85%. The SVR12 rate of the SOF/VEL/VOX 12 week group was 96.2% in POLARIS-1 and 97.8% in POLARIS-4. These results support the efficacy of SOF/VEL/VOX in the treatment of all DAA-experienced patients (12 weeks).

DAA-naïve

POLARIS-2 SOF/VELVOX did not meet its primary endpoint, yet a high cure rate of 95.2% at 8 weeks treatment was achieved in GT1, 2, 4, 5 & 6 patients and GT3 non-cirrhotic patients. In POLARIS-3 in GT3 cirrhotics, SVR12 rates for both 8 weeks SOF/VEL/VOX and 12 weeks SOF/VEL were both over 96% and were statistically superior relative to the pre-specified goal of 83%.These results support the efficacy of SOF/VEL/VOX in the treatment of DAA-naïve patients who have GT3 infection, regardless of cirrhosis status (8 weeks). Although POLARIS-2 did not meet its primary endpoint across all SOF/VEL/VOX treated patients, subgroup analysis of GT3 non-cirrhotic patients reported an SVR12 of 98.9% at 8 weeks in the SOF/VEL/VOX group compared with 96.6% at 12 weeks in the SOF/VEL group.

Overall in the POLARIS programme, high cure rates were achieved irrespective of cirrhotic status (with or without) and prior CHC treatment experience (DAA-naïve or DAA-experienced). Some patients with CHC are ineligible for IFN- or RBV-containing regimens due to contraindications and intolerance, and while some IFN- and RBV-free regimens – such as LDV/SOF, SOF+DCV, OBV/PTV/RTV±DSV – are recommended by NICE in discrete populations (see Section Table 3), SOF/VEL/VOX provides an IFN-free and RBV-free treatment option that is highly effective across all GTs. Furthermore, the 2016 EASL guidelines have recommended IFN-free regimens as the best options regardless of treatment history and cirrhosis status due to their efficacy, tolerability and ease of use (2). This guidance has been further developed in the UK consensus guidelines 2017 (5) where clinicians representing all major hepatitis C groups have advocated removal of IFN entirely, avoidance of RBV-containing regimens, and simplification of prescribing decisions to facilitate non-specialist community based treatment in situations with close proximity to the patient such as general practice, prisons, community pharmacies, and substance misuse services. Of 1,056 patients randomised to and receiving at least one dose of SOF/VEL/VOX in POLARIS-1, -2, -3 and -4 (FAS), 96% (1,014) were cured of their CHC, 2.8% (30) experienced virologic relapse after treatment, 0.09% (1) experienced on-treatment failure and one patient was also lost to follow-up. Across all patients exposed to the study drug, 0.4% (4) discontinued due to AEs and 0.2% (2) died, however both deaths were considered to be unrelated to the study treatment.

Baseline NS3 and/or NS5A RAVs did not impact on virological outcomes in the SOF/VEL/VOX treatment groups, regardless of GT, treatment history or cirrhosis status. Across the 4 POLARIS trials, SVR12 in those patients with baseline RAVs was 93.6-100.0% and without baseline RAVs was 97.7-100.0%.

HRQL questionnaires indicated no on-treatment decrements in HRQL in SOF/VEL/VOX treated patients. Improvements in HRQL were observed for most scales from the end of treatment to post-treatment week 4 and 12.

B.2.14.2. *Strengths and limitations of the clinical evidence base for the technology*

Strengths

- A comprehensive clinical trial program assessed the efficacy and safety of SOF/VEL/VOX at the SmPC recommended for a treatment duration of 8 or 12 weeks, dependent on treatment history and cirrhosis status:
    - Three pivotal multicentre, randomised, active- or placebo-controlled, Phase III studies POLARIS-1,-2 and -4 in adult patients with CHC GT1-6. These studies supports the pan-genotypic use of SOF/VEL/VOX for a treatment duration of 12 weeks for DAA-experienced (with or without cirrhosis) and 8 weeks for DAA-naïve patients (without cirrhosis; or with cirrhosis in GT1, 2 or 4).
    - One pivotal multicentre, randomised Phase III study (POLARIS-3) included adult patients with CHC GT3, with cirrhosis. This study supports the use of SOF/VEL/VOX for 8 weeks for DAA-naïve patients with GT3 infection who have cirrhosis.
- Other than POLARIS-1, the three other POLARIS trials had an active comparator (SOF/VEL), rather than placebo, which allows for head to head comparisons. All of the trials had larger numbers of patients than previous trials in hepatitis C, and patients were largely representative of the UK hepatitis C population because recruitment was conducted across a number European countries.
- POLARIS-1 was a placebo-controlled, double-blind study, and POLARIS-2, -3 and -4 were open label trials that used an active comparator, SOF/VEL, a licenced and NICE-recommended treatment option for patients with CHC GT1-6. The placebo-controlled design of POLARIS-1 allowed for an assessment of the contribution of the active drugs – SOF, VEL and VOX – to the safety profiled of the active treatment, while the double-blind design reduced the risk of bias in this assessment.
- All POLARIS studies were multicentre and used recognised and clinically valid endpoints. All of the POLARIS studies used SVR12 as the primary endpoint, which is recognised by regulatory agencies to be the appropriate and clinically endpoint in CHC trials. It is a hard endpoint, which not only increases confidence in the reported results but also helps to facilitate unbiased comparisons with other studies, which also use this endpoint.
- The POLARIS studies provide evidence for a wide range of patient subgroups that reflect patient characteristics seen in clinical practice. The trials included substantial proportions of patients with different stages of liver disease (from non-cirrhotic to fibrosis to compensated cirrhotic), previous treatment failure, high baseline HCV viral load, black race, older age, high BMI, CHC GT1a, and a non-CC IL28B genotype. Subgroup analyses across POLARIS-1, -2, -3 and -4 showed that SVR12 rates with SOF/VEL/VOX regimens were not substantially affected by any predefined characteristic.

Limitations:

- POLARIS-2,-3 and -4 were open-label in design. Using a double-blind design would have meant increasing the complexity of treatment administration, requiring additional placebo tablets in both arms of both studies, and thus increasing administration burden.
- No UK specific studies have been performed; however, the POLARIS trials have been conducted in populations that can be considered as broadly representative of the UK population. The POLARIS studies recruited patients across the United States, Canada, France, Germany, United Kingdom Australia and New Zealand. Nine patients over 6 sites (POLARIS-1), 12 patients over 5 sites (POLARIS-4), 47 patients over 8 sites (POLARIS-2) and 15 patients over 6 sites (POLARIS-3) were recruited in the UK. Subgroup analyses generally showed that SVR12 rates with SOF/VEL/VOX regimens were not affected by any predefined patient characteristic (see **Error! Reference source not found.**).

Relevance of the evidence base and the outcomes measured

The clinical evidence base presented herein reflects the entirety of the Phase III evidence base supporting the licensed indication for SOF/VEL/VOX, with the exception of DAA-naïve, GT3 cirrhotic patients, where the evidence presented herein is for 8 weeks of treatment with SOF/VEL/VOX, not 12 weeks as per the license. The license does however, include a footnote allowing 8 weeks of treatment to be considered in this population, which is supported by the findings of POLARIS-3. The clinical evidence base presented also addresses the decision problem defined by NICE. The patient populations enrolled into clinical trials included those with the highest unmet clinical need, such as those with GT3 infection and those with prior DAA-treatment history, and are representative of the real-world CHC population. The outcomes achieved within the clinical trials are therefore expected in real-world clinical practice.

The primary goal of treatment for CHC is to cure the infection by eradicating the hepatitis C virus. In this regard, treatment efficacy is measured as the proportion of patients in whom the virus is undetectable at a defined time point, typically 12 or 24 weeks following treatment cessation; this is referred to as an SVR (87). Long-term follow-up studies have shown that an SVR corresponds to a definitive cure of HCV infection in more than 99% of cases determining the efficacy of treatment for CHC (88).

Achieving SVR, and therefore being cured of CHC, is associated with a wide range of benefits, including regression of fibrosis and cirrhosis, and has been associated with a reduced rate of hepatic decompensation, a reduced risk for HCC and reduced rates of both liver and non-liver related mortality (65-69). In addition, patients experience improved HRQL (14, 89), require reduced healthcare utilisation (90), and importantly, are no longer at risk of transmitting HCV to others.

Through improving cure rates and potentially reducing onward transmission, SOF/VEL/VOX has the potential to positively impact public health by reducing the prevalence and incidence of CHC in the UK and thus reducing the long-term burden that it causes to the NHS.

External validity

Demographic data from the UK suggests that around two-thirds of patients with CHC are male (15, 91), with a median age at diagnosis of approximately 41 years and an interquartile range of 34–49 (4). There were generally more males enrolled in POLARIS-1 and -4 (76-80%) than the UK average, and compared with POLARIS-2 and -3 (50-76%). The age distribution seen across the POLARIS trials was generally consistent with demographic data (mean age was between 50 and 58 years). This is closely aligned with the mean age of 54 years for patients treated in the Expanded Access Programme in England (92).

The majority of patients across all POALRIS studies were White (78–91%), Black (0–15%) or Asian (1–10%). Subgroup analyses have demonstrated that demographic factors including race and ethnic group, as well as age and sex, did not have a substantial impact on the SVR12 rates achieved. The proportion of Black patients was very low in POLARIS-3 (<1%), reflecting the low incidence of GT3 CHC among Black patients in some geographical regions.

All trials presented in this submission provide evidence to support the licensed dose (400 mg SOF/100 mg VEL/100 mg VOX). All trials include treatment arms that are relevant to the licensed regimens (SOF/VEL or SOF/VEL/VOX) for the recommended treatment duration of 8 or 12 weeks depending on prior treatment history and cirrhotic state.

B.2.14.3. *Life expectancy*

While there are data clearly demonstrating that CHC is associated with increased morbidity and mortality, published data on the actual life expectancy of people with CHC are limited and dependent on the degree of liver fibrosis and ongoing addictive behaviour, especially alcohol (93).

A cohort study conducted in England compared the death rates of 2,285 patients with HCV infection to that seen in an age- and sex-matched English population and found that standardised mortality rates were 3-times higher than those expected in the general population (93). Mean age amongst those that died during the study (n=180) was 51.6 years, with an average of 27 years of life lost (93).

Data on patients with liver disease, from the British Society of Gastroenterology, highlight that the average age of someone dying with liver disease is 59 years compared to 82−84 years for heart and lung disease and stroke (94).

B.3. Cost effectiveness

B.3.1. *Published cost-effectiveness studies*

During the review, 119 studies were identified that presented economic data in hepatitis C. It was considered that studies using UK economic and resource inputs were most relevant, therefore the thirteen studies from a UK economic perspective were extracted in Table 44 below.

Table 44: Overview of economic models

Note: Historically, studies report patients as treatment-naïve (TN)/ treatment experienced (TE) rather than DAA-naïve/ DAA-experienced, thus patients have been identified as TN/TE in the following studies

Study	Summary of the model	Treatments	Patient population	QALYs	Costs	ICER
Marie et al. 2016 (95)	Markov model simulating a cohort of TN patients for a lifetime. The model structure is based on the models submitted to the NICE for HCV during previous health technology appraisals	Arm 1 (all): LDV/SOF 8 weeks Arm 2 (cirrhotic): LDV/SOF 12 weeks	TN, cirrhotic and non-cirrhotic	NR	Arm 1: £34,164 Arm 2: £32,568	Arm 1 vs 2: **Dominated**
Westerhout et al. 2015 (96)	Cost-utility model with two phases: anti-viral treatment period and lifespan outcomes	Arm 1: Peg-IFN-RBV 48 weeks Arm 2: SMV + Peg-IFN-RBV 24 weeks Arm 3: TVR + Peg-IFN-RBV 48 weeks Arm 4: BOC + Peg-IFN-RBV 48 weeks	GT1 and GT4 HCV	Arm 1 (TN) 11.651; (TE) 9.843 Arm 2 (TN) 12.776; (TE) 11.359 Arm 3 (TN) 12.618; (TE) 11.282 Arm 4 (TN) 12.570; (TE) 11.194	Arm 1 (TN) £25,358; (TE) £32,113 Arm 2 (TN) £36,298; (TE) £43,962 Arm 3 (TN) £40,241; (TE) £45,515 Arm 4 (TN) £41,099; (TE) £51,258	Arm 2 vs 1 (TN) £9,725; (TE) £7,819 Arm 2 vs 3: **Dominant** Arm 2 vs 4: **Dominant**
Cure et al 2015 (97)	Markov state-transition model with lifetime horizon	Arm 1 (all): GT1: SOF/ Peg-IFN-RBV 12 weeks or Peg-IFN-RBV 48 weeks or TVR + Peg-IFN-RBV 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-	Divided by GT and treatment history	NR	Cost Differentials GT1: £5,288; £4,902; £19,129 (TN IE) GT1: £63,903 (TN UI) GT2: £27,779 (TN IE)	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);

Study	Summary of the model	Treatments	Patient population	QALYs	Costs	ICER
		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 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			GT2: £20,251 (TN UI) GT2: £19,088; £22,339 (TE IE) GT2: £20,697 (TE UI) GT3: £24,970 (TN IE); £55,137 (TN UI); £19,634; £16,843 (TE IE); £58,828 (TE UI) GT4/5/6: £23,942 (TN)	£8,557; £12,246 (TE IE); £28,569 (TE UI) GT4/5/6: £26,797 (TN)
Howells et al. 2015 (98)	Markov model with a lifetime horizon	Arm 1: LDV/SOF 8 weeks Arm 2: LDV/SOF 12 weeks	Divided by GT, treatment history and cirrhosis status	NR	NR	GT1/GT4-TN non-cirrhotic: £8,894/£22,676 GT1/GT4-TN cirrhotic: £4,518 GT1/GT4-TE non-cirrhotic: £16,566 GT1/GT4-TE cirrhotic: £5,435

Study	Summary of the model	Treatments	Patient population	QALYs	Costs	ICER
McEwan et al. 2015a 474 (99)	Markov model with a lifetime horizon	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	QALY gains (GT1): Arm 1 vs 2: 1.95 Arm 1 vs null: 4.88 QALY gains (GT3): Arm 1 vs 3: 3.02 Arm 1 vs null: 5.85 QALY gains (GT4): Arm 1 vs 3: 3.07 Arm 1 vs null: 5.36	Cost Differentials (GT1): Arm 1 vs 2: £15,344 Arm 1 vs null: £20,864 Cost Differentials (GT3): Arm 1 vs 3: £93,362 Arm 1 vs null: £78,603 Cost Differentials (GT4): Arm 1 vs 3: £27,029 Arm 1 vs null: £18,701	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
Westerhout et al. 2014 (100)	cost-utility model with two phases: anti-viral treatment period and lifespan outcomes	Arm 1: SMV + Peg-IFN-RBV Arm 2: Peg-IFN-RBV Arm 3: TVR + Peg-IFN-RBV Arm 4: BOC + Peg-IFN-RBV	Divided by GT and treatment history	NR	NR	GT1 Arm 1 vs 2: £14,206 (TN), £9,793 (TE) Arm 1 vs 3/4: **Dominant** GT4: Arm 1 vs 2: £20,791 (TN), £11,662 (TE) Arm 1 vs 3/4: **Dominant**

Study	Summary of the model	Treatments	Patient population	QALYs	Costs	ICER
Cure et al. 2014 (101)	Markov model followed a cohort of patients over lifetime	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	NR	NR	GT1: £15,533 GT2: £12,180 GT3: £18,450 GT4/5/6: £26,797 GT1: £15,533 All: £17,981
Humphreys et al. 2012 (102)	Markov model over GT1 patients lifetime	Arm 1: BOC + Peg-IFN-RBV Arm 2: Peg-IFN-RBV	Divided by treatment history	NR	NR	TN: £11,601 TE: £2,909
Curtis et al. 2012 (103)	Markov model	Arm 1: TVR + Peg-IFN-RBV Arm 2: Peg-IFN-RBV	Divided by treatment history, responders and IL28B type	NR	NR	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. 2013 (104)	A Markov model based on the METAVIR severity of disease and an SVR health state. Once patients are in F4 (compensated cirrhosis) they can transition to decompensated cirrhosis or HCC. From here the only possible transition is to liver transplant	Arm 1: RGT Arm 2: SDT Arm 3: No treatment	Taken to match the MONARCH trial, there were no restrictions for genotype or treatment history	Arm 1 (RGT): 13.88 Arm 2 (SDT): 13.82 Arm 3: 11.68	Arm 1 (RGT): 29,762 Arm 2 (SDT): 29,866 Arm 3: 27,492	Arm 1 vs 2: **Dominant** Arm 1 vs 3: £1,032
Johnson et al. 2016 (105)	A Markov model based on grouped METAVIR scores, mild HCV (F0-F1) and moderate HCV (F2-F3)	Arm 1: OBV/PTV/ RTV and DSV ± RBV Arm 2: treatment regimens including Peg-IFN	Results are reported for GT1a, TN and TE			OMB/PTV/RTV + DSV ± RBV for treatment-naive and treatment-experienced patients indicated that it dominated all other regimens except Peg-

Study	Summary of the model	Treatments	Patient population	QALYs	Costs	ICER
						IFN-RBV. Compared with Peg-IFN-RBV, the incremental cost-effectiveness ratios were £13,864 and £10,258 QALY for TN and TE patients, respectively
McEwan et al. 2015b 448 (106)	A Markov model based on the METAVIR severity of disease and an SVR health state. Once patients are in F4 (compensated cirrhosis) they can transition to decompensated cirrhosis or HCC. From here the only possible transition is to liver transplant. This model is a the same structure as used for McEwan et al. 2013	Arm 1: SOF + DCV Arm 2: SOF + RBV	GT3, with separate results for TN, TE and IFN-ineligible	DCV+SOF v SOF+RBV TN: -0.129 TE: -0.242 IFN-ineligible: 0.197 DCV + SOF vs no treatment IFN-ineligible: 4.120	DCV+SOF v SOF+RBV TN: -12,904 TE: -13,702 IFN-ineligible: -13,382 DCV + SOF vs no treatment IFN-ineligible: £31,868	DCV+SOF vs SOF+RBV TN: **Dominant** TE: **Dominant** IFN-ineligible - **Dominant** DCV+SOF vs no treatment IFN-ineligible: £7,736
McEwan et al. 2017 (107)	A study using a published, validated HCV model was utilized to contrast clinical and cost outcomes for patients aged 30-70 years, stratified by METAVIR F0-F4	Hypothetical treatments	A number of starting health states, age groups, treatments and	NR	NR	Costs: £19,745 (70 years, F0) to £188,420 (30 years, F4) SVR is expected to be cost-effective at £20,000/QALY willingness-to-pay threshold

BOC, boceprevir; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; GT, genotype; LDV, ledipasvir; NR, not reported; Peg-IFN: pegalyted-interferon; RBV, ribavirin; RGT, response guided therapy; SDT, standard duration of therapy, SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; TN, treatment-naïve; TE, treatment-experienced; TVR, telaprevir; VEL, velpatasvir; VOX, voxilaprevir.

B.3.2. *Economic analysis*

B.3.2.1. *Patient population*

An economic evaluation was conducted to determine the cost-effectiveness of SOF/VEL/VOX treatment in patients with CHC. These patient groups are defined by HCV GT including those with or without cirrhosis, and any previous treatment with a DAA (DAA-naïve or DAA-experienced).

The cost-effectiveness of SOF/VEL/VOX was evaluated in two key sub-populations:

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

These sub-populations are narrower than the marketing authorisation for SOF/VEL/VOX. These populations reflect where SOF/VEL/VOX provides the most clinical benefit. For patients who have previously failed to achieve SVR with a DAA (DAA-experienced), there are currently no recommended treatment options; and for DAA-naïve patients with GT3 infection most current treatment options are of long duration (12 weeks) and require the addition of RBV.

Phase III SOF/VEL/VOX studies support the clinical benefit in these sub-populations. The licensed duration for SOF/VEL/VOX in DAA-naïve patients who have cirrhosis is 12 weeks, with the option of 8 weeks in those with GT3 infection. POLARIS-3 supports the use of SOF/VEL/VOX for 8 weeks of treatment (see Section B.2). As there is no evidence to support a treatment duration of 12 weeks, the economic analysis includes a sensitivity analysis using the cost of 12 weeks of therapy and 8 week efficacy.

Co-infected HCV/HIV patients have not been modelled separately in this analysis. This approach is considered conservative as HCV/HIV co-infected patients are likely to transition faster to more advanced CHC disease states if left untreated, and therefore would be more cost-effective compared to the mono-infected population for a given treatment. This has been discussed and agreed with NICE at the Decision Problem meeting for SOF/VEL/VOX.

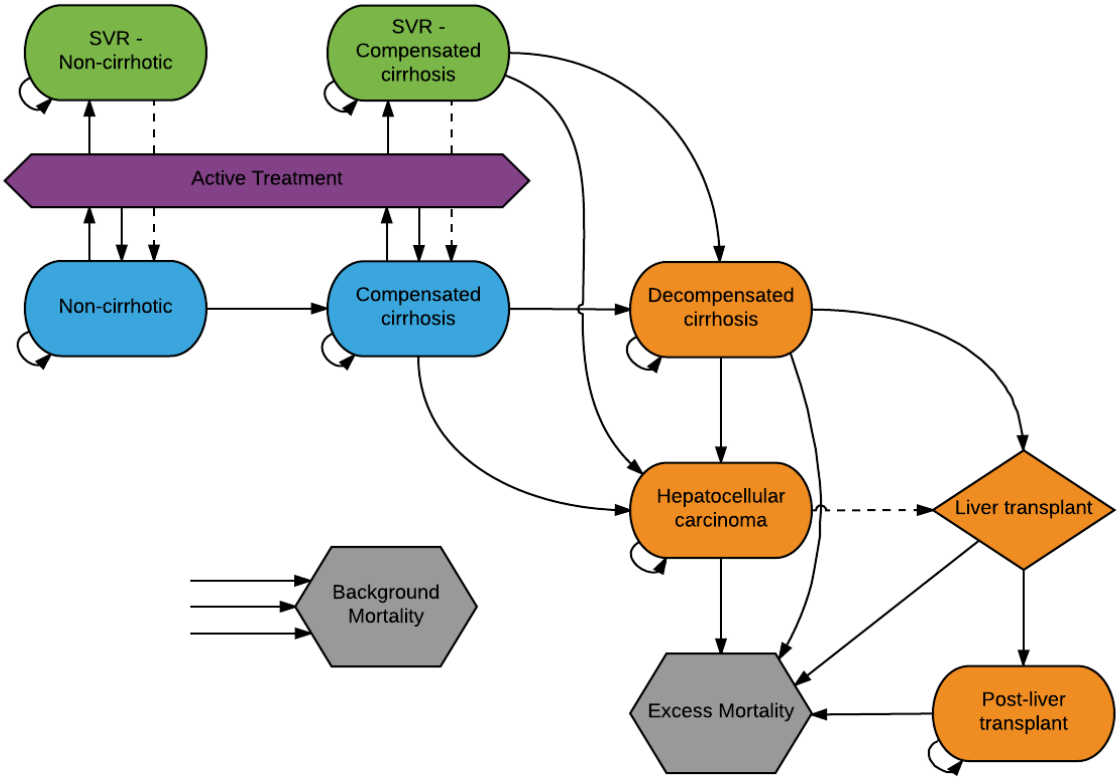
The treatment of patients who are post-liver transplant are not modelled separately in this submission due to a lack of data. This is consistent with the SOF/VEL, LDV/SOF and SOF NICE submissions. For the purpose of this submission, we assume these patients are modelled as part of the analyses described above based on their genotype and presence of cirrhosis.

B.3.2.2. *Model structure*

B.3.2.2.1. Type of de novo analysis

A Markov state-transition model was adapted from the model by Dusheiko and Roberts, (1995) (108). This structure allows the progression of the disease over the lifetime of a patient cohort to be quantified in terms of costs and health effects. The model structure is shown in Figure 3. The same model structure is used for all patients irrespective of HCV genotype or treatment experience. The model consists of nine health states with transition probabilities (TPs) between the states, and costs, mortality and morbidity associated with each state.

Figure 3. Markov model schematic for CHC



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

B.3.2.2.2. Justification of the chosen model structure

A Markov state-transition model was adapted from the model by Dusheiko and Roberts, 1995 (108) to describe the progression of disease over the lifetime of a patient cohort. The rationale for using this model is for two reasons, described below.

Firstly, this model structure represents the natural history of CHC and has been widely used and adapted for HTA purposes, including adaptations by the Southampton Health Technology Assessment Centre (SHTAC) in the UK for NICE (162, 163). This model has been further adapted in line with previous Gilead submissions to NICE for SOF/VEL (TA430), LDV/SOF (TA363) and SOF (TA330). In particular, the health states earlier in disease progression than compensated cirrhosis are represented as a single health state (non-cirrhotic), rather than being into mild and moderate states, or by METAVIR fibrosis score (F0-F4). As treatment decisions are determined on the presence or absence of cirrhosis, this model structure reflects current UK clinical practice.

Secondly, this structure offers the best fit for the Gilead pivotal Phase III trials for SOF/VEL/VOX (POALRIS-1-4), in which patients were split between non-cirrhotic and cirrhotic defined as per the Fibrotest® and Fibroscan® scores. A liver biopsy could be used to confirm the presence or absence of cirrhosis, although less than 11% of the overall study population (45/415) had cirrhosis status confirmed via liver biopsy. Invasive liver biopsy is no longer standard clinical practice in the UK CHC treatment pathway, and the POLARIS trials indicate this is reflective of the global CHC treatment pathway.

B.3.2.2.3. Clinical pathway and health states

The definitions of the individual health states are provided in Table 45.

Table 45. Health state definitions

State	Definition
Non-cirrhotic patients	Fibroscan® (in countries where locally approved) with a result of ≤12.5 kPa within ≤6 months of baseline/day 1[a] Fibrotest® score of ≤0.48 and an APRI of ≤1 performed during screening[a]
Cirrhotic patients	Fibroscan® (in countries where locally approved) showing cirrhosis or results ≥12.5 kPa[a] Fibrotest® score of >0.75 and an AST: platelet ratio index (APRI) of >2 performed during screening[a]
Decompensated cirrhosis	Clinical (major symptomatic)[b] and histological (cirrhosis)
SVR – Non-cirrhotic	Virological, 12 weeks after the end of therapy
SVR – Compensated cirrhosis	Virological, 12 weeks after the end of therapy
Hepatocellular carcinoma	Histological
Liver transplantation	Major clinical intervention procedure
Post-liver transplant	Clinical
Decompensated cirrhosis, hepatocellular carcinoma, liver transplantation, and post-liver transplant attributed death	Absorbing state, disease-specific death associated with having decompensated cirrhosis, liver transplant or hepatocellular carcinoma.
Background mortality	Mortality rate of the general population (not disease-specific)

AST: Aspartate transaminase; APRI: AST platelet ratio index; CHC: Chronic hepatitis C; SVR: sustained virologic response.
[a] Based on POLARIS clinical trials; [b] Major Symptomatic = clinical ascites, encephalopathy, and/or variceal hemorrhage

In the SOF/VEL/VOX clinical trials, the presence of cirrhosis was defined as any of the following:

- Liver biopsy showing cirrhosis (METAVIR score of 4 or Ishak score of ≥ 5)
- Fibrotest® score of >0.75 and an AST:platelet ratio index (APRI) of >2 performed during screening
- Fibroscan® with a result of >12.5 kPa

Non-cirrhotic patients were defined as any one of the following, unless the definition for cirrhosis (above) was met:

- Liver biopsy within 2 years of screening showing absence of cirrhosis
- Fibrotest® score ≤0.48 and APRI ≤1 performed during screening
- Fibroscan® with a result of ≤12.5 kPa within ≤ 6 months of baseline/day 1

The conversion between the Fibrotest®, Fibroscan® and the METAVIR scores is displayed in Table 46.

Table 46: Conversion between Fibrotest®, Fibroscan® and METAVIR scores

METAVIR	Fibrotest®	Fibroscan®
F0 F0-F1 F1	0.00–0.21 0.22–0.27 0.28–0.31	2.4–7.1 kPa
F1-F2 F2	0.32–0.48 0.49–0.58	7.1–9.5 kPa
F2-F3 F3	0.49–0.58 0.59–0.72	9.5–12.5 kPa
F3-F4 F4	0.73–0.74 0.75–1.00	≥12.5 kPa

F, fibrosis stage; kPa, Kilopascal.

According to the conversion between Fibrotest®/Fibroscan® and the METAVIR scores provided above, non-cirrhotic patients correspond to F0-F3 and cirrhotic patients to F4 in the METAVIR scores. Therefore, whenever data from the literature were available which reported METAVIR scores; these were converted using this algorithm.

The model captures two distinctive and critical aspects of the condition for patients and clinicians: the on-treatment phase (consisting of either active therapy or best supportive care)

and the post-treatment phase. As shown in Figure 3, the on-treatment phase ("Antiviral treatment") directs patients in the model to either:

- SVR health states of either "SVR – Non-cirrhotic" or "SVR – Cirrhosis", or
- Disease health states representing non-cirrhotic CHC or CHC with compensated cirrhosis

In these health states, patients can either remain in their existing health state, or progress to a worse health state in the direction indicated by the white arrows in Figure 3. These assumptions of disease progression have also been used by Grishchenko et al, 2009 (109) Hartwell et al, 2011 (110) and Shepherd et al, 2007 (111).

Non-cirrhotic and cirrhotic patients move to the SVR health state after completing treatment if they have undetectable HCV RNA 12 weeks after end of treatment, otherwise referred to as a cure. A patient who started treatment in the non-cirrhotic state and was subsequently cured would not become symptomatic again. However, cirrhotic patients who achieved SVR are still exposed to a risk of moving to the decompensated cirrhosis and the HCC states.

Recurrence and re-infection are considered in sensitivity analysis for both non-cirrhotic and cirrhotic patients by allowing them to transition to their initial health state following the reappearance of HCV. As well as in an additional exploratory analysis considering re-infection and onward transmission.

Although there is some evidence to suggest that antiviral treatment, even in the absence of a SVR, can delay disease progression, we made the simplifying assumption that treated patients who do not achieve SVR face an annual probability of progressing from no cirrhosis to compensated cirrhosis at the same rate as if they had not received antiviral treatment (112).

Patients in both compensated and decompensated cirrhosis can progress to HCC stage, with its associated costs and health-related quality of life (HRQL). Following liver transplantation, patients face a probability of dying or moving to the post-transplantation phase. In the post-transplantation phase patients remain at a higher risk of death compared with the general population.

For simplification, patients with HCC cannot transition to decompensated cirrhosis since this is expected to have little impact on the results, and we have no clinical or economic data on the impact of developing decompensated cirrhosis among people with HCC.

Although not represented on the transition diagram, age and gender specific general population mortality rates are applied to each health state in the model. The risk of death is however highest in the most severe states (i.e. decompensated cirrhosis, HCC, liver transplant, post-liver transplantation). The excess mortality associated with these health states is depicted in Figure 3.

Cycle length

To accommodate treatment duration, the cycle length was 2 weeks for the first 18 months, then 6 month cycle was applied. Thereafter, transitions occurred on an annual basis.

Shorter initial cycles allowed modelling different treatment strategies (ranging from eight to 24 weeks) with patients transiting to SVR in the same model at different cycles. Half-cycle correction was applied. Half-cycle correction was applied from year 3 onwards since shorter cycle lengths were applied in years 1-2.

B.3.2.3. *Key features of the analysis*

Table 47: Features of the economic analysis

Factor	Previous appraisals	Current appraisal	
	TA430	Chosen values	Justification
Time horizon	Lifetime (until patients reach 100 years of age)	Lifetime horizon (until patients reach 100 years of age). Shorter time horizons (model cohort reach age 50, 60 and 80 years old) can be implemented for sensitivity analyses (as in previous appraisals).	As previously reflected in NICE HTAs, due to the nature of chronic HCV, the 100-year-old horizon allows capturing the difference between treatments in terms of long-term costs and health benefits (19, 20). This is consistent with the NICE reference case which requires costs and effects to be measured over sufficient time horizon to fully capture the relative costs and benefits.
Source of utilities	QALYs	QALYs (see Section B.3.4)	As per NICE reference case
Source of costs	NHS and PSS	NHS and PSS (see Section B.3.5)	As per NICE reference case
Discount rate	3.5% for utilities and costs	3.5% for utilities and costs	As per NICE reference case
Perspective (NHS/PSS)	NHS and PSS	NHS and PSS	As per NICE reference case

HCV, hepatitis C virus; HTA, Health Technology Assessment; NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years.

B.3.2.4. *Intervention technology and comparators*

Treatment regimens are included as per their marketing authorisations and licensed doses, and as recommended by NICE, and are described in Table 48.

The intervention considered is SOF/VEL/VOX; a 12 week regimen for DAA-experienced patients (all GTs and regardless of cirrhosis status), and an 8 week regimen for DAA-naïve patients with GT3 infection, with and without cirrhosis. This aligns with the decision problem information provided in Section B.1.

Table 48: Intervention and comparator treatments

DAA-naïve / DAA-experienced	GT	CC/NC	Intervention/Comparator	Treatment duration (weeks)
DAA-experienced	All	All	SOF/VEL/VOX	12
			No treatment	-
DAA-naïve	3	CC	SOF/VEL/VOX	8
			SOF/VEL	12
			SOF + DCV + RBV	12
			SOF + RBV	24
			Peg-IFN2a + RBV	24
			SOF + Peg-IFN2a + RBV	12
			No treatment	-
		NC	SOF/VEL/VOX	8
			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.

B.3.3. *Clinical parameters and variables*

B.3.3.1. Incorporating the clinical data into the model

Key clinical data are listed in Table 49 and described further in the following sub sections.

Table 49: Clinical data implemented in the economic model

Characteristics	Data	Sources
Patient characteristics	Mean age at treatment initiation Weight	Published literature for mean age and weight (110) and probability of death (113)

	Probability of death	Assumptions applied for some GTs (see Table 50)
Treatment characteristics	SVR rates Rates of AEs Treatment durations	SOF/VEL/VOX clinical trials Comparator treatment trials and literature Expert opinion
Health related quality of life	Relative on treatment decrements	Younossi et al. 2016 (114)

AE, adverse event; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir; VOX, voxilaprevir.

B.3.3.1.1. Patient characteristics

Patient characteristics impact on drug dosage, certain TPs and mortality rates. The key patient characteristics include the mean age at treatment and the mean weight, which are consistent with previous NICE appraisals as well as a PHE surveillance report conducted in 2014 (115) (Table 50).

Table 50: Patient characteristics

Indication	Mean age at treatment (years)	Mean weight (kg)
DAA-experienced		
Pan-genotypic	45	79
DAA-naïve		
GT3 CC	40	79
GT3 NC	40	79

CC, cirrhotic; DAA, direct-acting antivirals; GT, genotype; NC, non-cirrhotic.

B.3.3.1.2. Background mortality

Background mortality was applied in the model using the Office for National Statistics (2013-2015) National Life Tables for England. It was assumed that the population entering the model comprises 61% men and 39% females (116). In line with the previous submissions to NICE for SOF, LDV/SOF and SOF/VEL, background mortality was only applied to patients after SVR assessment.

B.3.3.1.3. Treatment characteristics

Transition probabilities used in the model are dependent on whether a patient achieves an SVR or not following treatment. SVR rate inputs for SOF/VEL/VOX and comparators were obtained from relevant trials or SmPC. SVR rates used in the modelling are described in Section B.3.6.2.

Rates of AEs for SOF/VEL/VOX and comparators were obtained from relevant trials or SmPCs and are described in Section B.3.4.4. Unit costs of treating AEs were applied, as described in Section B.3.5.

Treatment durations were used to estimate drug acquisition costs and on-treatment monitoring costs.

B.3.3.1.4. HRQL

The impact of any AE during treatment was captured by monitoring the HRQL of a patient across the treatment course and applying this as a utility increment or decrement to baseline utility while on treatment.

Utility increments/decrements are generally expressed as a percentage because a multiplicative approach was used to estimate on-treatment quality of life, which involved application of the treatment-related decrement to baseline utilities. Utility increments/decrements were derived directly from the published literature. A disutility is only applied for treatment options that include Peg-IFN or RBV and assumes no utility modifier for all other non-IFN- or non-RBV-containing treatments. A full breakdown can be found in Table 63.

B.3.3.2. *Transition probabilities*

For the SOF/VEL submission several sources were considered for TPs, and it was concluded that the Kanwal et al 2014 study (117) was the most appropriate to use. After reviewing the literature and finding no better sources, the same approach will be taken for the SOF/VEL/VOX submission and TPs for non-cirrhotic to cirrhotic will be derived from Kanwal et al 2014 (117).

The annual TP was calculated by firstly taking the reported incidence rate of cirrhosis per 1,000 patient years, converting this to an annual incidence rate of cirrhosis per patient-year and then calculating the TP using the formula: $p = 1 - e^{-FPR*t}$.

For example, Kanwal found that in the 8,837 GT3 patients included in the study, the annual incidence of cirrhosis was 30 per 1,000 patients, giving an annual incidence rate of 0.03 per patient-year. Converting this to an annual probability gives the required TP of 0.0296 (rounded to 0.030).

This study was conducted amongst the cohort of the US armed forces veterans, coordinated across 128 treating facilities by the Health Services Research centre of the Department of Veterans Affairs. Within this population, over a period of 10 years from 2000 to 2009, the investigators evaluated the clinical progression of 110,484 patients with CHC GT1, 2, 3 and 4 in 88,384 (79%), 13,077 (11.8%), 8,337 (7.5%) and 1,082 (0.9%) patients, respectively (9). The authors concluded that, despite GT3 patients being younger on average than GT1 patients, they had a 40% higher risk of developing cirrhosis and a 66% higher relative risk of HCC. This large dataset was able to provide evidence for the genotype specific annual TP from non-cirrhotic to compensated cirrhosis in each of GT1, 2, 3 and 4. The Kanwal study was selected as the most appropriate source to inform this model transition, given its large size, recent publication, pan-genotypic coverage and previous use for HTA submission.

Where used previously in HTA submission, the above reported TP fell within the reported range of corresponding GT3 TPs (0.025 to 0.06) and was considered a conservative measure of actual risk of disease progression.

Given that the Kanwal study included patients with CHC GT1 (n=88,348), GT2 (n=13,077) and GT4 (n=1,082) as well as GT3, it was considered appropriate to calculate genotype-specific probabilities for all modelled genotypes from the Kanwal study, using identical methodology for GT1, GT2 and GT4 to that provided for GT3. The annual TPs calculated from the Kanwal data are provided in Table 51. In the DAA-experienced, pan-GT analysis, a weighted TP from non-cirrohitc to cirrhotic was estimated based on the distribution of GT1-6 patients in POLARIS-1.

Table 51. Transition probabilities

From	To	TP (annual probabilities)	Source	Comments
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 (117)	Assumes GT5 and GT6 are equivalent to GT4
Compensated cirrhosis	Decompensated cirrhosis	0.0438	Cardoso *et al.* 2010 (65)	Cardoso included patients stage at F3 and F4 and DCC was defined as several liver-related complications
	HCC	0.0631	Cardoso *et al.* 2010 (65)	Calculated
Compensated cirrhosis SVR	Decompensated cirrhosis	0.0064	Cardoso *et al.* 2010 (65)	Cardoso included patients stage at F3 and F4 and DCC was defined as several liver-related complications
	HCC	0.0128	Cardoso *et al.* 2010 (65)	Calculated
Decompensated cirrhosis	HCC	0.0631	Cardoso *et al.* 2010 (65)	Calculated
	Liver transplant	0.0220	Siebert 2005 (118)	-
	Death	0.2400	EAP data (EASL 2016) (2)	-
HCC	Death	0.4300	Fattovich *et al.*, 1997 (119)	Obtained from Shepherd *et al.*, 2007(111)
Liver transplant	Death, Yr1	0.2100	Bennett *et al.* 1997(120)	Obtained from Shepherd *et al.*, 2007(111)
Post-liver transplant	Death, Yr2	0.0570	Bennett *et al.* 1997 (120)	Obtained from Shepherd *et al.*, 2007(111)

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

B.3.3.2. Clinical expert assessment of applicability of clinical parameters

This model was based on the models submitted to NICE for the appraisal of SOF/VEL, LDV/SOF and SOF. The model structure, assumptions, and inputs for the submitted models have been previously discussed and validated with two external clinical experts (a senior consultant and a nurse specialist) from England. Both clinical experts were selected based upon their roles within the NHS as clinical leads at a regional CHC treatment centre that treats >100 CHC patients per year.

The core assumptions that the clinical experts were asked to assess were based upon monitoring and treatment of Grade 3 and 4 AEs only where relevant literature was unavailable.

The clinical experts approached have previously attended advisory boards with Gilead Sciences Ltd. They have also previously attended advisory boards run by Janssen, MSD, Abbvie, Boehringer Ingelheim and Bristol Myers Squibb.

The medium used to collect these assumptions was through direct interview. The outputs were then validated to ensure they were consistent with current practice within advisory board discussions, incorporating an average of 8 clinical experts from England and Scotland.

Since these assumptions have been consistently used in both the SOF/VEL, LDV/SOF and the SOF models, no further clinical expert input was sourced for this submission. As part of the clinical expert validation of the LDV/SOF model, the feasibility of modelling patients co-infected with HCV and HIV separately was discussed. The clinical experts agreed that patients co-infected with HCV and HIV would be treated with the same regimens and respond to treatment in the same way as mono-infected HCV patients. The clinical experts agreed that modelling mono-infected and co-infected patients together was a reasonable and conservative approach. Given that the same approach has been taken in the SOF/VEL model, no further clinical expert input to this modelling assumption was sourced for this submission. Where significant differences existed in the modelling approach for the SOF/VEL cost-effectiveness model as compared to the LDV/SOF and SOF models, these were also validated by clinical expert opinion.

Two clinical experts were consulted regarding the following modelling assumptions:

The use of the data published by Kanwal et al to inform the model annual transition probability from the non-cirrhotic health state to the compensated cirrhosis health state

The clinical experts agreed that an assumption of faster progression of liver fibrosis in CHC GT3 disease compared to other HCV genotypes was consistent with current clinical understanding. On reviewing the output of the targeted literature reviews previously developed for the SOF/VEL submission to NICE, the clinical experts agreed that the size of the CHC patient population analysed in the Kanwal study (117), and its recent date of publication, supported its use as a source of GT-specific TPs for the model. Furthermore, the clinical experts agreed that the TP calculated by Kanwal for patients with GT3 was within the range of annual TPs reported in the other relevant studies from the targeted literature review. As such, it was agreed that using the Kanwal TP was a reasonable approach to take in the model and consistent with current clinical understanding of CHC disease progression.

The use of SVR rates from individual trials to inform model comparisons rather than the results of the network meta-analysis

The use of SVRs from individuals trials in the model, instead of an NMA was previously validated by expert opinion for the SOF/VEL submission, and accepted by NICE.

B.3.4. *Measurement and valuation of health effects*

B.3.4.1. *Health-related quality-of-life data from clinical trials*

Details of the treatment-specific HRQL utility increments and decrements derived from clinical studies can be found in the base-case de novo model inputs Section B.3.6.5.

B.3.4.2. *Mapping*

Not applicable.

B.3.4.3. *Health-related quality-of-life studies*

See Appendix H.

B.3.4.4. *Adverse reactions*

The overall impact of any AE during treatment would be captured by monitoring the HRQL of a patient across the treatment course and applying this as a utility decrement to baseline utility while on treatment.

B.3.4.5. *Health-related quality-of-life data used in the cost-effectiveness analysis*

Baseline QOL in this model is defined by the health state in which the patient enters the model. Health state utilities, which are the same across all the indications, are presented in Table 52. Treatment-specific HRQL utility increments and decrements derived from clinical studies are described in the base-case de novo model inputs Section 5.6.1, to avoid duplicated information.

Estimates were obtained from the systematic literature reviews of cost-effectiveness and HRQL studies described in Section B.3.6.5 and **Error! Reference source not found.**. The utilities chosen for the current model were those also used by UK HTAs (Hartwell et al, 2011 (110), Shepherd et al, 2007 (111)) and were predominantly based on the UK trial on mild HCV by Wright et al, 2006 (112). Patients achieving SVR are assumed to have an increase in utility of 0.04, resulting in utilities of 0.79 and 0.59 after treatment, for patients that reached SVR with non-cirrhotic disease and compensated cirrhosis respectively. Previous models have referenced a utility increment post-SVR of 0.05 (112), however the value used in this model is based on data from Vera-Llonch et al, 2013 (112), selected as the most recent data with the least uncertainty.

As illustrated by Wright et al, 2006 (112), HRQL declines as CHC disease progresses to more advanced disease health states (Table 52). Patients with non-cirrhotic disease have an

average utility of 0.75 at baseline. This falls to 0.55 and 0.45 for patients with compensated cirrhosis and decompensated cirrhosis, respectively. A utility increment of 0.04 was assumed for patients with an SVR regardless of liver fibrosis stage at the time of receiving treatments. In patients with more advanced liver disease such as HCC and prior to undergoing liver transplantation utility is even lower (0.45) (112).

Table 52: Summary of utility values for cost-effectiveness analysis

Health-state	Utility	Source	Justification
Baseline – non-cirrhotic	0.75[a]	Wright et al, 2006 (112) (UK mild HCV trial)	EQ-5D as preferred in the reference case. Publications that used this utility: -Hartwell et al, 2011 (110) -Grishchenko et al, 2009 (109) -Shepherd et al, 2007 (111)
Baseline – compensated cirrhosis	0.55[a]	Wright et al, 2006 (112) (UK mild HCV trial)	EQ-5D as preferred in the reference case. Publications that used this utility: -Hartwell et al, 2011 (110) -Grishchenko et al, 2009 (109)
SVR (utility increment)	0.04[a]	Vera-Llonch et al, (2013) (121)	Most recent data with less uncertainty than Wright et al, (2006) (112)
Non-cirrhotic with SVR	0.79[a]	Calculation	-
Compensated cirrhotic with SVR	0.59[a]	Calculation	-
HCC	0.45[a]	Wright et al, (2006) (112) (UK mild HCV trial)	EQ-5D as preferred in the reference case. Publications that used this utility: -Hartwell et al, 2011 (110) -Grishchenko et al, 2009 (109) -Shepherd et al, 2007 (111)
Liver transplant	0.45[a]	Wright et al, 2006 (112) (UK mild HCV trial)	EQ-5D as preferred in the reference case. Publications that used this utility: -Hartwell et al, 2011 (110) -Shepherd et al, 2007 (111)
Post-liver transplant	0.67[a]	Wright et al, 2006 (112) (UK mild HCV trial)	EQ-5D as preferred in the reference case. Publications that used this utility: -Hartwell et al, 2011 (110)

EQ-5D, EuroQol-5 dimension; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virologic response.
[a] Detail of ranges used for sensitivity analyses outlined in **Error! Reference source not found.**.

Liver fibrosis does not occur at the same rate in all individuals, and does not seem to progress linearly. In the non-cirrhotic (non-SVR) health state, patients may feel mild to severe tiredness, jaundice, loss of appetite, nausea and vomiting, soreness in the area of the liver, fever, increased moodiness and depression or joint pain. As the disease progresses, more signs and symptoms are present. This may include hypertrophic

osteoarthropathy, development of ascites and hypogonadism. These complications are due to the decreased functioning of the liver. Further scarring (fibrosis) of the liver results in a progression of CHC to the health state decompensated cirrhosis or can develop into hepatocellular carcinoma. As these health states can be life-threatening, a liver transplant may be an option to decrease the risk of mortality. Liver transplants have risks and complications due to immunosuppressive management needed. These risks and complications contribute to a lower QOL compared with a healthy person.

HRQL is assumed constant for as long as the patient remains in one health state and it changes when the patients moves through the different health states. Within each healthstate, it is assumed that all patients have the same utility. See Section B.3.3.2 for details on clinical expert assessment of applicability of inputs for the model.

B.3.5. *Cost and healthcare resource use identification, measurement and valuation*

See Appendix I for how relevant cost and healthcare resource data were identified.

B.3.5.1. *Intervention and comparators' drug costs*

Unit costs of the drugs in the SOF-based and comparator regimens are presented in Table 53 (list prices). Estimates for comparators were obtained from the British National Formulary (August 2017). Note that all analyses have been conducted at the NHS list price.

Table 53: Treatment unit costs

Drug	Cost per pack (List)	Cost per pack (PAS)	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; LDV, ledipasvir; mg, milligrams; Peg-IFN2a, pegylated-interferon 2a; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

B.3.5.2. *Intervention and comparators' monitoring costs*

Monitoring costs refer to the costs of monitoring the patient while they are treated with either SOF/VEL/VOX or a comparator therapy.

The unit costs used to estimate the monitoring costs are displayed in Table 54. The resource use was taken from Shepherd et al, 2007 (111) and the costs were inflated to 2015-2016 where newer cost sources were not available.

Table 54: Monitoring resource use unit costs

Item	Unit cost	Cost year	Inflated to £2015-2016	Source
OUTPATIENT APPOINTMENT				
Gastroenterology -	£144.44	2015-2016	£144.44	National Schedule of Reference

Item	Unit cost	Cost year	Inflated to £2015-2016	Source
Consultant Led Outpatient Attendances				Costs Year: 2015-2016 (122)
Gastroenterology – Non-Consultant Led Outpatient Attendances	£96.90	2015-2016	£96.90	National Schedule of Reference Costs Year: 2015-2016 (122)
INPATIENT CARE (DAY CASE)				
Clerking in patient (1hour)	£10.18	2003-2004	£13.45	Shepherd et al, 2007 (111)
TEST AND INVESTIGATIONS				
Virology				
HCV screen (RNA) = SVR test	£11.33	2003-2004	£14.97	Shepherd et al, 2007 (111)
HBV	£5.18	2003-2004	£6.84	Shepherd et al, 2007 (111)
Anti-HIV	£13.50	2011-2012	£14.19	Prof. Dusheiko
HIV RNA	£35.00	2011-2012	£36.80	Prof. Dusheiko
Chemical pathology				
Liver function tests	£3.60	2003-2004	£4.76	Shepherd et al, 2007 (111)
Alfa-fetoprotein	£1.31	2003-2004	£1.73	Shepherd et al, 2007 (111)
Alfa-Antitrypsin	£5.50	2003-2004	£7.27	Shepherd et al, 2007 (111)
Thyrotrophic	£3.60	2003-2004	£4.76	Shepherd et al, 2007 (111)
Free T4	£3.60	2003-2004	£4.76	Shepherd et al, 2007 (111)
Caeruloplasmin	£6.60	2003-2004	£8.72	Shepherd et al, 2007 (111)
Iron	£4.30	2003-2004	£5.68	Shepherd et al, 2007 (111)
Urea and electrolytes	£5.60	2003-2004	£7.40	Shepherd et al, 2007 (111)
Glucose	£2.50	2003-2004	£3.30	Shepherd et al, 2007 (111)
Pregnancy test	£0.25	2003-2004	£0.33	Shepherd et al, 2007 (111)
Thyroid function tests	£13.30	2003-2004	£17.57	Shepherd et al, 2007 (111)
Alanine aminotransferase	£3.60	2003-2004	£4.76	Shepherd et al, 2007 (111)
Haematology				
Full blood count	£2.20	2003-2004	£2.91	Shepherd et al, 2007 (111)
Ferritin	£10.00	2003-2004	£13.21	Shepherd et al, 2007 (111)
Blood clotting factors (INR)	£2.40	2003-2004	£3.17	Shepherd et al, 2007 (111)
Blood group	£2.20	2003-2004	£2.91	Shepherd et al, 2007 (111)
Immunology / chemistry				
Autoantibodies	£22.30	2003-2004	£29.46	Shepherd et al, 2007 (111)
Immunoglobulins	£2.20	2003-2004	£2.91	Shepherd et al, 2007 (111)
Cryoglobulin	£11.90	2003-2004	£15.72	Shepherd et al, 2007 (111)

Item	Unit cost	Cost year	Inflated to £2015-2016	Source
Radiology				
Ultrasound scan of liver	£48.00	2003-2004	£63.42	Shepherd et al, 2007 (111)
Chest X-ray	£15.00	2003-2004	£19.82	Shepherd et al, 2007 (111)
Ultrasound guided biopsy	£173.00	2003-2004	£228.56	Shepherd et al, 2007 (111)
Ultrasound of liver	£7.20	2003-2004	£9.51	Shepherd et al, 2007 (111)
ECG	£31.00	2003-2004	£40.96	Shepherd et al, 2007 (111)
MRI liver	£206.00	2002-2003	£286.30	Wright et al, 2006 (112)
Molecular pathology				
HCV quantitative viral load	£152.27	2003-2004	£201.18	Shepherd et al, 2007 (111)
Other tests				
Pulmonary function tests	£1.00	2003-2004	£1.32	Shepherd et al, 2007 (111)
HCV genotype	£148.00	2003-2004	£195.53	Shepherd et al, 2007 (111)
Procedures				
Liver biopsy	£126.00	2003-2004	£166.47	Shepherd et al, 2007 (111)
Fibroscan®	£50.00	2008-2009	£55.62	Stevenson et al 2012 (page 67) (123)
Fibrotest®	£50.00	2008-2009	£55.62	Stevenson et al 2012 (page 67) (123)
Endoscopy diagnosis	£110.00	2002-2003	£152.88	Wright et al, 2006 (112)

ECG, Electrocardiography; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; kg, Kilogram; MRI, magnetic resonance imaging; PSSRU, Personal Social Services Research Unit.

Table 55 provides total costs for each of the monitoring phases calculated for the non-cirrhotic and cirrhotic patients. These costs include detailed assessments at the start, during, and end of treatment. For patients receiving no treatment, the model assumes that six weeks of monitoring is conducted, which is likely to be a conservative assumption.

Table 55: Monitoring cost summary per monitoring phase and treatment

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.

B.3.5.3. *Intervention and comparators' health-state unit costs and resource use*

Costs associated with each health state are shown in Table 56. These health state costs are independent of the monitoring costs because these are used in health states outside of treatment administration. The non-cirrhotic health state costs is a combination of mild and moderate non-cirrhotic status, weighted by a 83/17 split between mild and moderate non-cirrhotic health states[a].

The costs chosen for inclusion as model inputs were those used by the most recent HTAs, apart from the costs for patients who reached SVR which were from Wright et al, 2006, since these were based on UK studies (112). The costs for the most advanced stages of the disease were from an observational study on patients recruited from three hepatology centres in London, Newcastle and Southampton; the costs for mild disease were collected from the UK mild hepatitis C RCT; the costs for the liver transplantation were obtained from Longworth et al, 2014 (124). Costs were reported for each phase of liver transplantation: assessment, candidacy, transplant, and post-transplant. The liver transplant cost is equal to the sum of the first three costs. For the post-liver transplant cost, Longworth et al, 2014 (124) did not provide the split between the first and the second year after transplantation. These costs were estimated assuming a 87/13 split between the first and the second year based on the relation between these costs in Wright et al, 2006 (112). Costs of non-cirrhotic and cirrhotic patients who reached SVR were from Grishchenko et al, 2009 (109) because the costs collected from the UK mild hepatitis C RCT (which were used by Shepherd et al, 2007 (111) and Hartwell et al, 2011 (110)) did not split between non-cirrhotic and cirrhotic patients. All costs have been updated to 2015/2016 costs using the HCHS Pay and Prices Index (125).

[a] Based on 83% F0-F2 (mild) and 17% F3 (moderate), derived from HCV TherapyWatch market research data.

Table 56: Health state costs

Health state *Disaggregated costs*	Annual costs	Cost year	Inflated-values to £2015-2016	Source
Non-cirrhotic, mild	£138	2002-2003	£192	Wright et al, 2006 (112)
Non-cirrhotic, moderate	£730	2002-2003	£1,015	Wright et al, 2006 (112)
Non-cirrhotic[a]	-	-	£332	Calculation
Non-cirrhotic with SVR (mild)	£202	2006-2007	£240	Grishchenko et al, 2009 (109)
Non-cirrhotic with SVR (moderate)	£247	2006-2007	£294	Grishchenko et al, 2009 (109)
Non-cirrhotic with SVR[a]	-	-	£249	Calculation
Compensated cirrhosis	£1,138	2002-2003	£1,582	Wright et al, 2006 (112)
Pharmacy			£395	Calculation (Total costs divided by 4)
Hospitalisation			£395	Calculation (Total costs divided by 4)
Outpatientt[b]			£791	Calculation (sum of emergency and ambulatory costs)
Emergency			£395	Calculation (Total costs divided by 4)
Ambulatory			£395	Calculation (Total costs divided by 4)
Compensated cirrhosis with SVR	£437	2006-2007	£520	Grishchenko et al, 2009 (109)
Pharmacy			£130	Calculation (Total costs divided by 4)
Hospitalisation			£130	Calculation (Total costs divided by 4)
Outpatient[b]			£260	Calculation (sum of emergency and ambulatory costs)
Emergency			£130	Calculation (Total costs divided by 4)
Ambulatory			£130	Calculation (Total costs divided by 4)
Decompensated cirrhosis	£9,121	2002-2003	£12,676	Wright et al, 2006 (112)
Pharmacy			£3,169	Calculation (Total costs divided by 4)
Hospitalisation			£3,169	Calculation (Total costs divided by 4)
Outpatient[b]			£6,338	Calculation (sum of emergency and ambulatory costs)
Emergency			£3,169	Calculation (Total costs divided by 4)
Ambulatory			£3,169	Calculation (Total costs divided by 4)
HCC	£8,127	2002-2003	£11,295	Wright et al, 2006 (112)
Pharmacy			£2,824	Calculation (Total costs divided by 4)
Hospitalisation			£2,824	Calculation (Total costs divided by 4)
Outpatient[b]			£5,547	Calculation (sum of emergency and ambulatory costs)
Emergency			£2,824	Calculation (Total costs divided by 4)
Ambulatory			£2,824	Calculation (Total costs divided by 4)
Liver transplant	£83,505	2012-2013	£86,324	Longworth et al 2014 (124)
Pharmacy			£21,581	Calculation (Total costs divided by 4)
Hospitalisation			£21,581	Calculation (Total costs divided by 4)
Outpatient[b]			£43,162	Calculation (sum of emergency and

Health state *Disaggregated costs*	Annual costs	Cost year	Inflated-values to £2015-2016	Source
				ambulatory costs)
Emergency			£21,581	Calculation (Total costs divided by 4)
Ambulatory			£21,581	Calculation (Total costs divided by 4)
Post-liver transplant follow-up phase (0-12 months)	£27,512	2012-2013	£28,441	Longworth et al 2014 (124); Split between post-liver transplant year 1 and year 2 cost based on Wright et al 2006 (112)
Post-liver transplant follow-up phase (12-24 months)	£4,111	2012-2013	£4,250	

HCC, hepatocellular carcinoma; SVR, sustained virologic 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] Outpatient costs are the sums of emergency and ambulatory costs.

B.3.5.4. *Intervention and comparators' adverse reaction unit costs and resource use*

The costs associated with treatment-related adverse events include costs of inpatient and outpatient care, GP visits and visits to specialists, as well as drug costs. The unit cost and resource use for the drugs selected to treat each adverse event are presented in Table 57 and Table 58.

Data were obtained from the BNF August 2017 and NHS England Reference costs. No inpatient costs were considered because most of these adverse events are treated during outpatient visits, according to expert opinion (111). Outpatient, GP and specialist costs are shown in Table 59.

Table 57: Adverse event drug unit costs

Adverse event	Drug	Cost per pack	Unit dose	Quantity/ pack	Source
Nausea	Metoclopramide	£0.72	10 mg	28	BNF, 3rd August 2017
Vomiting	Metoclopramide	£0.72	10 mg	28	BNF, 3rd August 2017
Diarrhoea	Loperamide	£0.96	2 mg	30	BNF, 3rd August 2017
Pruritus	Chlorphenamine	£0.76	4 mg	28	BNF, 3rd August 2017
Rash	Hydrocortisone 1% 15g	£0.99	NA	1	BNF, 3rd August 2017
Anaemia (Epo)	Binocrit® (epoetin alfa)	£331.85	10,000 units	1	BNF, 3rd August 2017
Anaemia (blood transfusion)	NA	£1,071.67	NA	1	National Schedule of Reference Costs - Year 2015-2016 - NHS trusts and NHS foundation trusts - Elective Inpatient HRG Data; Single Plasma Exchange, Leucophoresis or Red Cell Exchange, with length of stay 2 days or less, 19 years and over (SA13A) (122) (126)(123)(122)(36)(32)(32)(30) (25) (12)
Thrombocytopenia	Revolade® (eltrombopag)	£1,540.00	50 mg	28	BNF, 3rd August 2017

Adverse event	Drug	Cost per pack	Unit dose	Quantity/ pack	Source
Neutropenia	Neupogen® (filgrastim)	£52.70	600 µg/ml	0.5	BNF, 3rd August 2017
Depression	Citalopram	£0.81	20 mg	28	BNF, 3rd August 2017

BNF, British national Formulary; HRG, healthcare resource group; NA, Not applicable.

Table 58: Adverse event drug treatment dosing and duration

Adverse event	Drug	Dose	% treated for	Weekly costs	Weeks of treatment	Source
Nausea	Metoclopramide	30 mg/day	100%	£0.54	4	Telaprevir manufacturer's submission to NICE (TA252)
Vomiting	Metoclopramide	30 mg/day	100%	£0.54	4	Telaprevir manufacturer's submission to NICE (TA252)
Diarrhoea	Loperamide	2 mg/day	100%	£0.22	4.3	Telaprevir manufacturer's submission to NICE (TA252)
Pruritus	Chlorphenamine	16 mg/day	100%	£0.76	4	Telaprevir manufacturer's submission to NICE (TA252)
Rash	Hydrocortisone 1% 15g	NA	100%	£0.25	4	Telaprevir manufacturer's submission to NICE (TA252); Assumption: 1 tube for a 4-week treatment
Anaemia (Epo)	Binocrit® (epoetin alfa)	40,000 units/week	1%	£13.27	4	Gao et al, 2012 (127); Assumption: 4-week treatment; % patients treated based on the average of three HCV centres in the UK
Anaemia (blood transfusion)[a]	NA	1	0.7%	£7.50	NA (<2 days)	Assumption: only one carried out; % patients treated based on the average of three HCV centres in the UK
Thrombocytopenia	Revolade® (eltrombopag)	50mg/day	100%	£385.00	4	BNF, 3rd August 2017; Assumption: 4-week treatment
Neutropenia	Neupogen® (filgrastim)	395 µg/d = 5*79	100%	£485.72	2	BNF, 3rd August 2017
Depression	Citalopram	20 mg/d	100%	£0.20	4	BNF, 3rd August 2017; Assumption: 4-week treatment

BNF, British National Formulary; epo, erythropoietin; NA, not applicable; NICE, National Institute for Health and Care Excellence.

[a] HRG "Single Plasma Exchange, Leukapheresis or Red Cell Exchange, with length of stay 2 days or less, 19 ears and over".

Table 59: Adverse event management cost

Adverse event	Items	% of patients	Units	Cost	Total cost (for % who receive treatment)	Source
Nausea	Outpatient	0%	0	£0.00	£0.00	KOL Opinion
	GP	0%	0	£0.00	£0.00	KOL Opinion
	Specialist	0%	0	£0.00	£0.00	KOL Opinion
Vomiting	Outpatient	0%	0	£0.00	£0.00	KOL Opinion
	GP	0%	0	£0.00	£0.00	KOL Opinion
	Specialist	0%	0	£0.00	£0.00	KOL Opinion
Diarrhoea	Outpatient	0%	0	£0.00	£0.00	KOL Opinion
	GP	0%	0	£0.00	£0.00	KOL Opinion
	Specialist	0%	0	£0.00	£0.00	KOL Opinion
Pruritus	Outpatient	0%	0	£0.00	£0.00	KOL Opinion
	GP	0%	0	£0.00	£0.00	KOL Opinion
	Specialist	0%	0	£0.00	£0.00	KOL Opinion
Rash	Outpatient	100%	4	£40.00	£160.00	KOL Opinion; PSSRU unit costs 2016 - Hospital, day ward; Each visit is assumed to take 1 hour (128)
	GP	0%	0	£0.00	£0.00	KOL Opinion
	Specialist	100%	2	£259.94	£519.88	KOL Opinion; National Schedule of Reference Costs Year 2015-16 - Consultant-led costs for Hepatology (122)(126)(123)(122)(36)(32)(32)(25)(12)
Anaemia (Epo)	Outpatient	100%	6	£40.00	£240.00	KOL Opinion; PSSRU unit costs 2016 - Hospital, day ward; Each visit is assumed to take 1 hour (128)
	GP	0%	0	£0.00	£0.00	KOL Opinion
	Specialist	50%	1	£259.94	£129.97	KOL Opinion; National Schedule of Reference Costs Year 2015-16 - Consultant-led costs for Hepatology (122)
Anaemia (blood transfusion)	Outpatient	NA	NA	NA	NA	Assumed to be included in the HRG cost
	GP	0%	0	£0.00	£0.00	KOL Opinion
	Specialist	50%	1	£259.94	£129.97	KOL Opinion; National Schedule of Reference Costs

Adverse event	Items	% of patients	Units	Cost	Total cost (for % who receive treatment)	Source
						Year 2015-16 - Consultant-led costs for Hepatology (122)(25)(12)
Thrombocytopenia	Outpatient	100%	6	£40.00	£240.00	KOL Opinion; PSSRU unit costs 2016 - Hospital, day ward; Each visit is assumed to take 1 hour (128) (24)(11)
	GP	0%	0	£0.00	£0.00	KOL Opinion
	Specialist	50%	1	£259.94	£129.97	KOL Opinion; National Schedule of Reference Costs Year 2015-16 - Consultant-led costs for Hepatology (122, 126)(119, 123)(118, 122)(32, 36)(28, 32)(28, 32) (25)(12)
Neutropenia	Outpatient	100%	6	£40.00	£240.00	KOL Opinion; PSSRU unit costs 2016 - Hospital, day ward; Each visit is assumed to take 1 hour (128)
	GP	0%	0	£0.00	£0.00	KOL Opinion
	Specialist	50%	1	£259.94	£129.97	KOL Opinion; National Schedule of Reference Costs Year 2015-16 - Consultant-led costs for Hepatology (122)
Depression	Outpatient	0%	0	£0.00	£0.00	KOL Opinion
	GP	100%	8	£13.33	£106.67	KOL Opinion; PSSRU unit costs 2016 – Registrar group (128)
	Specialist	0%	0	£0.00	£0.00	KOL Opinion

GP, general practitioner; HRG, healthcare resource group; KOL, key opinion leader; PSSRU, Personal Social Services Research Unit.

B.3.5.5. *Miscellaneous unit costs and resource use*

Not applicable.

B.3.6. *Summary of base-case analysis inputs and assumptions*

B.3.6.1. *Summary of base-case analysis inputs*

The generic model inputs have been previously reported in these tables/sections:

- Patient characteristics – Table 50
- TPs – Table 51
- Health state HRQL – Table 52
- Costs – Section B.3.5

Inputs specific to each indication are presented in this section. These include:

- SVRs
- Treatment duration
- Treatment-related AEs
- Treatment-specific QOL
    - The utility decrements are expressed as a percentage due to using a multiplicative approach

B.3.6.2. *SVR*

Table 60: SVR rates for DAA-experienced (all GTs) and DAA-naïve patients with GT3 infection (with or without cirrhosis)

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) POLARIS 4 (DAA-experienced population) (to be run as sensitivity analysis: 97.8%)
			No treatment	0%	POLARIS 1 (placebo arm) (DAA-experienced population)
DAA-naïve	3	CC	SOF/VEL/VOX	96.4%	POLARIS 3 (DAA-naïve population)
			SOF/VEL	96.3%	POLARIS 3 (DAA-naïve population) ASTRAL 3 (to be run as sensitivity analysis)
			SOF + DCV + RBV	83.3%	ALLY 3+ (DAA-naïve population)
			SOF + RBV	66.3%	ASTRAL 3 (DAA-naïve population)
			Peg-IFN2a + RBV	29.7%	Sovaldi SmPC [FISSION] (TN population)
			SOF + Peg-IFN2a + RBV	91.3%	BOSON (TN population)
			No treatment	0%	POLARIS 1 (placebo arm) (treatment-naive population)
		NC	SOF/VEL/VOX	98.9%	POLARIS 2 (DAA-naïve population)
			Peg-IFN2a + RBV	71.2%	Sovaldi SmPC [FISSION] (TN population)
			SOF + Peg-IFN2a + RBV	95.8%	BOSON (TN population)
			SOF/VEL	96.6%	POLARIS 2 (DAA-naïve population) ASTRAL 3 (TN population) (to be run as sensitivity analysis)
			SOF + DCV	96.3%	ALLY-3, DCV SmPC; TA364 limits this to F3 only
			No treatment	0%	POLARIS 1 (placebo arm) (treatment-naive population)

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; TN, treatment-naïve; VEL, velpatasvir; VOX, voxilaprevir.

B.3.6.3. *Treatment duration*

Table 61: Treatment duration for DAA-experienced (all GTs) and DAA-naïve patients with GT3 infection (with or without cirrhosis)

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	# weeks	% patients	# weeks	% patients[a]	# weeks	
DAA-experienced (All GTs, CC/NC)							
SOF/VEL/VOX (12 weeks)	99.6% (262/263)	12.0	0.4% (1/263)	12.0	0.0%	0.0	POLARIS-1
No treatment	0.0%	0.0	0.0%	0.0	100.0%	0.0	POALRIS-1 (placebo arm)
DAA-naïve (GT3, CC)							
SOF/VEL/VOX (8 weeks)	100.0%	8.0	0.0%	0.0	0.0%	0.0	POLARIS-2
SOF/VEL (12 weeks)	99.55% (438/440)	12.0	0.45% (2/440)	12.0	0.0%	0.0	POLARIS-2
SOF + DCV + RBV (12 weeks)	95.8% (23/24)	12.0	0.0%	0.0	4.2% (1/24)	12.0	ALLY-3+
SOF + RBV (24 weeks)	98.4% (246/250)	24.0	0.4% (1/250)	21.5	1.2%	21.5	VALENCE (129); Average number of weeks for discontinuation due to AEs and other reason obtained from CSR, Table 4 in appendix assuming patients discontinued in the middle of each interval
Peg-IFN2a + RBV (24 weeks)	89.3% (217/243)	24.0	10.7% (26/243)	24.0	0.0%	0.0	FISSION

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% patients	# weeks	% patients	# weeks	% patients[a]	# weeks	
SOF + Peg-IFN2a + RBV (12 weeks)	100.0%	12.0	0.0%	0.0	0.0%	0.0	BOSON trial (130)
No treatment	0.0%	0.0	0.0%	0.0	100.0%	0.0	No treatment
DAA-naïve (GT3, NC)							
SOF/VEL/VOX (8 weeks)	100.0%	8.0	0.0%	0.0	0.0%	0.0	POLARIS-2
Peg-IFN2a + RBV (24 weeks)	76.1% (134/176)	24.0	10.2% (18/176)	10.8	13.6%	11.9	Assumed equal to 12 weeks from FISSION (81)
SOF + Peg-IFN2a + RBV (12 weeks)	100.0%	12.0	0.0%	0.0	0.0%	0.0	BOSON trial (130)
SOF/VEL (12 weeks)	99.55% (438/440)	12.0	0.45% (2/440)	12.0	0.0%	0.0	POLARIS-2
SOF + DCV (12 weeks)	99.0% (100/101)	12.0	0.0%	0.0	1.0%	8.0	ALLY-3 (131)
No treatment	0.0%	0.0	0.0%	0.0	100.0%	0.0	No treatment

AE, adverse event; CSR, clinical study report; DAA, direct-acting antiviral; DCV, daclatasvir; GT, genotype; HCV, hepatitis C virus; Peg-IFN2a, pegylated-interferon alfa-2a; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

[a] Calculated as 100%-sum of the other categories

B.3.6.4. *Treatment-related adverse events*

Table 62: Treatment safety for DAA-experienced (all GTs) and DAA-naïve patients with GT3 infection (with or without cirrhosis)

Strategy	Nausea	Vomiting	Diarrhoea	Pruritus	Rash	Anaemia (EPO)	Anaemia (Blood trans-fusion)	Thrombocytopenia	Neutro-penia	Depression	Severe liver injury	Source
DAA-experienced (All GTs, CC/NC)												
SOF/VEL/VOX (12 weeks)	14.07%	1.14%	17.87%	2.28%	1.52%	0.38%	0.00%	0.00%	0.00%	2.28%	0.00%	POLARIS-1
DAA-naïve (GT3, CC)												
SOF/VEL/VOX (8 weeks)	15.97%	3.19%	17.56%	1.60%	1.20%	0.40%	0.00%	0.00%	0.00%	1.00%	0.00%	POLARIS-2
SOF/VEL (12 weeks)	4.64%	3.31%	29.14%	3.97%	1.99%	0.66%	0.00%	0.00%	0.00%	0.66%	0.00%	POLARIS -4
SOF+ DCV + RBV (12 weeks)	12.50%	4.17%	4.17%	4.17%	4.17%	0.00%	0.00%	0.00%	0.00%	4.17%	0.00%	ALLY 3+
SOF + RBV (24 weeks)[a]												
Peg-IFN2a + RBV (24 weeks)	0.4% (1/243)	0.0%	0.0%	0.0%	0.0%	0.8% (2/243)	0.8% (2/243)	2.1% (5/243)	3.3% (8/243)	0.4% (1/243)	0.0%	FISSION (81)
SOF + Peg-IFN2a + RBV (12 weeks)	0.0%	0.3% (1/327)	0.0%	0.0%	0.3% (1/327)	2.1% (7/327)	2.1% (7/327)	0.3% (1/327)	7.0% (23/327)	0.3% (1/327)	0.0%	Assumed equal to NEUTRINO (81)
DAA-naïve (GT3, NC)												
SOF/VEL/VOX (8 weeks)	15.97%	3.19%	17.56%	1.60%	1.20%	0.40%	0.00%	0.00%	0.00%	1.00%	0.00%	POLARIS-2
Peg-IFN2a + RBV (24 weeks)	0.4% (1/243)	0.0%	0.0%	0.0%	0.0%	0.8% (2/243)	0.8% (2/243)	2.1% (5/243)	3.3% (8/243)	0.4% (1/243)	0.0%	FISSION (81)
SOF + Peg-IFN2a + RBV (12 weeks)	0.0%	0.3% (1/327)	0.0%	0.0%	0.3% (1/327)	2.1% (7/327)	2.1% (7/327)	0.3% (1/327)	7.0% (23/327)	0.3% (1/327)	0.0%	Assumed equal to NEUTRINO (81)
SOF/VEL (12 weeks)	4.64%	3.31%	29.14%	3.97%	1.99%	0.66%	0.00%	0.00%	0.00%	0.66%	0.00%	POLARIS -4
SOF + DCV (12 weeks)	11.84%	0.66%	8.55%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	ALLY-3

DAA, direct-acting antiviral; DCV, daclatasvir; GT, genotype; HCV, hepatitis C virus; Peg-IFN2a, pegylated-interferon alfa-2a; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.
[a] No clinical trial data availabl

B.3.6.5. *Treatment-specific quality of life*

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

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) from Younossi et al. 2016 (132)
DAA-naïve (GT3, CC)		
SOF/VEL/VOX (8 weeks)	0.0%	Assumed equal to SOF/VEL(12 weeks) from Younossi et al. 2016 (132)
SOF/VEL (12 weeks)	0.0%	Younossi et al. 2016 (132)
SOF/DCV + RBV (12 weeks)	-2.5%	Assumed equal to SOF + RBV from Younossi et al. 2016 (132)
SOF + RBV (24 weeks)	-2.5%	Younossi et al. 2016 (132)
Peg-IFN2a + RBV (24 weeks)	-4.7%	Younossi et al. 2016 (132)
SOF + Peg-IFN2a + RBV (12 weeks)	-4.7%	Younossi et al. 2016 (132)
DAA-naïve (GT3, NC)		
SOF/VEL/VOX (8 weeks)	0.0%	Younossi et al. 2016 (132)
Peg-IFN2a + RBV (24 weeks)	-4.7%	Younossi et al. 2016 (132)
SOF + Peg-IFN2a + RBV (12 weeks)	-4.7%	Younossi et al. 2016 (132)
SOF/VEL (12 weeks)	0.0%	Younossi et al. 2016 (132)
SOF + DCV (12 weeks)	0.0%	Younossi et al. 2016 (132)

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.

B.3.7. *Base-case results*

Overall, base-case results indicate that SOF/VEL/VOX 12 week is highly cost-effective in DAA-experienced patients with a an ICER of under £10,000 per QALY compared to no treatment.

In non-cirrhotic DAA-naïve GT3 patients SOF/VEL/VOX 8 week is highly cost-effective, dominating treatment with SOF/VEL, SOF + Peg-IFN2a + RBV and SOF + DCV, and producing 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 is cost-effective, dominating treatment with SOF + Peg-IFN2a + RBV, SOF + DCV + RBV and SOF+ RBV, and producing small ICERs versus Peg-IFN2a + RBV and no treatment. Against SOF/VEL, SOF/VEL/VOX is equivalent in efficacy (the marginal difference in QALYs is due to modelling limitation rather than differences in efficacy – further described in B.1.5.5.2) and cost-saving.

Detailed results tables are presented in the tables below. All comparators are listed within the results tables. Comparators are ranked by incremental QALYs, with any dominated (or extendedly dominated) strategies appearing below the strategies on the cost-effectiveness frontier. Results include an ICER to the first strategy (no treatment or Peg-IFN2a + RBV) as well as the ICER to strategy above.

B.3.7.1. *Base-case incremental cost-effectiveness analysis results – DAA-experienced patients*

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

Treatment	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER versus No treatment (£)	ICER Incremental (£)
No treatment	23,262	14.83	10.01	-	-	-	-	-
SOF/VEL/VOX (12 wks)	53,922	19.06	13.77	30,660	4.23	3.76	8,153	8,153

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

B.3.7.2. *Base-case incremental cost-effectiveness analysis results – DAA-naive patients with GT3 infection and compensated cirrhosis*

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

Treatment	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER versus No treatment (£)	ICER Incremental (£)
No treatment	36,262	9.36	4.98	-	-	-	-	-
Peg-IFN2a + RBV (24 wks)	37,510	11.94	6.61	1,248	2.59	1.63	765	765
SOF/VEL/VOX (8 wks)	51,289	17.14	9.98	15,027	7.78	5.00	3,004	4,088
SOF/VEL (12 wks)	60,449	17.16	9.99	24,187	7.81	5.01[a]	4,825	863,724
SOF + Peg-IFN2a + RBV (12 wks)	59,961	16.76	9.72	23,699	7.40	4.75	4,992	**Dominated** by SOF/VEL/VOX (8 wks)

SOF + DCV + RBV (12 wks)	83,447	16.12	9.31	47,185	6.77	4.34	10,873	**Dominated** by SOF/VEL/VOX (8 wks)
SOF+ RBV (24 wks)	98,661	14.86	8.49	62,399	5.51	3.51	17,760	**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.

B.3.1.1 *Base-case incremental cost-effectiveness analysis results – DAA-naive patients with GT3 infection and non-cirrhotic*

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

Treatment	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER versus Peg-IFN2a + RBV (24 wks) (£)	ICER Incremental (£)
Peg-IFN2a + RBV (24 wks)	12,256	20.85	16.03	-	-	-	-	-
SOF/VEL/VOX (8 wks)	32,917	21.87	17.27	20,661	1.02	1.24	16,654	16,654
No treatment	18,938	18.12	12.83	6,682	-2.73	-3.20	**Dominated** by Peg-IFN2a + RBV (24 wks)	**Dominated** by Peg-IFN2a + RBV (24 wks)

Sofosbuvir + Peg-IFN2a + RBV (12 wks)	41,303	21.76	17.13	29,047	0.90	1.09	26,596	**Dominated** by SOF/VEL/VOX (8 wks)
SOF/VEL (12 wks)	42,519	21.79	17.17	30,262	0.93	1.14	26,594	**Dominated** by SOF/VEL/VOX (8 wks)
SOF + DCV (12 wks)	62,698	21.81	17.20	50,441	0.96	1.17	43,137	**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.

B.3.8. *Sensitivity analyses*

B.3.8.1. *Probabilistic sensitivity analysis*

B.3.8.1.1. Inputs

A PSA was undertaken to quantify the parameter uncertainty in the economic model. The results are presented as the probability of being cost effective at a threshold of £20,000 per QALY and £30,000 per QALY, and also as cost-effectiveness acceptability curves (CEACs).

The following groups of parameter values were included in the PSA:

- SVR rates
- Utilities
- Health state costs
- TPs

These have been grouped into generic and treatment-specific PSA inputs and are reported below.

Generic PSA inputs

Health state utilities were assumed to be Beta distributed except for those associated with SVR utility increments for which gamma distributions were used. Costs were assumed to be Gamma distributed except for treatment costs which were assumed to be uniformly distributed. A more detailed description of the distributions and parameters can be found in Table 67 below.

Table 67: Generic PSA input values

Variable	Distribution and parameters	Source
Health state costs		
Non-cirrhotic disease	Gamma; α=61.5; β=5.3	Wright, 2006 (133)
Cirrhotic disease	Gamma; α=61.5; β=25.4	Wright, 2006 (112)
Decompensated cirrhosis	Gamma; α=61.5; β=203.5	Wright, 2006 (112)
Non-cirrhotic disease - SVR	Gamma; α=61.5; β=4.0	Grishchenko, 2009 (109)
Cirrhotic disease - SVR	Gamma; α=61.5; β=8.3	Grishchenko, 2009 (109)
Decompensated cirrhosis - SVR	Gamma; α=61.5; β=203.5	Assumption
Hepatocellular carcinoma	Gamma; α=61.5; β=181.4	Wright, 2006 (112)
Liver transplant	Gamma; α=61.5; β=1386.0	Longworth, 2014 (124)
Post-liver transplant – Year 1	Gamma; α=61.5; β=456.7	Longworth, 2014 (124)
Post-liver transplant – Year 2	Gamma; α=61.5; β=68.2	Longworth, 2014 (124)
Utility weights		

Variable	Distribution and parameters	Source
Non-cirrhotic - without treatment	Beta; α=681.8; β=225.7	Wright, 2006 (UK mild HCV trial) (112)
Cirrhotic - without treatment	Beta; α=46.6; β=38.1	Wright, 2006 (UK mild HCV trial) (112)
Decompensated cirrhosis - without treatment	Beta; α=123.8; β=151.3	Wright, 2006 (UK mild HCV trial) (112)
SVR - Utility increment	Gamma; α=0.8; β=0.1	Vera-Llonch et al, 2013 (121)
Hepatocellular carcinoma	Beta; α=123.8; β=151.3	Wright, 2006 (UK mild HCV trial) (112)
Liver transplant	Beta; α=123.8; β=151.3	Wright, 2006 (UK mild HCV trial) (112)
Post-liver transplant	Beta; α=33.3; β=16.4	Wright, 2006 (UK mild HCV trial) (112)
Transition probabilities		
From compensated cirrhosis to decompensated cirrhosis	Beta; α=32.5; β=710.0	Cardoso, 2010 (65) - 95% CI calculated based on Cardoso 2010 (65)
From compensated cirrhosis to HCC	Beta; α=50, β=744	Cardoso, 2010 (65) - 95% CI calculated based on Cardoso 2010 (65)
From compensated cirrhosis with SVR to decompensated cirrhosis	Beta; α=3.7; β=577.4	Cardoso, 2010 (65) - 95% CI calculated based on Cardoso 2010 (65)
From compensated cirrhosis with SVR to HCC	Beta; α=7; β=502	Cardoso, 2010 (65) - 95% CI calculated based on Cardoso 2010 (65)
From decompensated cirrhosis to HCC	Beta; α=50; β=744	Cardoso, 2010 (65) - 95% CI calculated based on Cardoso 2010 (65) Assumed equal to transition probability of compensated cirrhosis to HCC
From decompensated cirrhosis to liver transplant	Beta; α=15; β=667	Siebert, 2005 (118)
From decompensated cirrhosis to death	Beta; α=46.5; β=147.2	EAP data (EASL 2016) - Assumed 95% CI based on +/-25% range
From decompensated cirrhosis with SVR to HCC	Beta; α=50; β=744	Assumption
From decompensated cirrhosis with SVR to liver transplant	Beta; α=15; β=667	Assumption
From decompensated cirrhosis with SVR to death	Beta; α=58.4; β=1133.5	EAP data (EASL 2016) - Assumed 95% CI based on +/-25% range
From HCC to death	Beta; α=117.1; β=155.2	Fattovich, 1997 (119) - Beta parameters from Shepherd et al 2007 (111)
From liver transplant to death	Beta; α=16.3; β=61.2	Bennett, 1997 (120) - Beta parameters from Shepherd et al 2007 (111)
From post-liver transplant to death	Beta; α=22.9; β=378.9	Bennett, 1997 (120) - Beta parameters from Shepherd et al 2007 (111)

Indication- and genotype-specific PSA inputs

The TP from non-cirrhotic to cirrhotic was dependent on HCV GT. Treatment-related utility decrements are indication-specific.

TP from non-cirrhotic to cirrhotic were assumed to follow a beta distribution, as presented in Table 68. We have assumed that GT5 and GT6 TP from non-cirrhotic to cirrhotic are equivalent to GT4, due to a lack of published evidence.

Table 68: Genotype-specific PSA inputs – TP form non-cirrhotic to cirrhotic

Variable	Base-case	Lower limit	Upper limit	SE	Distribution	α	β
GT1/1a/1b	0.0213	0.0209	0.0217	0.0002	Beta	11101	505337
GT2	0.0165	0.0125	0.0175	0.0006	Beta	876	51885
GT3	0.0296	0.0278	0.0313	0.0009	Beta	1069	34567
GT4	0.0202	0.0167	0.0244	0.0021	Beta	87	4169
GT5/6*	0.0202	0.0167	0.0244	0.0021	Beta	87	4169

*Assumption
GT, genotype; SE, standard error.

Utility decrements were assumed to follow Gamma distribution. The 95% confidence intervals of utility decrements were estimated by plus or minus 20% of base-case value. SVRs were assumed to follow Beta distribution if the rate is not equal to 100% and follow Normal distribution otherwise.

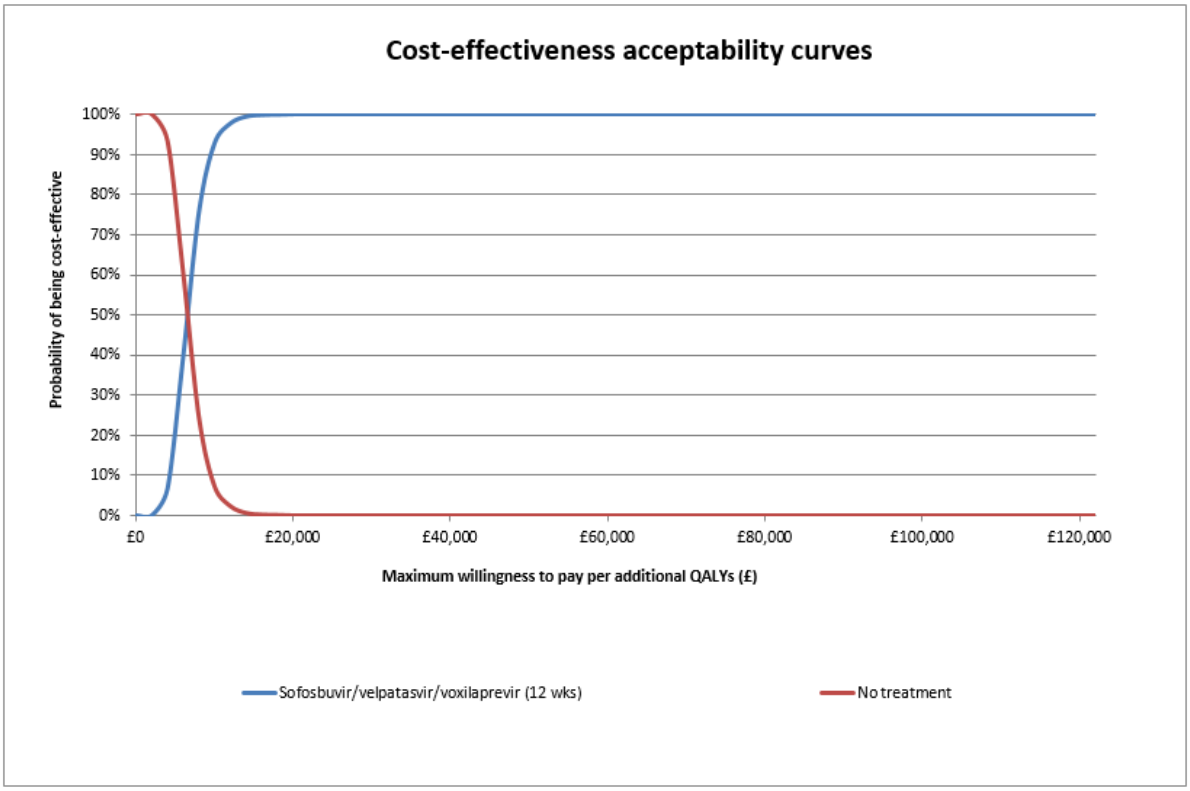
B.3.8.1.2. Results

DAA-experienced patients

Table 69: Probability of cost-effectiveness: DAA-experienced (pan-GT and all non-cirrhotic/compensated cirrhosis) (list price)

Threshold	Probability of cost-effectiveness
£20,000	100%
£30,000	100%

Table 70: Multiple CEACs: DAA-experienced (pan-GT and all non-cirrhotic/compensated cirrhosis) (list price)



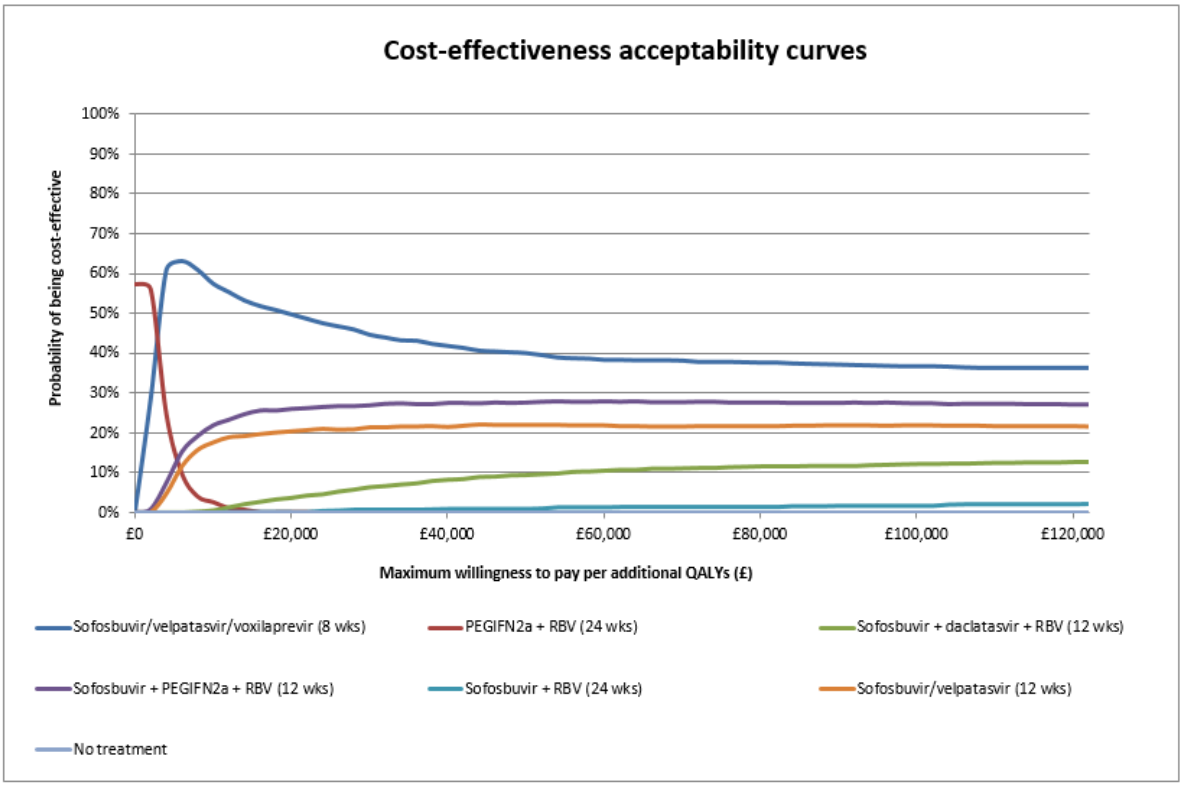
DAA-naïve patients, GT3 infection

Compensated cirrhosis

Table 71: Probability of cost-effectiveness: DAA-naïve, GT3 infection, compensated cirrhosis (list price)

Threshold	Probability of cost-effectiveness
£20,000	49%
£30,000	44%

Figure 4: Multiple CEACs: DAA-naïve, GT3 infection, compensated cirrhosis (list price)

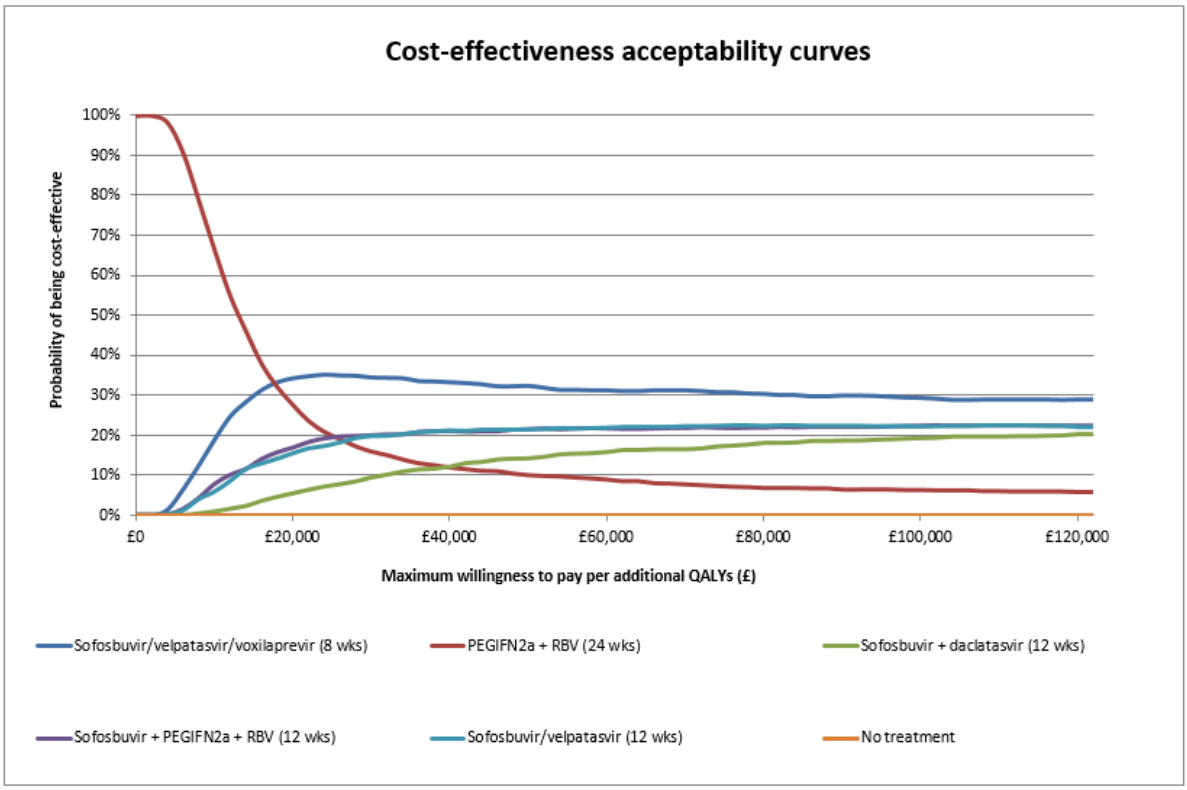


Non-cirrhotic patients

Table 72: Probability of cost-effectiveness: DAA-naïve, GT3 infection, non-cirrhotic (list price)

Threshold	Probability of cost-effectiveness
£20,000	36%
£30,000	35%

Figure 5: Multiple CEACs: DAA-naïve, GT3 infection, non-cirrhotic (list price)



B.3.8.1.3. Discussion of variation between base-case and PSA results

The probabilistic results are consistent with the deterministic results presented in the base-case results (Section B.3.7).

DAA-experienced patients

- The probability that SOF/VEL/VOX is the most cost-effective option at a threshold of £20,000 per QALY is 100% for DAA-experienced patients
- The probability that SOF/VEL/VOX is the most cost-effective option at a threshold of £30,000 per QALY is 100% for DAA-experienced patients.

DAA-naïve patients, GT3 infection, compensated cirrhosis

- The probability that SOF/VEL/VOX is the most cost-effective option at a threshold of £20,000 per QALY is 49% for DAA-naïve, GT3 infection, with compensated cirrhosis
- The probability that SOF/VEL/VOX is the most cost-effective option at a threshold of £30,000 per QALY is 44% for DAA-naïve, GT3 infection, with compensated cirrhosis

DAA-naïve patients, GT3 infection, non-cirrhotic

- The probability that SOF/VEL/VOX is the most cost-effective option at a threshold of £20,000 per QALY is 36% for DAA-naïve, GT3 infection, non-cirrhotic
- The probability that SOF/VEL/VOX is the most cost-effective option at a threshold of £30,000 per QALY is 35% for DAA-naïve, GT3 infection, non-cirrhotic

B.3.8.2. *Deterministic sensitivity analysis (DSA)*

B.3.8.2.1. Inputs

In order to assess the uncertainty of the results, the model includes one way DSA. In the DSA, the input values are varied one at a time to show the impact of each variable on the model results.

The results of the DSA are presented using Tornado diagrams. The impact of the top ten drivers on the model results (ICERs) is presented in a table and in the form of a tornado diagram for each analysis.

Generic DSA inputs

The generic inputs varied in the DSA are: treatment costs, health state costs, utility values, TPs, discount rates and the probability of death for the general population. Probability of death was varied by +/- 25% of the base-case inputs. All other generic DSA inputs with their minimum and maximum values are presented in Table 73.

Within the DSA the impact of assuming re-infection (transition probability from SVR to no SVR) was tested. Note that this analysis only considers re-infection and not reductions in disease transmission that would also be associated with successful treatment. This analysis is therefore likely to underestimate the cost-effectiveness of treatment. A further exploratory analysis considering both re-infection and onward transmission is presented in section B.3.8.3.

Table 73: Generic DSA input values

Parameter	Base-case	Min	Max	Source
Health state costs				
Non-cirrhotic disease – No treatment	£603	£452	£754	Assumption: +/- 25% of the BC
Cirrhotic disease – No treatment – Pharmacy	£395	£296	£494	Assumption: +/- 25% of the BC
Cirrhotic disease – No treatment – Hospitalisation	£395	£296	£494	Assumption: +/- 25% of the BC

Parameter	Base-case	Min	Max	Source
Cirrhotic disease – No treatment – Outpatient	£791	£593	£989	Assumption: +/- 25% of the BC
Cirrhotic disease – No treatment – Emergency	£395	£296	£494	Assumption: +/- 25% of the BC
Cirrhotic disease – No treatment – Ambulatory	£395	£296	£494	Assumption: +/- 25% of the BC
Decompensated cirrhosis - Pharmacy	£3,169	£2,377	£3,961	Assumption: +/- 25% of the BC
Decompensated cirrhosis – Hospitalisation	£3,169	£2,377	£3,961	Assumption: +/- 25% of the BC
Decompensated cirrhosis – Outpatient	£6,338	£4,754	£7,923	Assumption: +/- 25% of the BC
Decompensated cirrhosis – Emergency	£3,169	£2,377	£3,961	Assumption: +/- 25% of the BC
Decompensated cirrhosis – Ambulatory	£3,169	£2,377	£3,961	Assumption: +/- 25% of the BC
Non-cirrhotic disease – SVR	£267	£200	£334	Assumption: +/- 25% of the BC
Cirrhotic disease – SVR - Pharmacy	£130	£98	£163	Assumption: +/- 25% of the BC
Cirrhotic disease – SVR – Hospitalisation	£130	£98	£163	Assumption: +/- 25% of the BC
Cirrhotic disease – SVR – Outpatient	£260	£195	£325	Assumption: +/- 25% of the BC
Cirrhotic disease – SVR – Emergency	£130	£98	£163	Assumption: +/- 25% of the BC
Cirrhotic disease – SVR – Ambulatory	£130	£98	£163	Assumption: +/- 25% of the BC
Decompensated cirrhosis - SVR -Pharmacy	£3,169	£2,377	£3,961	Assumption: +/- 25% of the BC
Decompensated cirrhosis - SVR - Hospitalisation	£3,169	£2,377	£3,961	Assumption: +/- 25% of the BC
Decompensated cirrhosis - SVR - Outpatient	£6,338	£4,754	£7,923	Assumption: +/- 25% of the BC
Decompensated cirrhosis - SVR - Emergency	£3,169	£2,377	£3,961	Assumption: +/- 25% of the BC
Decompensated cirrhosis - SVR - Ambulatory	£3,169	£2,377	£3,961	Assumption: +/- 25% of the BC
Hepatocellular carcinoma - Pharmacy	£2,824	£2,118	£3,530	Assumption: +/- 25% of the BC
Hepatocellular carcinoma – Hospitalisation	£2,824	£2,118	£3,530	Assumption: +/- 25% of the BC
Hepatocellular carcinoma – Outpatient	£5,647	£4,235	£7,059	Assumption: +/- 25% of the BC
Hepatocellular carcinoma – Emergency	£2,824	£2,118	£3,530	Assumption: +/- 25% of the BC
Hepatocellular carcinoma – Ambulatory	£2,824	£2,118	£3,530	Assumption: +/- 25% of the BC
Liver transplant - Pharmacy	£21,581	£16,186	£26,976	Assumption: +/- 25% of the BC
Liver transplant – Hospitalisation	£21,581	£16,186	£26,976	Assumption: +/- 25% of the BC
Liver transplant – Outpatient	£43,162	£32,372	£53,953	Assumption: +/- 25% of the BC
Liver transplant – Emergency	£21,581	£16,186	£26,976	Assumption: +/- 25% of the BC
Liver transplant – Ambulatory	£21,581	£16,186	£26,976	Assumption: +/- 25% of the BC
Post-liver transplant – Year 1	£28,441	£21,331	£35,551	Assumption: +/- 25% of the BC
Post-liver transplant – Year 2	£4,250	£3,188	£5,313	Assumption: +/- 25% of the BC

Parameter	Base-case	Min	Max	Source
Utility weights				
Non-cirrhotic	0.751	0.601	0.902	Assumption: +/- 20% of the BC
Cirrhotic	0.550	0.440	0.660	Assumption: +/- 20% of the BC
Decompensated cirrhosis	0.450	0.360	0.540	Assumption: +/- 20% of the BC
SVR - Utility increment	0.040	0.032	0.048	Assumption: +/- 20% of the BC
Hepatocellular carcinoma	0.450	0.360	0.540	Assumption: +/- 20% of the BC
Liver transplant	0.450	0.360	0.540	Assumption: +/- 20% of the BC
Post-liver transplant	0.670	0.536	0.804	Assumption: +/- 20% of the BC
Transition probabilities				
From compensated cirrhosis to decompensated cirrhosis	0.044	0.029	0.058	Based on the PSA distribution
From compensated cirrhosis to HCC	0.023	0.019	0.027	Based on the PSA distribution
From compensated cirrhosis with SVR to decompensated cirrhosis	0.006	0.000	0.013	Based on the PSA distribution
From compensated cirrhosis with SVR to HCC	0.007	0.003	0.019	Based on the PSA distribution
From decompensated cirrhosis to HCC	0.014	0.002	0.039	Based on the PSA distribution
From decompensated cirrhosis to liver transplant	0.020	0.012	0.056	Based on the PSA distribution
From decompensated cirrhosis to death	0.130	0.111	0.150	Based on the PSA distribution
From decompensated cirrhosis with SVR to HCC	0.014	0.002	0.039	Based on the PSA distribution
From decompensated cirrhosis with SVR to liver transplant	0.020	0.012	0.056	Based on the PSA distribution
From decompensated cirrhosis with SVR to death	0.130	0.111	0.150	Based on the PSA distribution
From HCC to death	0.430	0.372	0.489	Based on the PSA distribution
From liver transplant to death	0.210	0.127	0.307	Based on the PSA distribution
From post-liver transplant to death	0.057	0.037	0.082	Based on the PSA distribution
From non-cirrhotic SVR to non-cirrhotic (re-infection)	0.000	0.000	0.100	Based on the PSA distribution
From compensated cirrhotic SVR to compensated cirrhotic (re-infection)	0.000	0.000	0.100	Assumption
From decompensated cirrhotic SVR to decompensated cirrhotic (re-infection)	0.000	0.000	0.100	Assumption
From HCC to liver transplant	0.000	0.000	0.100	Assumption
Discounting				
Outcomes	3.5%	0.0%	6.0%	NICE guidelines
Costs	3.5%	0.0%	6.0%	NICE guidelines

B.3.8.2.2. Indication-specific DSA inputs

In addition to the generic inputs listed in Table 73, a number of indication-specific variables were varied in the DSA. The method to estimate lower and upper inputs for these variables are presented below. The full set of upper and lower ranges for every indication are not reported due to the large number of indications and parameters. However, these are accessible within the model.

The approach taken to estimate the maximum and minimum values for each indication-specific DSA input value is consistent with the NICE submissions for SOF, LDV/SOF and SOF/VEL. Where 95% CI could be derived from the PSA inputs, then these were used for the lower and upper inputs in the DSA (for treatment-specific SVR rates (see Table 75), and for the indication-specific TP from non-cirrhotic to cirrhotic). Health state costs were varied by +/-25% of their base-case value. Treatment-specific utility decrements were varied by +/-20% of their base-case value. These ranges were validated by a clinical expert and health economist during model validation.

Table 74: Indication-specific DSA input values

Variables	Method to estimate lower and upper inputs for the DSA
Treatment-specific AE rates	Between 0% and 25%
Health state cost while on treatment	+/- 25% of base-case value
Treatment-specific utility decrement	+/- 20% of base-case value
TP from non-cirrhotic to cirrhotic	95% CI estimated from the PSA

AE, Adverse event; CI, Confidence interval; DSA, Deterministic sensitivity analysis; PSA, Probabilistic sensitivity analysis; SVR, Sustained virologic response.

Table 75: SVR DSA input values

Parameter	Base-case	Min	Max	Source
SVR rates				
DAA-experienced				
SOF/VEL/VOX 12 weeks	96.20%	93.58%	98.15%	95% CI
DAA-naïve, GT3, CC				
SOF/VEL/VOX 8 weeks	96.36%	92.17%	98.99%	95% CI
Peg-IFN + RBV 24 weeks	29.70%	21.20%	38.97%	95% CI
SOF + DCV + RBV 12 weeks	88.33%	63.56%	96.20%	95% CI
SOF + Peg-IFN + RBV 12 weeks	91.30%	85.08%	95.97%	95% CI
SOF + RBV 24 weeks	66.30%	56.80%	75.19%	95% CI
SOF/VEL 12 weeks	96.33%	92.10%	98.98%	95% CI

Parameter	Base-case	Min	Max	Source
DAA-naïve, GT3, NC				
SOF/VEL/VOX 8 weeks	98.90%	95.89%	99.97%	95% CI
Peg-IFN + RBV 24 weeks	71.20%	61.99%	79.60%	95% CI
SOF + DCV 12 weeks	97.33%	92.70%	99.67%	95% CI
SOF + Peg-IFN + RBV 12 weeks	95.80%	91.11%	98.78%	95% CI
SOF/VEL 12 weeks	96.63%	92.03%	99.29%	95% CI

B.3.8.2.3. Results

Full ICER results tables for the deterministic sensitivity analysis can be found in Appendix L.

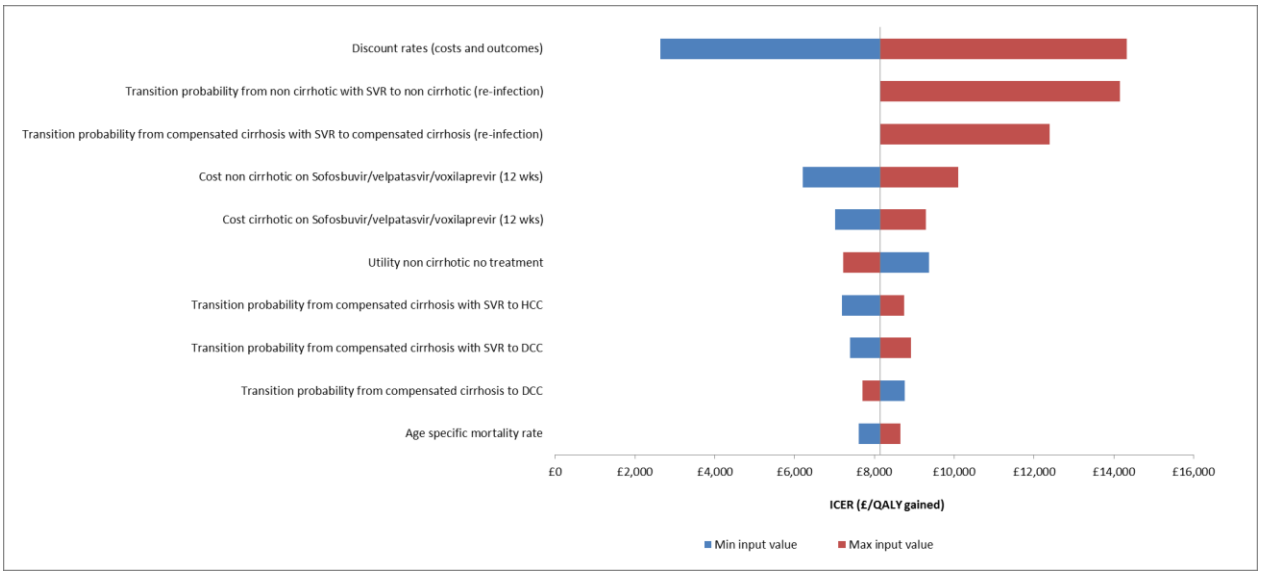
DAA-experienced patients

SOF/VEL/VOX 12 weeks vs no treatment

In this comparison, the ICER was most sensitive to the discount rate (varied between 0% and 6%), the transition probability from compensated cirrhosis with SVR to compensated cirrhosis (re-infection, and the cost of SOF/VEL/VOX (12 weeks).

The base-case ICER is £8,153 per QALY gained for SOF/VEL/VOX vs no treatment. Across all parameters varied in this DSA, the ICER for SOF/VEL/VOX vs no treatment did not exceed £20,000 per QALY.

Figure 6: Tornado diagram: DAA-experienced (pan-GT and all non-cirrhotic/compensated cirrhosis): SOF/VEL/VOX 12 weeks vs no treatment (list price)



DAA-naïve patients, GT3 infection

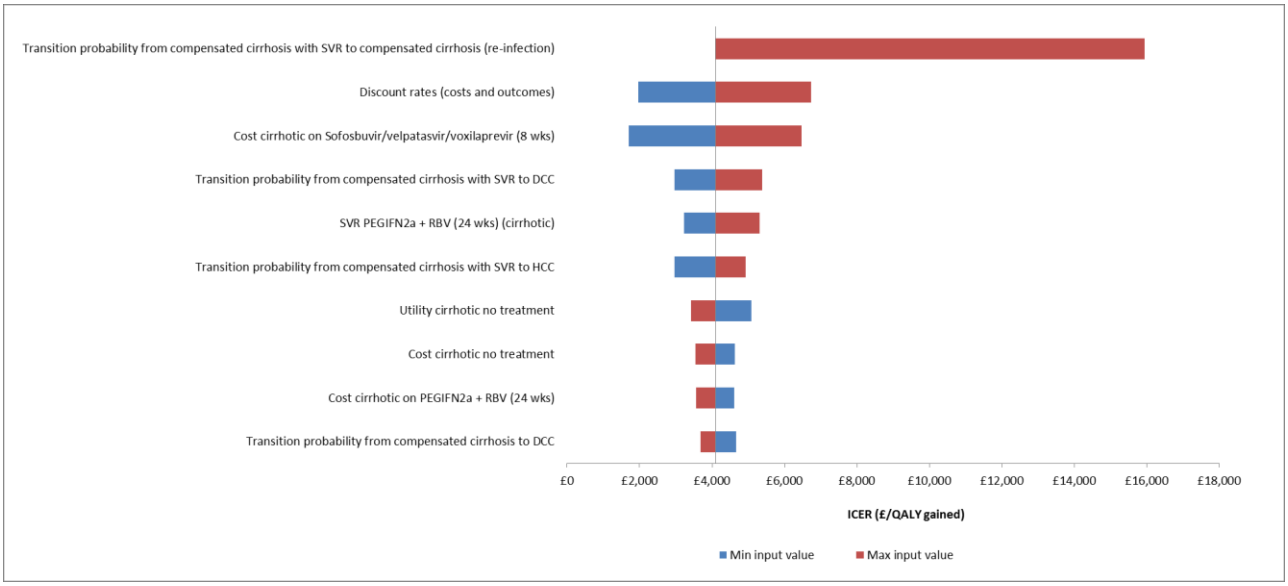
Compensated cirrhosis

SOF/VEL/VOX 8 weeks vs Peg-IFN2a + RBV 24 weeks (list price)

In this comparison, the ICER was most sensitive to the transition probability from compensated cirrhosis with SVR to compensated cirrhosis (re-infection), the discount rate (varied between 0% and 6%), and the cost of cirrhotic status on SOF/VEL/VOX (8 weeks).

The base-case ICER is £4,088 per QALY gained for SOF/VEL/VOX vs Peg-IFN2a + RBV 24 weeks. Across all parameters varied in this DSA, the ICER for SOF/VEL/VOX vs Peg-IFN2a + RBV 24 weeks did not exceed £20,000 per QALY (Figure 7).

Figure 7: Tornado diagram: DAA-naïve, GT3, with compensated cirrhosis: SOF/VEL/VOX 8 weeks vs Peg-IFN2a+RBV 24 weeks (list price)



SOF/VEL/VOX 8 weeks vs SOF + DCV + RBV 12 weeks (list price)

SOF/VEL/VOX was dominant in the base case, and remains dominant in all scenarios, except where the SVR for SOF + DCV + RBV (12 weeks) is increased to the upper 95% confidence limit; in this scenario SOF/VEL/VOX is less effective and less costly than SOF + DCV + RBV. This result is unsurprising given the wide confidence intervals in the SOF + DCV + RBV SVR.

SOF/VEL/VOX 8 weeks vs SOF + Peg-IFN2a + RBV 12 weeks (list price)

SOF/VEL/VOX was dominant in the base case, and remains dominant in all scenarios, except where the cost of SOF + Peg-IFN2a + RBV (12 weeks) is reduced by 25%; in this scenario an ICER of £5,269 was observed.

SOF/VEL/VOX 8 weeks vs SOF+RBV 24 weeks (list price)

SOF/VEL/VOX was dominant in the base case, and remains dominant in all scenarios.

SOF/VEL/VOX 8 weeks vs SOF/VEL 12 weeks (list price)

In the base case SOF/VEL/VOX has similar QALYs to SOF/VEL, but is cost saving. In this comparison, SOF/VEL/VOX remained less costly, with two exceptions:

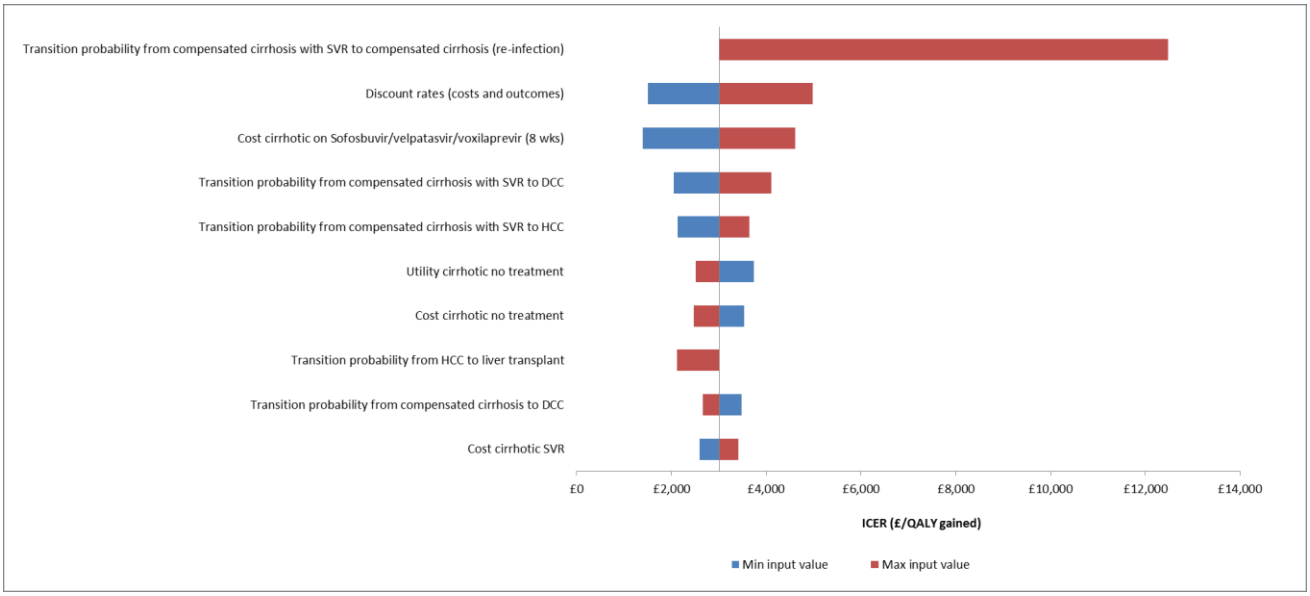
- SOF/VEL/VOX dominates when the SVR of SOF/VEL/VOX is increased to the upper 95% confidence interval
- SOF/VEL/VOX dominates when the SVR of SOF/VEL is decreased to the lower 95% confidence interval

SOF/VEL/VOX 8 weeks vs no treatment (list price)

In this comparison, the ICER was most sensitive to the transition probability from compensated cirrhosis with SVR to compensated cirrhosis (re-infection), the discount rate (varied between 0% and 6%), and the cost of cirrhotic state on SOF/VEL/VOX (8 weeks).

The base-case ICER is £3,004 per QALY gained for SOF/VEL/VOX vs no treatment. Across all parameters varied in this DSA, the ICER for SOF/VEL/VOX vs no treatment did not exceed £20,000 per QALY.

Figure 8: Tornado diagram: DAA-naïve, GT3, with compensated cirrhosis: SOF/VEL/VOX 8 weeks vs no treatment (list price)



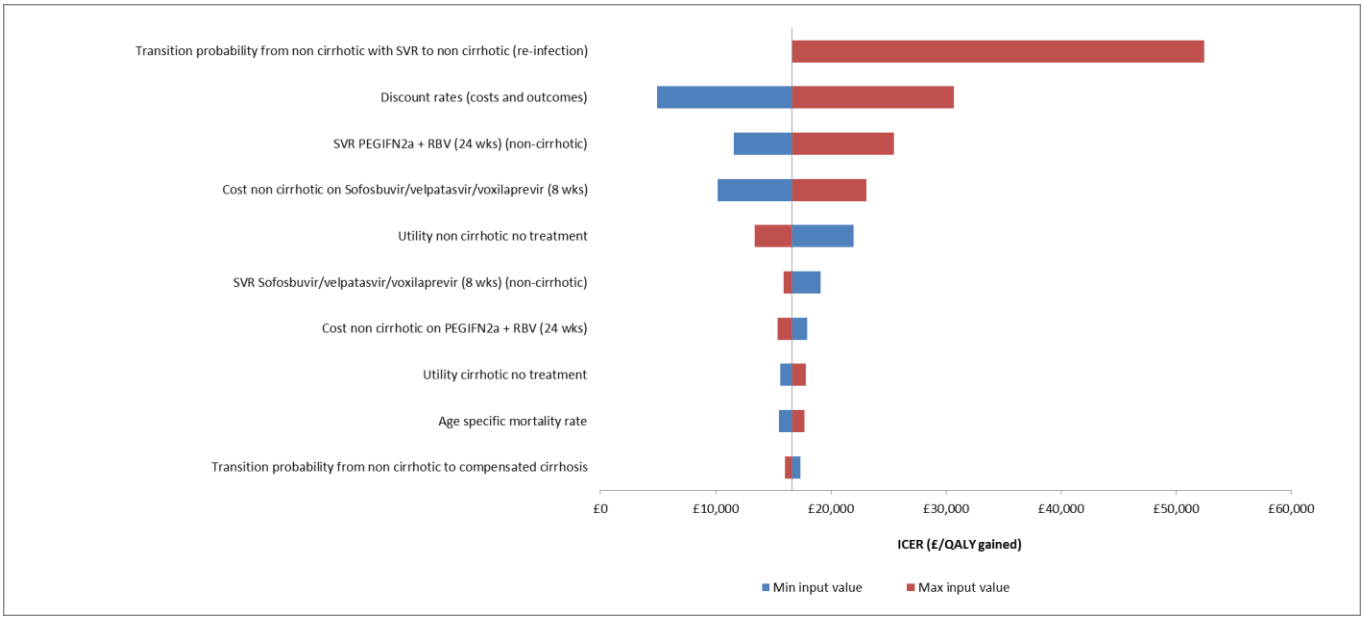
DAA-naïve patients, GT3 infection

Non-cirrhotic

SOF/VEL/VOX 8 weeks vs Peg-IFN2a + RBV 24 weeks (list price)

The base-case ICER is £16,654 per QALY gained for SOF/VEL/VOX vs Peg-IFN2a + RBV. In this comparison, the ICER was most sensitive to the transition probability from non-cirrhotic with SVR to non-cirrhotic (re-infection), the discount rate (varied between 0% and 6%), and the the Peg-IFN2a + RBV (24 weeks) SVR.

Figure 9: Tornado diagram: DAA-naïve, GT3 infection, non-cirrhotic: SOF/VEL/VOX 8 weeks vs Peg-IFN2a + RBV 24 weeks (list price)



SOF/VEL/VOX 8 weeks vs SOF + DCV 12 weeks (list price)

SOF/VEL/VOX was dominant in the base case, and remains dominant in all scenarios, with two exceptions:

- Where the SVR for SOF + DCV (12 weeks) is increased to the upper 95% confidence limit; in this scenario SOF/VEL/VOX is less effective and less costly than SOF + DCV.
- Where the SVR of SOF/VEL/VOX (8 weeks) is decreased to the lower 95% confidence limit; in this scenario SOF/VEL/VOX is less effective and less costly than SOF + DCV.

SOF/VEL/VOX 8 weeks vs SOF + PegIFN + RBV 12 weeks (list price)

SOF/VEL/VOX was dominant in the base case, and remains dominant in all scenarios, with one exception:

- Where the cost of SOF + Peg-IFN2a + RBV (12 weeks) is decreased, an ICER of £10,647 was observed.

SOF/VEL/VOX 8 weeks vs SOF/VEL 12 weeks (list price)

SOF/VEL/VOX was dominant in the base case, and remains dominant in all scenarios, with three exceptions:

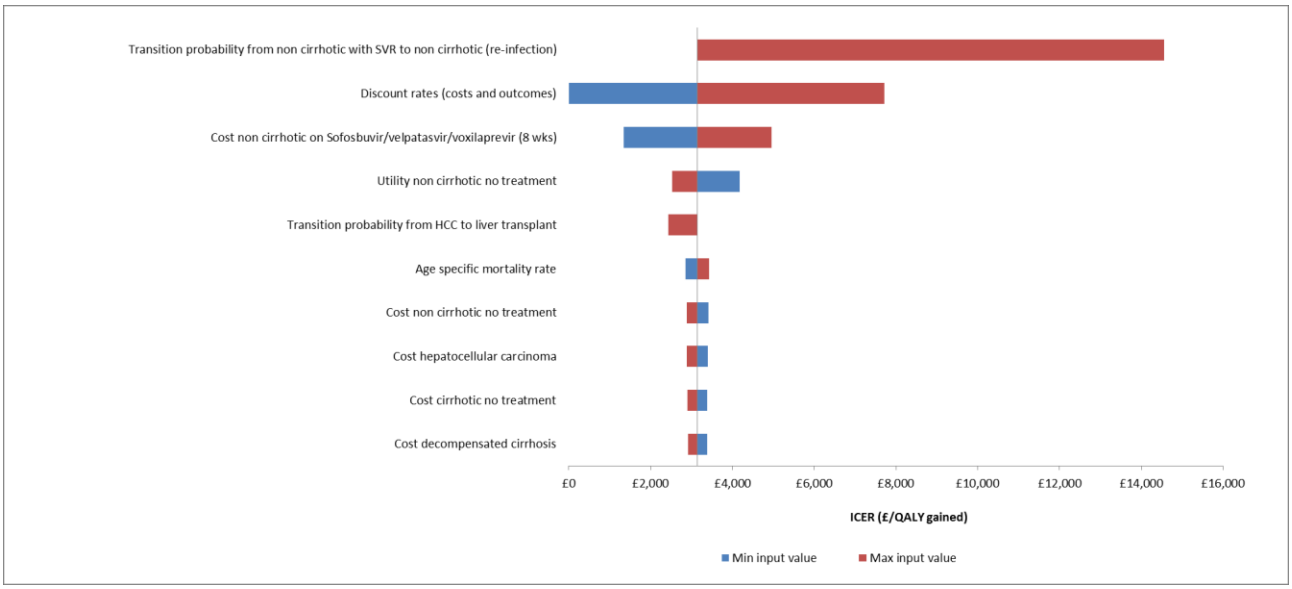
- Where the SVR for SOF/VEL (12 weeks) is increased to the upper 95% confidence limit; in this scenario SOF/VEL/VOX is less effective and less costly
- Where the SVR for SOF/VEL/VOX (8 weeks) is decreased to the lower 95% confidence limit; in this scenario SOF/VEL/VOX is less effective and less costly
- Where the cost of SOF/VEL (12 weeks) is decreased, an ICER of £6,881 was observed.

SOF/VEL/VOX 8 weeks vs no treatment (list price)

In this comparison, the ICER was most sensitive to the transition probability from non-cirrhotic with SVR to non-cirrhotic (re-infection), the discount rate (varied between 0% and 6%), and the cost of SOF/VEL/VOX (8 weeks).

The base-case ICER is £3,148 per QALY gained for SOF/VEL/VOX vs no treatment. Across all parameters varied in this DSA, the ICER for SOF/VEL/VOX vs no treatment did not exceed £20,000 per QALY.

Figure 10: Tornado diagram: DAA-naïve, GT3 infection, non-cirrhotic: SOF/VEL/VOX 8 weeks vs no treatment (list price)



B.3.8.3. *Scenario analysis*

Scenario analyses were conducted to provide additional cost-effectiveness evidence.

DAA-experienced patients

Alternative SVR source for SOF/VEL/VOX

In the base case comparison vs no treatment, the SVR rate from the POLARIS-1 trial was used. This was deemed the most appropriate source for the base case as DAA-experienced patients in England are likely to have failed a prior combination which included an NS5A inhibitor, for which in the inclusion criteria for POLARIS-1 are relevant.

In this scenario analysis, the effect of using an SVR for this treatment from an alternate source (POLARIS-4) was explored. Note that in POLARIS-4 all patients had failed DAA treatment with a combination not containing an NS5A inhibitor; the majority failing therapy with SOF+RBV± Peg-IFN2a (74% in the SOF/VEL/VOX arm) with most of the remainder having failed SOF+SIM (noting that this is not reimbursed in the England). The results are presented in Table 76.

Table 76: Scenario analysis results: DAA-experienced (pan-GT and all non-cirrhotic/compensated cirrhosis) with POLARIS-4 SVR for SOF/VEL/VOX (list price)

Treatment	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER versus No treatment (£)	ICER Incremental (£)
No treatment	23,262	14.83	10.01	-	-	-	-	-
SOF/VEL/VOX (12 weeks)	53,753	19.10	13.81	30,490	4.27	3.80	8,021	8,021

SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

Alternative TP for progression from non-cirrhotic to compensated cirrhosis

In the base case comparison vs no treatment, the transition probability of moving from non-cirrhotic to cirrhotic was blended from the transition probabilities for from each GT using patient numbers in each GT as weighting from the POLARIS-1 trial. As an alternative approach, it was assumed that the transition probability was equal to the transition probability for GT3 (i.e. the highest risk of progression). The results are presented in Table 77.

Table 77: Scenario analysis results: DAA-experienced (pan-GT and all non-cirrhotic/compensated cirrhosis) with GT3 TP (list price)

Treatment	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER versus No treatment (£)	ICER Incremental (£)
No treatment	24,473	14.45	9.64	-	-	-	-	-
SOF/VEL/VOX (12 wks)	53,968	19.04	13.76	29,496	4.59	4.11	7,171	7,171

SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

As another alternative approach, it was assumed that the transition probability was equal to the transition probability for GT1 (a lower risk of progression, and the most prevalent sub-population of CHC). The results are presented in Table 78.

Table 78: Scenario analysis results: DAA-experienced (pan-GT and all non-cirrhotic/compensated cirrhosis) with GT1 TP (list price)

Treatment	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER versus No treatment (£)	ICER Incremental (£)
No treatment	22,987	14.91	10.09	-	-	-	-	-
SOF/VEL/VOX (12 weeks)	53,912	19.06	13.77	30,925	4.15	3.68	8,399	8,399

SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

Alternative distribution of non-cirrhotic to compensated cirrhosis

In the base case comparison vs no treatment, the ratio of non-cirrhotic to cirrhotic patients was 63.3:36.7. In this scenario, the ratio of non-cirrhotic to cirrhotic patients was adjusted to use the POLARIS-1 trial (58.6:41.4). The results are presented in Table 79.

Table 79: Scenario analysis results: DAA-experienced (pan-GT and all non-cirrhotic/compensated cirrhosis) with POLARIS-1 non-cirrhotic:compensated cirrhotic ratio (list price)

Treatment	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER versus No treatment (£)	ICER Incremental (£)
No treatment	25,110	14.01	9.26	-	-	-	-	-
SOF/VEL/VOX (12 weeks)	55,504	18.68	13.16	30,394	4.67	3.89	7,807	7,807

SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

DAA-naïve patients, GT3 infection

Compensated cirrhosis

Alternative SVR source for SOF/VEL

In the base case comparison vs SOF/VEL (12 weeks), the SVR rate from the POLARIS-3 trial was used. In this scenario analysis, the effect of using an SVR for this treatment from an alternate source (ASTRAL-3) was explored.

In this scenario, SOF/VEL/VOX (8 weeks) dominates SOF/VEL (12 weeks).

Table 80: Scenario analysis results: DAA-naïve (GT3 infection, with compensated cirrhosis) with SOF/VEL (12 weeks) SVR from ASTRAL-3 (list price)

Treatment	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER versus No treatment (£)	ICER Incremental (£)
No treatment	36,262	9.36	4.98	-	-	-	-	-
Peg-IFN2a + RBV (24 weeks)	37,510	11.94	6.61	1,248	2.59	1.63	765	765
SOF/VEL/VOX (8 weeks)	51,289	17.14	9.98	15,027	7.78	5.00	3,004	4,088
SOF + Peg-IFN2a + RBV (12 weeks)	59,961	16.76	9.72	23,699	7.40	4.75	4,992	**Dominated** by SOF/VEL/VOX (8 weeks)
SOF/VEL (12 weeks)	61,334	16.75	9.73	25,073	7.40	4.75	5,277	**Dominated** by SOF/VEL/VOX (8 weeks)

SOF + DCV + RBV (12 weeks)	83,447	16.12	9.31	47,185	6.77	4.34	10,873	**Dominated** by SOF/VEL/VOX (8 weeks)
SOF + RBV (24 weeks)	98,661	14.86	8.49	62,399	5.51	3.51	17,760	**Dominated** by SOF/VEL/VOX (8 weeks)

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

Alternative treatment duration for SOF/VEL/VOX

In the base-case analysis, SOF/VEL/VOX was assumed to be administered for 8 weeks. The SOF/VEL/VOX SmPC posology cautiously extends treatment to 12 weeks in DAA-naïve compensated cirrhotic patients, but there is no data to support this within the POLARIS programme. With no 12 week efficacy data available, this scenario extends the treatment cost to reflect 12 weeks of treatment. The results are reported in Table 81.

Table 81: Scenario analysis results: DAA-naïve (GT3 infection, with compensated cirrhosis) with 12 weeks duration of SOF/VEL/VOX (list price)

Treatment	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER versus No treatment (£)	ICER Incremental (£)
No treatment	36,262	9.36	4.98	-	-	-	-	-
Peg-IFN2a + RBV (24 weeks)	37,510	11.94	6.61	1,248	2.59	1.63	765	765
SOF/VEL (12 weeks)	60,449	17.16	9.99	24,187	7.81	5.01	4,825	6,784
SOF/VEL/VOX (12 weeks)	66,285	17.16	9.99	30,024	7.81	5.01	5,987	3,394,377

SOF + Peg-IFN2a + RBV (12 weeks)	59,961	16.76	9.72	23,699	7.40	4.75	4,992	**Extendedly dominated** by No treatment and SOF/VEL (12 weeks)
SOF + DCV + RBV (12 weeks)	83,447	16.12	9.31	47,185	6.77	4.34	10,873	**Dominated** by SOF + Peg-IFN2a + RBV (12 weeks)
SOF + RBV (24 weeks)	98,661	14.86	8.49	62,399	5.51	3.51	17,760	**Dominated** by SOF + Peg-IFN2a + RBV (12 weeks)

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

DAA-naïve patients, GT3 infection

Non-cirrhotic

Alternative SVR source for SOF/VEL

In the base case comparison vs SOF/VEL (12 weeks), the SVR rate from the POLARIS-3 trial was used. In this scenario analysis, the effect of using an SVR for this treatment from an alternate source (ASTRAL-3) was explored. The results are presented in Table 82.

Table 82: Scenario analysis results: DAA-naïve (GT3 infection, non-cirrhotic) using SOF/VEL (12 weeks) SVR from ASTRAL-3

Treatment	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER versus Peg-IFN2a + RBV (24 weeks) (£)	ICER Incremental (£)
Peg-IFN2a + RBV (24 weeks)	12,256	20.85	16.03	-	-	-	-	-

SOF/VEL/VOX (8 weeks)	32,917	21.87	17.27	20,661	1.02	1.24	16,654	16,654
No treatment	18,938	18.12	12.83	6,682	-2.73	-3.20	-2,088	**Dominated** by Peg-IFN2a + RBV (24 weeks)
SOF + Peg-IFN2a + RBV (12 weeks)	41,303	21.76	17.13	29,047	0.90	1.09	26,596	**Dominated** by SOF/VEL/VOX (8 weeks)
SOF/VEL (12 weeks)	42,460	21.80	17.19	30,204	0.95	1.15	26,208	**Dominated** by SOF/VEL/VOX (8 weeks)
SOF + DCV (12 weeks)	62,698	21.81	17.20	50,441	0.96	1.17	43,137	**Dominated** by SOF/VEL/VOX (8 weeks)

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

Dynamic transmission modelling- Exploratory Analysis

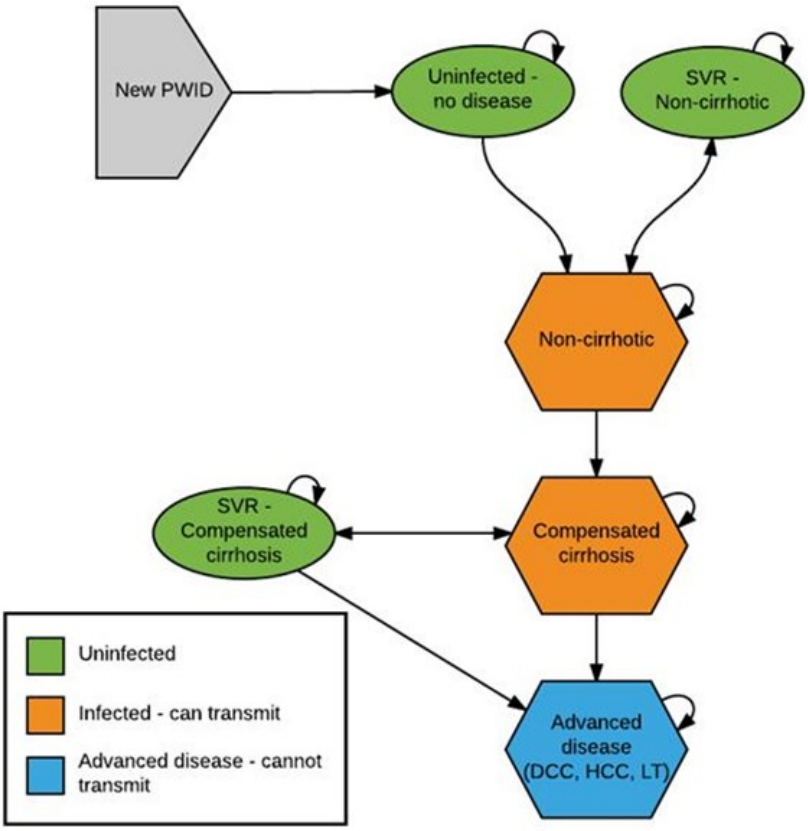
An additional, exploratory, scenario analysis was undertaken to assess the impact of onward transmission and re-infection within the model. The key objective of this analysis was to enhance the current model to address prior criticisms from the ERG/NICE Appraisal Committee, by incorporating consideration for re-infection and onward transmission. Unlike the simplified scenario analysis only assuming re-infection presented in the DSA, this analysis considers both reinfection and onward transmission, and should therefore provide a more reasonable estimate of the cost-effectiveness in the presence of these effects. This analysis was only conducted for the GT3 DAA-naïve population (as the impact of onward transmission and re-infection is expected to be minimal in the DAA-experienced population).

This analysis utilises a separate model structure, created in R, which can be run from within the main Excel model. The analysis uses a dynamic transmission framework with the same underlying structure as the main Markov model detailed in this submission with the addition of states to capture onward transmission and re-infection. The key modification from the Markov model is the inclusion of uninfected persons, and the possibility for these persons to become infected. The rate of infection is determined by a constant probability of infection (by genotype) and the number of currently infected persons able to transmit disease relative to persons at risk of infection. For this analysis we assume that only people who inject drugs (PWID) can transmit disease or become infected, whereas those who are not injecting or have ceased injecting (ex-PWID) are at no risk. By reducing the number of infected persons who can transmit the rate of new infection will decrease; the converse applies if the number of infected persons increases. In addition following successful treatment PWID re-enter the susceptible population pool and may become re-infected.

This modelling approach allows the quantification of both the benefits of treatment to those who avoid infection as a result of others' treatment, as well as and the potential for successfully treated patients to become re-infected following treatment. This modelling approach incorporates both the positive impact from reducing onward transmission and the negative consequences of re-infection. The modelling approach used for this analysis is described by M. Madin-Warburton et al. 2016.

The model structure is aligned with the Markov model, with the addition of a state capturing uninfected people without HCV as well as additional transitions allowing those who have achieved SVR to become re-infected (with equal probability to those who have never been infected) (Figure 3). The model population is also divided into two: PWID and ex-PWID, where PWID may become infected and infect others, whereas ex-PWID are no longer at risk of infection or onward transmission. PWID may cease use and become ex-PWID after an average of 11 years (134). It is assumed that the populations within PWID and ex-PWID are homogeneous (all members are identical).

Figure 11: Scenario analysis: Dynamic transmission model structure



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.

At baseline it is assumed that 37.5% of PWID are infected with one of HCV GT1-4 (GT5-6 are excluded from the model due to their relative rarity in the England). To address data gaps in the model inputs, a calibration exercise was completed. This involved systematically assessing the fit of the model to existing outcomes data by applying parameters (probabilities of infection with GT1-4 and replacement rate of PWID) in order to predict outcomes, and then repeatedly adjusting these parameters to investigate whether changes improved/degraded fit. The best fitting set of parameters are then utilised within the model. The model was fitted to match genotype prevalence data reported in a Public Health England (PHE) report (135), assuming that no treatment was given and GT prevalence (Table 83) remains constant over time, as well as an assumption that the total population size and ratio of PWID to ex-PWID (1/6:5/6) remains constant over time.

Table 83: Genotype distribution among PWID at baseline

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.

For the analysis it was assumed that 5% of infected PWID and 7% of infected ex-PWID are treated per year, reflecting the relative difficulty in identifying, diagnosing and treating PWID. As this analysis only considered GT3 it is assumed that GT1, 2 and 4 are treated in line with current guidelines (assuming an SVR of 95%); costs associated with these GTs are not considered.

Results of the scenario analysis are presented in Table 84. Note that the cost, QALY and LY outcomes are not directly comparable to the base-case results of the analysis as the populations being considered differ (this scenario includes all PWID/ex-PWID regardless of cirrhosis status or treatment, whereas the base case considered patients with specified cirrhosis status receiving treatment), however the ICER results are comparable.

The results of the analysis are broadly in line with the base case, with an improvement in ICERs for all treatments vs. no treatment, indicating that the benefits from reducing onward transmission outweigh the increase in re-infection. SOF/VEL/VOX dominates all treatments with the exception of no treatment (ICER: £2,600/QALY) and Peg-IFN2a + RBV (ICER: £11,489/QALY).

Table 84: Scenario analysis: exploratory analysis using dynamic transmission modelling framework

Treatment	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER versus No treatment (£)	ICER Incremental (£)
No treatment	6,078	25.50	20.84	-	-	-	-	-
Peg-IFN2a + RBV (24 weeks)	5,625	25.73	21.11	-453	0.23	0.27	**Dominates** no treatment	**Dominates** no treatment
SOF/VEL/VOX (8 weeks)	7,142	25.86	21.24	1,064	0.36	0.40	2,660	11,489
SOF+ Peg-IFN2a + RBV (12 weeks)	7,850	25.85	21.23	1,772	0.35	0.39	4,544	**Dominated** by SOF/VEL/VOX (8 weeks)
SOF/VEL (12 weeks)	7,934	25.86	21.23	1,856	0.36	0.39	4,759	**Dominated** by SOF/VEL/VOX (8 weeks)
SOF + DCV (12 weeks)	9,962	25.76	21.18	3,884	0.26	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.

B.3.8.4. *Summary of sensitivity analyses results*

The PSA results have been summarized in Section B.3.8.1.3.

Across the DSA conducted, the economic results were found to be sensitive to the treatment probabilities from non-cirrhotic with SVR to non-cirrhotic (re-infection), discount rate applied for costs and outcomes and treatment costs. The key drivers and their impact on ICERs are reported in more detail in Section B.3.8.2.3.

Scenario analyses were conducted for DAA-experienced patients (all GTs and cirrhosis status) and DAA-naïve patients with GT3 infection (split by compensated cirrhosis and non-cirrhotic). In order to include these comparator treatments, assumptions were required to enable to model to be appropriately modified. These assumptions and results are clearly reported in Section B.3.8.3).

B.3.9. *Subgroup analysis*

Not applicable.

B.3.10. *Validation*

B.3.10.1. *Validation of cost-effectiveness analysis*

The model used for this submission is an updated version of that submitted and accepted previously by NICE for SOF, LDV/SOF and SOL/VEL. The versions of the model have previously undergone internal and external validation.

The internal validation was conducted by a senior consultant health economist. Three specific tasks were undertaken. Firstly, the model was assessed using the Phillips et al, (2004) (136) checklist. Secondly, the manual checking of formulae and model code was conducted. Thirdly, extreme value test was applied to verify the internal calculations and logic in the model. These tests included:

- Remove excess mortality for advanced liver disease
- Remove background mortality in addition to excess mortality.
- Test an equal rate of SVR between both arms of the model. 100% efficacy
- Test an equal rate of SVR AND an equal treatment duration between both arms of the model. 50% efficacy
- Set all health state utility values to 1.
- Turn off probability of DCC
- Model a non-cirrhotic cohort with a 100% SVR rate.

No additional external validation was sought for this submission, as the structure, assumptions and data sources had not changed since the SOF/VEL submission in 2016. Previous validations have included an external health economist undertaking a comprehensive validation of the assumptions and results of the model.

B.3.11. *Interpretation and conclusions of economic evidence*

B.3.11.1. *Summary of results*

DAA-experienced patients

Overall, base-case results indicate that SOF/VEL/VOX 12 week is highly cost-effective in DAA-experienced patients with a an ICER of under £10,000 per QALY compared to no treatment. This was reflected in the PSA and DSA, with the PSA showing a 100% probability of cost-effectiveness at a threshold of £20,000/QALY and no scenario in the DSA exceeding this threshold.

There are no licensed and reimbursed treatment options for DAA-experienced patients in the UK. However, the UK Consensus Guideline 2017 recommends the use of GLE/PIB and SOF/VEL/VOX once available. It is important to note that the guidelines were compiled prior to the confirmation of the European license for GLE/PIB and SOF/VEL/VOX. Thus, it is anticipated that the guidance will be updated to reflect the final licenses.

DAA-naïve patients, GT3 infection, non-cirrhotics

In DAA-naïve patients with GT3 infection who are non-cirrhotic, SOF/VEL/VOX 8 week is highly cost-effective, dominating treatment with SOF/VEL, SOF + Peg-IFN2a + RBV and SOF + DCV, and producing ICERs of £16,654/QALY and £3,148/QALY compared with Peg-IFN2a + RBV and no treatment, respectively.

PSA results showed that at a threshold of £20,000/QALY SOF/VEL/VOX has the highest probability of cost-effectiveness of all available treatments (36%).

DSA results versus no treatment showed that results were most sensitive to allowing reinfection within the Markov model. However, no scenario analysis exceeded an ICER of £20,000/QALY.

DAA-naïve patients, GT3 infection, compensated cirrhosis

In DAA-naïve patients with GT3 infection and compensated cirrhosis, SOF/VEL/VOX 8 week is cost-effective, dominating treatment with SOF + Peg-IFN2a + RBV, SOF + DCV + RBV and SOF+ RBV, and producing small ICERs versus Peg-IFN2a + RBV and no treatment (£4,088/QALY and £3,004/QALY, respectively). Compared to SOF/VEL, SOF/VEL/VOX is cost-saving and equivalent in efficacy (the marginal difference in QALYs is due to modelling limitation rather than differences in efficacy – described in B.3.11.5.2).

PSA results showed that at a threshold of £20,000/QALY SOF/VEL/VOX has the highest probability of cost-effectiveness of all available treatments (49%).

DSA results versus no treatment were consistent with the non-cirrhotic population, with no scenario exceeding an ICER of £30,000/QALY. The efficacy of SOF/VEL/VOX 12 week in DAA-naïve patients with GT3 infection and compensated cirrhosis is unknown as the POLARIS trials only considered 8 week therapy in this population. The scenario examining

SOF/VEL/VOX 12 week therefore had to assume equal efficacy to 8 weeks of therapy, but with additional treatment and monitoring costs due to the additional regimen duration, the finding that this scenario is cost-increasing, is therefore unsurprising.

Exploratory Analysis

An additional exploratory scenario utilising a dynamic transmission model was also included in the submission. The objective of this analysis was to investigated the cost-effectiveness of SOF/VEL/VOX in a DAA-naïve GT3 population (not stratified by cirrhosis status) accounting for reinfection and onward transmission.

Model results were consistent with the Markov model and showed that SOF/VEL/VOX remained cost-effective when reinfection and onward transmission are considered. SOF/VEL/VOX 8 week dominated treatment with SOF+ Peg-IFN2a + RBV, SOF/VEL and SOF + DCV, and produced ICERs of £11,669/QALY and £2,660/QALY versus Peg-IFN2a + RBV and no treatment respectively.

The small improvement in ICERs for SOF/VEL/VOX indicates that at the expected treatment levels the reductions in onward transmission are likely to outweigh increases in reinfection, thereby offering a wider public health benefit.

B.3.11.2. *Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?*

At present there are no published economic models exploring the cost-effectiveness of any SOF/VEL/VOX based regimen in CHC.

For the other therapies included in the model, the modelling approach and results are consistent with those produced and approved in appraisal of SOF/VEL (TA 463).

B.3.11.3. *Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem?*

The results of this analysis are relevant to all population groups considered (DAA-experienced patients and DAA-naïve patients with GT3 infection [with or without cirrhosis]). The clinical data included within the model directly reflects that from Phase III clinical trials in these patients (POLARIS-1-4; see Section 77B.2.6 for clinical data).

B.3.11.4. *How relevant (generalisable) is the analysis to clinical practice in England?*

The comparators used within the model are consistent with recommendations from both the EASL 2016 and UK Consensus Guidelines 2017, and in line with clinical practice in England (5). Where possible, the inputs selected for the model were those considered the most appropriate by NICE in previous cost-effectiveness analyses, and UK studies have been prioritised to ensure the model is generalisable to the UK population (and specifically in terms of patient characteristics, TPs and health state costs).

In addition, the POLARIS trials used to inform the analysis were all multinational trials, including UK-based sites. SVR rates across all trials were very high, and while it was not feasible to stratify the few failures by country, this indicates trial results are consistent across included countries. In the base case comparison for DAA-experienced patients vs no treatment, the SVR rate from the POLARIS-1 trial was used. This was deemed the most appropriate source for the base case as DAA-experienced patients in England are likely to have failed a prior combination which included an NS5A inhibitor, for which the inclusion criteria for POLARIS-1 are relevant. In a scenario analysis, the effect of using an SVR from an alternate source (POLARIS-4) was explored. In POLARIS-4 all patients had failed DAA treatment with a combination not containing an NS5A inhibitor; the majority failing therapy with SOF + RBV ± Peg-IFN2a (74% in the SOF/VEL/VOX arm) with most of the remainder having failed SOF + SIM.

B.3.11.5. *What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?*

B.3.11.5.1. Strengths of the evaluation

The modelling approach reflects the natural history of CHC. By choosing a Markov model the costs, QALYs and clinical effectiveness can be extrapolated beyond the duration of the clinical trials to assess the long-term impact of this new treatment for CHC. An additional exploratory analysis utilising a dynamic transmission model is also included to explore elements absent from the Markov model (specifically, onward transmission and reinfection).

The Markov model structure is similar to that used in previous cost-effectiveness analyses and CHC NICE appraisals, including SOF (TA330), LDV/SOF (TA363) and SOF/VEL (TA430). As with these previously-accepted NICE appraisal models, the decision was made to reflect clinical practice and the design of the clinical trials, by combining F0-F3 CHC patients into a single non-cirrhotic health state.

The model has fundamentally remained unchanged from the version submitted to support the SOF/VEL submission. All cost inputs have been updated where possible, and where no new literature was identified (see Appendices for results of the economic systematic literature review) costs were inflated to 2015-2016 costs or the most recent version of the British National Formulary (August 2017). The comparators included in the model reflect current UK Clinical Guidelines, while including some select historic treatments (e.g. SOF + PegIFN + RBV) for consistency between appraisals.

The model includes all key health effects: SVR, AEs and HRQL. The model has been populated with clinical data from Phase III clinical trials for SOF/VEL/VOX (POLARIS-1-4). For DAA-experienced patients, where no recommended treatments are currently available, this directly reflects clinical practice. In DAA-naïve patients with GT3 infection, this includes a direct comparison to SOF/VEL, which at the time of submission is the most commonly used therapy for this population within the NHS (data on file).

The data for the clinical effectiveness of the comparator treatments was obtained from Phase III clinical trials, when available, and from a systematic literature review. The systematic literature reviews previously conducted to support the SOF/VEL NICE submission were updated in order to obtain information on relevant economic evaluations, utilities, TPs, health state costs and resource use. It should be noted that very few new studies were identified, and that inputs in the model largely remain unchanged from the SOF/VEL NICE-accepted model. Treatment-specific disutility information was updated based on a 2016 paper by Younossi et al. (137) offering a more comprehensive source for disutility information than previously available.

Extensive deterministic and probabilistic sensitivity analyses were conducted. Results of the deterministic analysis were presented as tornado diagrams (in non-dominant scenarios) and the key drivers of the base-case ICER were reported. A comprehensive PSA was conducted to quantify parameter uncertainty and determine the probability of SOF/VEL/VOX being cost-effective. The model's results were robust to variations in these parameters and the ICERs were often below £30,000 per QALY, with a high probability of being most cost-effective at that threshold.

The updated model was thoroughly validated by two internal health economists and a clinical expert validated the clinical inputs. The previous SOF/VEL model (which this model was largely based) was also validate by two internal health economists, a statistician, an external health economist and a clinical expert.

An additional exploratory scenario analysis was conducted using a dynamic transmission model in order to reflect previous ERG comments. The dynamic model scenario captured the impact of reductions in onward transmission and increases in re-infection associated with the treatment, and found that the Markov model results were robust and potentially conservative. The dynamic model reflected the Markov model in structure, with the addition of states captured the uninfected population. Key clinical parameters (including probabilities of infection by GT) within the model were calibrated using data from a PHE report.

Dynamic transmission models are relatively complex by nature and therefore some simplifying assumptions where made. Among these it was assumed that the population was homogeneous (all persons within the PWID and ex-PWID states were the same). In reality, individuals are likely to have different networks of contacts and therefore likelihood of infection. However, an analysis fully incorporating the full spectrum of individuals would be extremely complex, and it is limited by available data. By considering re-infection and onward transmission, this analysis should provide an estimate of effect of treatment on the wider societal population, and the influence of considering these elements on the cost and quality of life results of the cost-effectiveness analysis.

B.3.11.5.2. Weaknesses of the evaluation

NMA

Similar to the SOF, LDV/SOF and SOF/VEL NICE submissions, no robust NMA was possible for SOF/VEL/VOX (as described in Section B.2.8). Therefore, it was considered more appropriate to populate the economic model with efficacy data from individual studies. This allowed the economic model to be populated with efficacy data that was stratified by cirrhosis status and include relevant comparators. This approach was considered to be more transparent and in line with the comparators included within the NICE scope.

Modelling Simplifications

The Markov model assumes that patients cannot die while on treatment, which is aligned with the POLARIS studies and the approach within the NICE submissions for SOF, LDV/SOF and SOF/VEL. However, this simplifying assumption has an impact on the QALY result when comparing treatments of different durations.

For example, when SOF/VEL/VOX 8 weeks is compared with SOF/VEL 12 weeks (in DAA-naïve patients with GT3 infection and compensated cirrhosis), SOF/VEL offers patients a small benefit that is unrelated to treatment efficacy (i.e. from avoided mortality). In this scenario, despite the SVR of SOF/VEL/VOX being marginally greater than SOF/VEL (96.4% vs 96.3%), treatment with SOF/VEL appears to generate more QALYs (5.01 vs 5.00); this outcome is purely a result of modelling assumptions. The impact of the assumption is however conservative for SOF/VEL/VOX, as treatment is equal to, or of shorter duration than, its comparators; the cost-effectiveness of SOF/VEL/VOX 8 week is therefore slightly underestimated.

The Markov model does not consider re-infection once a person achieves an SVR, which may not appropriately reflect the life of some patients with CHC, nor reductions in onward transmission associated with successful treatment, this limitation has been highlighted by previous ERG reviews and is a restriction of using a Markov approach. In response to previous ERG comments an exploratory scenario analysis was undertaken utilising a dynamic modelling approach, the analysis showed that the Markov model results are robust. Reductions in onward transmission appears to outweigh re-infection, resulting in slightly improved cost-effectiveness results for SOF/VEL/VOX.

B.3.11.6. *What further analyses could be carried out to enhance the robustness or completeness of the results?*

Not applicable.

B.4. References

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Single technology appraisal

Sofosbuvir-velpatasvir-voxilaprevir for treating chronic hepatitis C [ID1055]

Dear Paige,

The Evidence Review Group, Southampton Health Technology Assessments Centre, and the technical team at NICE have looked at the submission received on 24 August 2017 from Gilead Sciences. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on 3 October 2017. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as [redacted] in turquoise, and all information submitted as [redacted] in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Marcela Haasova, Technical Lead (Marcela.Haasova@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Helen Knight
Associate Director – Appraisals
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Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

A1. **Priority question:** Section B2. The company submission (CS) directs the reader to Appendix D for full details of the methods for the selection of clinical evidence included. Appendix D.1.1.9 Prisma diagram indicates 108 studies included in the qualitative synthesis, with 92 studies represented in Appendix D.1.1.10 Table 3, and 4 studies included in the main body of the CS section B.2.2. Please explain how the 4 studies included in the main body of the CS (POLARIS-1, POLARIS-2, POLARIS-3 and POLARIS-4) were selected from the 108 studies identified by searching.

A2. **Priority question:** Section B2. The text of the CS in this section does not cross-reference any of the references in the reference list referenced to indicate the sources of data for the POLARIS-1, POLARIS-2, POLARIS-3 and POLARIS-4 trials. Please indicate where data for these four trials were taken from.

A3. **Priority question:** Section B2. The company focused on genotype 3 (GT3) in their consideration of treatment naive patients. However, the CS table 13 and Table 16 do not contain baseline or outcome data for the GT3, treatment-naive, non-cirrhotic subgroup of participants enrolled into the POLARIS 2 study. Please .provide the baseline characteristics and demographics of the GT3 treatment-naive, non-cirrhotic patients in both arms of the POLARIS 2 study and the outcome data and adverse event data for this group (as have been presented for the whole POLARIS 2 study in section B2.6.3 and section B.2.11.3.

A4. Section B.2.3.1 Table 9. In the 'Duration of study' row, follow up is described as 'up to 24 weeks'. Is this 24 weeks including the 8-12 week treatment period, or 24 weeks in addition to the 8-12 week treatment period?

A5. Section B.2.3.1 Table 9. The published paper[1] states that patients were stratified by three factors: genotype, cirrhosis status, and treatment history. However, in addition to the three factors listed in the published paper, the CS (Table 9) also includes 'Treatment-naïve' and 'Treatment-experienced with an IFN-based regimen'. Please clarify if these strata were within 'treatment history' or if an additional aspect of treatment history was used to stratify patients?

A6. Section B.2.3.4 Table13. The following discrepancies in the baseline characteristics were identified between the CS and the published paper.[1] For each of these, please clarify which is the correct value.

a) The mean age (range) of patients in the SOF/VEL arm of the POLARIS 2 study is given as 52 (19-82) whereas in the published paper[1] it is given as 55 (19-82).
b) The number (proportion) of males in the SOF/VEL arm of the POLARIS 3 study is given as 83 (76.1) whereas in the published paper[1] it is given as 100 (92).

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c) The value (range) for BMI in the SOF/VEL arm of the POLARIS 3 study is given as 27.8 (17.8-50.4) whereas in the published paper[1] it is given as 27.3 (17.8-45.5).

A7. Section B.2.3.4 Table 13. There appears to be an error in Table 13, Polaris 3: Number of patients receiving at least one concomitant medication shows SOF/VEL/VOX as n=153 and SOF/VEL as n=132, however the number of participants per trial arm is reported as SOF/VEL/VOX n=110 and SOF/VEL n=109. Please confirm the correct number of participants receiving at least one concomitant medication in each trial arm.

A8. Section B.2.6.1.2 Table 21. States SVR24 data not available until 2018. Published paper[2] says "Of the 253 patients with a sustained virologic response at week 12 after treatment, 249 returned for the post-treatment week 24 visit. All 249 patients had a sustained virologic response at that time." Please would the company indicate whether this post-treatment week 24 visit data provides the SVR24 (albeit with missing data for four patients)?

A9. Section B2.6.1.2 Development of resistance. Please clarify the following:
a) The number and proportion of patients with baseline NS3 and/or NS5A resistance-associated variants. The CS reports 78.8% but the published paper[2] reports only those with viral sequence data available as 205/248 (83%).

b) What did the results of NS3, NS5A and NS5B gene sequencing show for the 6 patients for whom baseline and post-virologic failure sequencing were available? Supplementary material to the published paper (Bourliere 2017, Table S5) suggests no new NS3 resistance-associated substitutions were acquired and one patient acquired a new NS5A resistance associated substitution (Y93H).

A10. Section B.2.6.2.2 Table 28. Please clarify the discrepancy between the published paper[2] and the CS Table 28 in respect of the data indicated in the table below.

	From CS Table 28 SOF/VEL, 12 weeks, N=151	**Bourliere et al. 2017**
Completed study treatment	13/149 (8.7)	14 (9%)
Discontinued study treatment	1/1 (100.0)	
On-treatment virologic failure	1/151 (0.7)	1 (1%)

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A11. **Priority question:** Section B.2.6.3.2 Table 31. Please clarify the discrepancy between the SVR24 values for POLARIS 2 reported in table 31 (SOF/VEL/VOX 476/501 (95.0%); SOF/VEL 431/440 (98%)) and the data reported in the published paper[1] which states that "In the sofosbuvir-velpatasvir-voxilaprevir group, 466 patients with SVR at post-treatment week 12 returned for the post-treatment week 24 visit, and all but one patient had SVR at that visit." and "In the sofosbuvir-velpatasvir group, 424 patients with SVR at post-treatment week 12 returned for the post-treatment week 24 visit, and all but one patient had SVR at that visit." Also clarify the discrepancy for POLARIS 3 SVR24 between the data reported in Table 36 and the published paper.[1]

A12. **Priority question:** Section B.2.6.2.3 Table 33. Please explain what the denominators are for the 'Relapse' row and two of the rows within this section "Completed study treatment" and "Discontinued study treatment".

A13. Section B.2.11.1. Please explain the difference between "treatment-emergent" and treatment-related" adverse events. In particular, please clarify the difference between data reported in the CS B.2.11.1 Table 40, row "Grade 3 or above treatment related AE" and that in the POLARIS 1&4 trial publication[2] Supplementary material Table S11 Highest Grade, Grade 3 (Severe) which shows a greater number of events.

A14. Section B.2.11.2. Table 41 does not contain entries for dizziness or arthralgia but these appear in the published paper[2] Table 3 as having occurred in at least 5% of participants. Please clarify this difference.

A15. Section B.2.11.4 Table 43. [redacted] patients of the 110 in the SOF/VEL/VOX group experienced an adverse event. This would be [redacted] as reported in the published paper and not [redacted] as reported in Table 43. Please confirm if this is the case?

A16. Section B.2.11.2. Table 43 does not contain an entries for asthenia but this appears in the published paper[2] Table 3 as having occurred in at least 5% of participants. Please clarify this difference.

A17. **Literature searching**: Appendix D.1.1.5 Table 1 what is the rationale for the exclusion of the drug terms listed in line 21 [(amantadine or thymosin or albuferon or daclatasvir or vitamin d or balapiravir or tegobuvir or filibuvir or danoprevir or pioglitazone or viramidine or albinterferon or albuferon or interferon beta 1a or vitamin B).mp.]. In particular, it is noted that this list includes daclatasvir which appears in line 4 of the same search strategy [Daclatasvir/ or (daclatasvir or daklinza$).mp.]

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A18. **Priority question:** Appendix D.1.1.6 Table 2. What were the eligibility criteria for Study Design? The text here is a duplicate of the text from the row above providing details on the eligible outcomes.

A19. Appendix D.1.1.6 Table 2. Were studies of patients with decompensated cirrhosis excluded from the systematic review?

A20. Appendix D.1.1.6 Table 2. Were combinations of the individual interventions/comparators listed in the table included in the systematic review?

A21. **Priority question:** Appendix D.1.1.10 Table 3. Please add lists of the studies with reference numbers to cells of this table where indicated. A reference list of included studies is provided (D.1.1.11) but this does not indicate which references apply to which patient groups in the table. Also it is noted that the number of studies represented in Appendix D Table 3 is 92, whereas the number of studies included in the qualitative synthesis is given as 108. Please explain the reason(s) for this difference.

Table 1. Overview on number of studies identified by HCV GT and previous treatment experience

Number of studies	DAA-naïve		DAA-experienced	
	SVR12	SVR24	SVR12	SVR24
GT1	36 (please add studies with reference IDs)	8 (please add studies with reference IDs)	5 (please add studies with reference IDs)	9 (please add studies with reference IDs)
GT2	0	4 (please add studies with reference IDs)	0	1 (please add studies with reference IDs)
GT3	11 (please add studies with reference IDs)	5 (please add studies with reference IDs)	0	1 (please add studies with reference IDs)
GT4	6 (please add studies with reference IDs)	3 (please add studies with reference IDs)	0	0
GT6	3 (please add studies with reference IDs)	0	0	0

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Section B: Clarification on cost-effectiveness data

B1. **Priority question.** In addition to the lists of studies (with reference identifiers) requested for Table 3 in Appendix D.1.1.10 please also provide the SVR rates for the studies identified in the company searches for genotype 3 (i.e. SVR12 for the 11 studies GT3 DAA-naive, SVR24 for the 5 studies GT3 DAA-naive, and SVR24 for the single study GT3 DAA-experienced. In addition please check that no studies reporting SVR rates for GT3 were missed from the table; the total number of studies included in the table is 92, not 108 as identified in your systematic review.

B2. **Priority question.** Please add references for the trials used in Table 60 for SVR rates and provide a rationale for the choice of study used in the economic model.

B3. **Priority question.** Please clarify how the SVR values for SOF + DCV + RBV for treatment naive patients with cirrhosis are derived as the ALLY 3 trial was for SOF + DCV, rather than SOF + DCV + RBV (CS Table 60).

B4. Please confirm whether the values for SOF + RBV for treatment naive patients with cirrhosis should be 77.3%, rather than 66.3% as these appear to be the values in ASTRAL 3 (CS Table 60).

B5. Please confirm whether the values for SOF + RBV for treatment naive patients without cirrhosis should be 97.3%, rather than 96.3% as reported in Table 60.

B6. Please explain why SOF / VEL has not been included as a comparator for DAA experienced patients, even though evidence for this group is available in Polaris 4?

B7. **Priority question**: The company's decision problem for the DAA-naïve population focuses on the GT3 subgroup only, whereas other genotypes are included in the final scope from NICE. Please reconsider whether it is necessary to provide analyses for other genotypes within the DAA-naïve population or provide further justification for excluding them. In addition, please confirm that you are aware and accept that the committee will not be able to recommend the technology to the breadth of the marketing authorisation if these subgroups are excluded from the company's analyses.

B8. **Priority question.** Please clarify why a treatment duration of 12 weeks has been used in the model for cirrhotic patients receiving SOF/PEG/RBV, whilst the recommended treatment duration is for 24 weeks according NICE Technology Appraisal TA330.

B9. **Priority question.** The CS section B.3.6.5 Table 63, page 157 reports that treatment-specific QoL for patients with GT3 have been taken from Younossi et al. (2016) (ref 132). However, this reference does not appear to report these values.

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Please provide the correct reference(s) for these QoL and/or explain how they have been derived, and update the table if appropriate.

B10. **Priority question.** Please explain why the transition probabilities used from Cardoso et al (2010) differ from those reported in Table 2 of that study (CS Table 51).

From	To	TP (annual probabilities)	Source
Compensated cirrhosis	Decompensated cirrhosis	0.0438	Cardoso *et al.* 2010 (65)
	HCC	0.0631	Cardoso *et al.* 2010 (65)
Compensated cirrhosis SVR	Decompensated cirrhosis	0.0064	Cardoso *et al.* 2010 (65)
	HCC	0.0128	Cardoso *et al.* 2010 (65)
Decompensated cirrhosis	HCC	0.0631	Cardoso *et al.* 2010 (65)

B11. Please explain the discrepancies in the following AE costs as reported in CS and the model.

i. In CS Table 58, the weekly AE cost of anaemia (epo) is reported as £13.27 but the model uses a value of £2.21

ii. In CS Table 59, the total AE cost of anaemia treatment (epo) in outpatient setting is reported as £240.00 whereas the model uses a value of £2.40. Similarly, the cost of specialist is reported as £129.97 in the CS versus £1.30 used in the model.

iii. In CS Table 59, the total cost of anaemia treatment (blood transfusion) is reported as £129.97 but the model uses the value of £0.91.

B12. **Priority question:** Tables 64, 69, 76, 77, 78 and 79 show results for a population including all genotypes but it is not clear how these have been calculated as the model provides results for specific genotype populations. For instance, Table 64 titled "Base-case results: DAA-experienced (pan-GT and all non-cirrhotic/compensated cirrhosis) (list price)" in the CS with an ICER of £8,153 per QALY gained is the model's result for a genotype 3 sub-population and not all genotypes as stated in the CS.

a. Please clarify whether the results reported in these tables are only for a specific genotype or for all genotypes.

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b. If the results are for DAA-experienced all-genotypes combined or for DAA-experienced GT3 subgroup only, please provide the GT-specific results.

B13. **Literature searching:** In Appendix H Table 24 (HRQL search strings) the search is shown as identifying 726 references, whereas in Appendix H.1.8 Figure 7 the number of records identified through database searching is given as 932. Please clarify the discrepancy. For the clinical evidence (Appendix D table 1 and Figure 1) and the cost-effectiveness studies (Appendix G Table 21 and Figure 6) the values in the table and corresponding figure match.

Section C: Textual clarifications and additional points

C1. Section B.2.4 Table18. There appears to be duplication of text in the column "Data management and withdrawals" (second bullet point) as shown with underlining in this reproduction of the text: "For categorical HCV RNA data, if a data point was missing, and was preceded and followed by values that were a success (<LLOQ TND and/or <LLOQ detected) then the missing data point was termed a bracketed success; otherwise the data point was termed a bracketed failure (≥LLOQ detected), otherwise, the data point was termed a bracketed failure (i.e. ≥LLOQ detected) ", can you please provide the correct text.

References

1. Jacobson IM, Lawitz E, Gane EJ, Willems BE, Ruane PJ, Nahass RG, et al. Efficacy of 8 Weeks of Sofosbuvir, Velpatasvir, and Voxilaprevir in Patients With Chronic HCV Infection: 2 Phase 3 Randomized Trials. *Gastroenterology* 2017;153(1):113-22.
2. Bourliere M, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M, et al. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. *The New England journal of medicine* 2017;376(22):2134-46.

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Single technology appraisal

Sofosbuvir-velpatasvir-voxilaprevir for treating chronic hepatitis C [ID1055]

Dear Paige,

The Evidence Review Group, Southampton Health Technology Assessments Centre, and the technical team at NICE have looked at the submission received on 24 August 2017 from Gilead Sciences. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on 3 October 2017. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Marcela Haasova, Technical Lead (Marcela.Haasova@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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From reading the questions below, Gilead recognises that there was confusion between the initial POLARIS Clinical Study Reports (CSRs) (only SVR 12 data), the updated POLARIS CSRs (updated with SVR 24 data), and the POLARIS Publications.

For the NICE submission, all evidence for the POLARIS trials was **taken exclusively from the CSRs,** and where available the updated CSRs (containing SVR24 data) were utilised. The rationale for this approach was to ensure consistency and accuracy throughout the submission as the CSRs provide more granular detail when compared the publications. In addition, by using the CSRs all required evidence from each trial was taken from a single source; this ensures that factors such as data cut off and reporting are consistent both within trial and between trials, maximising the comparability.

Unless otherwise stated this approach was taken throughout.

Section A: Clarification on effectiveness data

A1. **Priority question:** Section B2. The company submission (CS) directs the reader to Appendix D for full details of the methods for the selection of clinical evidence included. Appendix D.1.1.9 Prisma diagram indicates 108 studies included in the qualitative synthesis, with 92 studies represented in Appendix D.1.1.10 Table 3, and 4 studies included in the main body of the CS section B.2.2. Please explain how the 4 studies included in the main body of the CS (POLARIS-1, POLARIS-2, POLARIS-3 and POLARIS-4) were selected from the 108 studies identified by searching.

The POLARIS studies (1-4) were not identified through the systematic literature search, as the associated publications were not available at the time the search was conducted (March 2017). The evidence from the POLARIS studies was taken from the available CSRs. The POLARIS CSRs were the only source of evidence investigating the efficacy and safety of SOF/VEL/VOX for the treatment of chronic hepatitis C (CHC).

A2. **Priority question:** Section B2. The text of the CS in this section does not cross-reference any of the references in the reference list referenced to indicate the sources of data for the POLARIS-1, POLARIS-2, POLARIS-3 and POLARIS-4 trials. Please indicate where data for these four trials were taken from.

Data for the POLARIS1-4 studies was taken from the relevant CSRs (1-4). Full details are given in the reference list below, and the CSRs themselves are included in the original submission reference pack. Where available, endpoint data were taken from updated CSRs (i.e. CSRs updated to contain SVR24 data).

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A3. **Priority question:** Section B2. The company focused on genotype 3 (GT3) in their consideration of treatment naive patients. However, the CS table 13 and Table 16 do not contain baseline or outcome data for the GT3, treatment-naive, non-cirrhotic subgroup of participants enrolled into the POLARIS 2 study. Please provide the baseline characteristics and demographics of the GT3 treatment-naive, non-cirrhotic patients in both arms of the POLARIS 2 study and the outcome data and adverse event data for this group (as have been presented for the whole POLARIS 2 study in section B2.6.3 and section B.2.11.3.

Treatment history categorisation

The submission and POLARIS trials refer to several categories of prior treatment experience:

- Treatment naïve: patients have received no prior therapy for HCV
- Treatment experienced: patients have received prior therapy for HCV with any regimen (e.g. interferon based or DAA based)
- DAA-naïve: patients have not received any prior DAA therapy for HCV, however they may have received prior non-DAA therapy (e.g. interferon based) – this category includes 'treatment naïve' patients as well as 'treatment experienced' patients whose previous treatment did not include a DAA
- DAA-experienced: patients have received prior DAA therapy for HCV – this category is a subset of the 'treatment experienced' group

Within the submission, we focused on GT3 DAA-Naïve patients. There were three supporting points for this rationale:

(1) The POLARIS clinical trial program primarily categorise patients as either DAA-naïve or DAA-experienced. Only DAA-naïve patients were included within the POLARIS-2 and -3 trials, including a mixture of treatment naïve patients as well as non-DAA treatment experienced patients (e.g. Peg-IFN+RBV experienced patients).

(2) Recent clinical guidelines (e.g. EASL 2016 (5)) categorises patients by DAA-naïve or DAA- experienced patients

(3) In current UK clinical practice, treatment with a non-DAA regimen does not alter therapy recommendation. Thus, aligning with the definition of DAA- naïve patients.

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POLARIS-2 GT3 subgroup

POLARIS-2 aimed to only recruit patients with CHC who were non-cirrhotic. Of the GT3 subgroup, however, [redacted] patient was later classified as cirrhotic in the SOF/VEL/VOX arm.

Baseline characteristics and demographics for DAA-naïve patients with GT3 infection (both study arms) are displayed in the table below. Note that the treatment history categories align with the description above, i.e. 'treatment experienced' patients may have received previous therapy with any DAA or non-DAA based regimen, however in the POLARIS-2 trial none of the 'treatment experienced' patients had received prior treatment with DAAs; all 'treatment experienced' patients were therefore categorised as DAA-naïve.

Table 1: POLARIS-2: Characteristics and demographics of GT3 patients, SAS

Characteristic	SOF/VEL/VOX [redacted]	SOF/VEL [redacted]
Mean age (range), years	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]
Mean BMI (range), kg/m^2	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Other	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]
Cirrhosis, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
IL28B genotype, n (%)		
CC	[redacted]	[redacted]
Non-CC	[redacted]	[redacted]
CT	[redacted]	[redacted]
TT	[redacted]	[redacted]
Baseline HCV RNA, log10 IU/mL, mean (SD)	[redacted]	[redacted]
Baseline HCV RNA category		
<800,000 IU/mL, n (%)	[redacted]	[redacted]
≥800,000 IU/mL, n (%)	[redacted]	[redacted]
Baseline ALT (U/L), mean (SD)	[redacted]	[redacted]
Baseline ALT category		
≤1.5 x ULN, n (%)	[redacted]	[redacted]
>1.5 x ULN, n (%)	[redacted]	[redacted]

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Characteristic	SOF/VEL/VOX [redacted]	SOF/VEL [redacted]
Type of previous HCV treatment, n/total (%)		
Treatment-naïve	[redacted]	[redacted]
Treatment-experienced	[redacted]	[redacted]
DAA Naïve	[redacted]	[redacted]
Peg-IFN+RBV	[redacted]	[redacted]
Other	[redacted]	[redacted]
DAA Experienced	[redacted]	[redacted]
Estimated GFR (mL/min), mean (SD)	[redacted]	[redacted]

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; Peg-IFN, pegylated interferon; ribonucleic acid; RNA, ribonucleic acid; SOF, sofosbuvir; SD, standard deviation; ULN, upper limit of normal; VEL, velpatasvir; VOX, voxilaprevir.

Outcome data for GT3 patients is presented in Table 16 of the Appendix, and we've presented below for ease of reference (Table 2). Note that adverse event data were not split by genotype as genotype of infection does not influence adverse events (there is no influence of genotype between host and drug).

Table 2: POLARIS-2; SVR 12 and virological outcomes by genotype for GT3 patients (FAS)

	SOF/VEL/VOX [redacted]	SOF/VEL [redacted]
SVR12, n/N (%)	[redacted]	[redacted]
Overall virological failure	[redacted]	[redacted]
Relapse	[redacted]	[redacted]
Completed study treatment	[redacted]	[redacted]
Discontinued study treatment	[redacted]	[redacted]
On-treatment virological Failure	[redacted]	[redacted]
Other	[redacted]	[redacted]

GT, genotype; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir; VOX, voxilaprevir.

A4. Section B.2.3.1 Table 9. In the 'Duration of study' row, follow up is described as 'up to 24 weeks'. Is this 24 weeks including the 8-12 week treatment period, or 24 weeks in addition to the 8-12 week treatment period?

The 24 weeks follow-up includes the 8-12 week treatment period. A detailed breakdown of the treatment and follow-up length for each of the POLARIS studies is given below, alongside the patient disposition diagrams for each trial (note that the patient disposition

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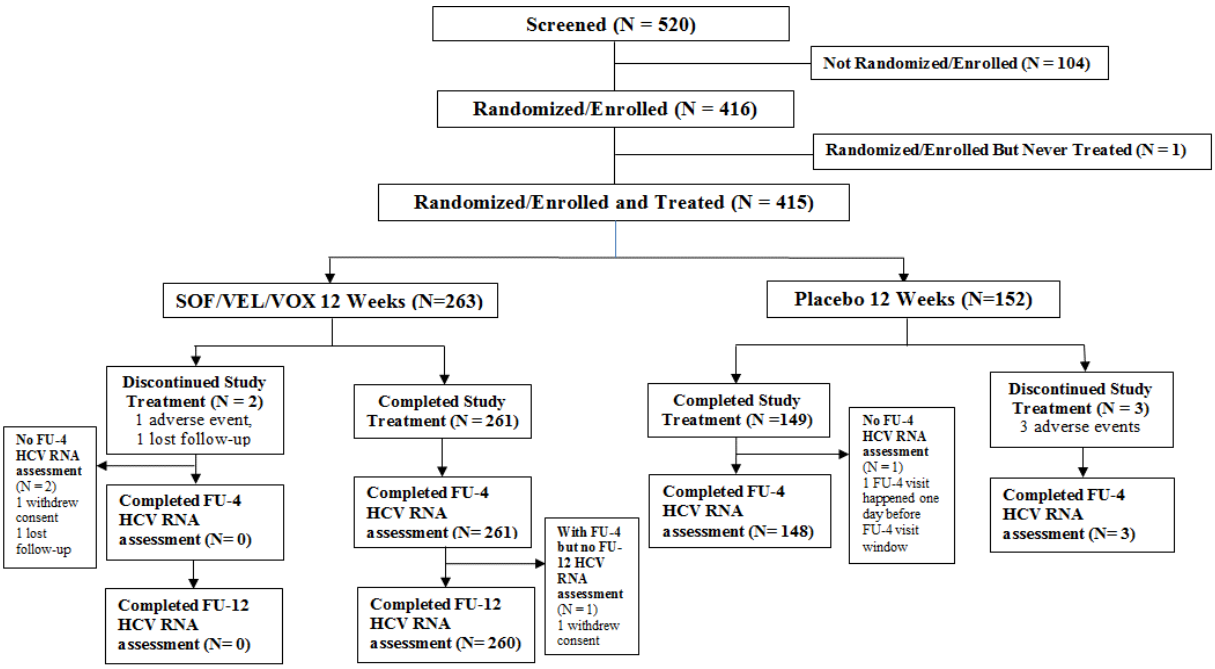
diagrams are also given in Appendix D.1.2.1 of the main submission, but are provided here for ease of reference).

In the POLARIS-1 study (see Figure 1):

- SOF/VEL/VOX treatment arm: 12 weeks treatment + 12 weeks follow-up
- Placebo treatment arm: 12 weeks treatment + 4 weeks follow-up

Figure 1: Patient disposition in POLARIS-1



FU-x = follow-up visit at x weeks after discontinuing treatment; HCV, hepatitis C virus; RNA, ribonucleic acid; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

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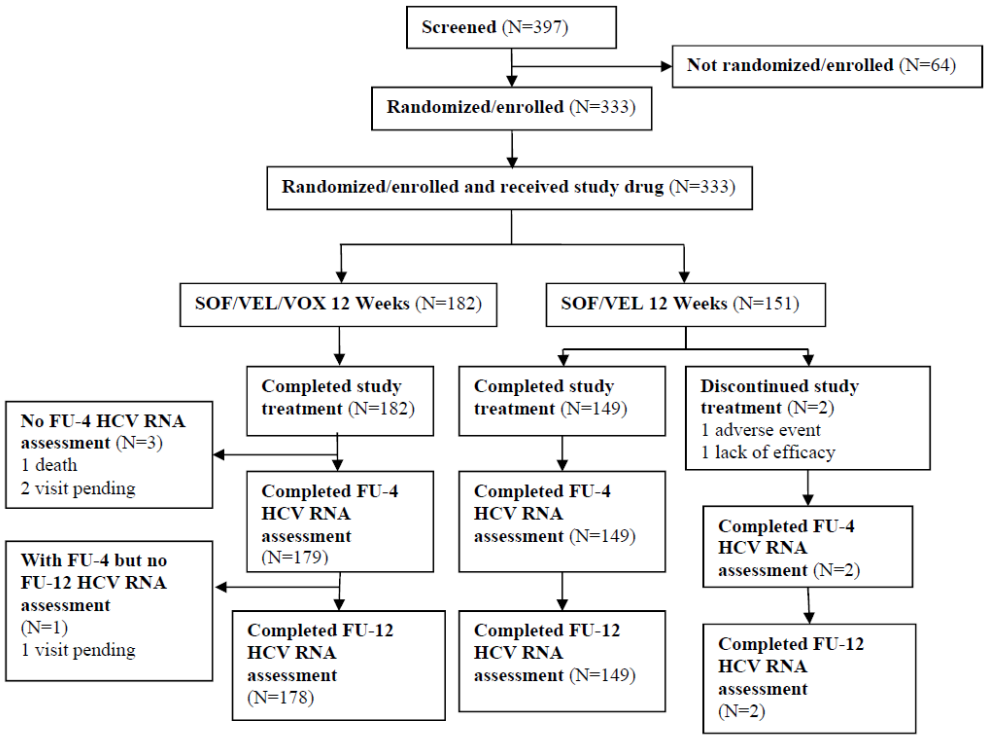
In the POLARIS-4 study (Figure 2):

- SOF/VEL/VOX treatment arm: 12 weeks treatment + 12 weeks follow-up
- SOLF/VEL treatment arm: 12 weeks treatment + 12 weeks follow-up

Figure 2: Patient disposition in POLARIS-4



FU-x = follow-up visit at x weeks after discontinuing treatment; HCV, hepatitis C virus; RNA, ribonucleic acid; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

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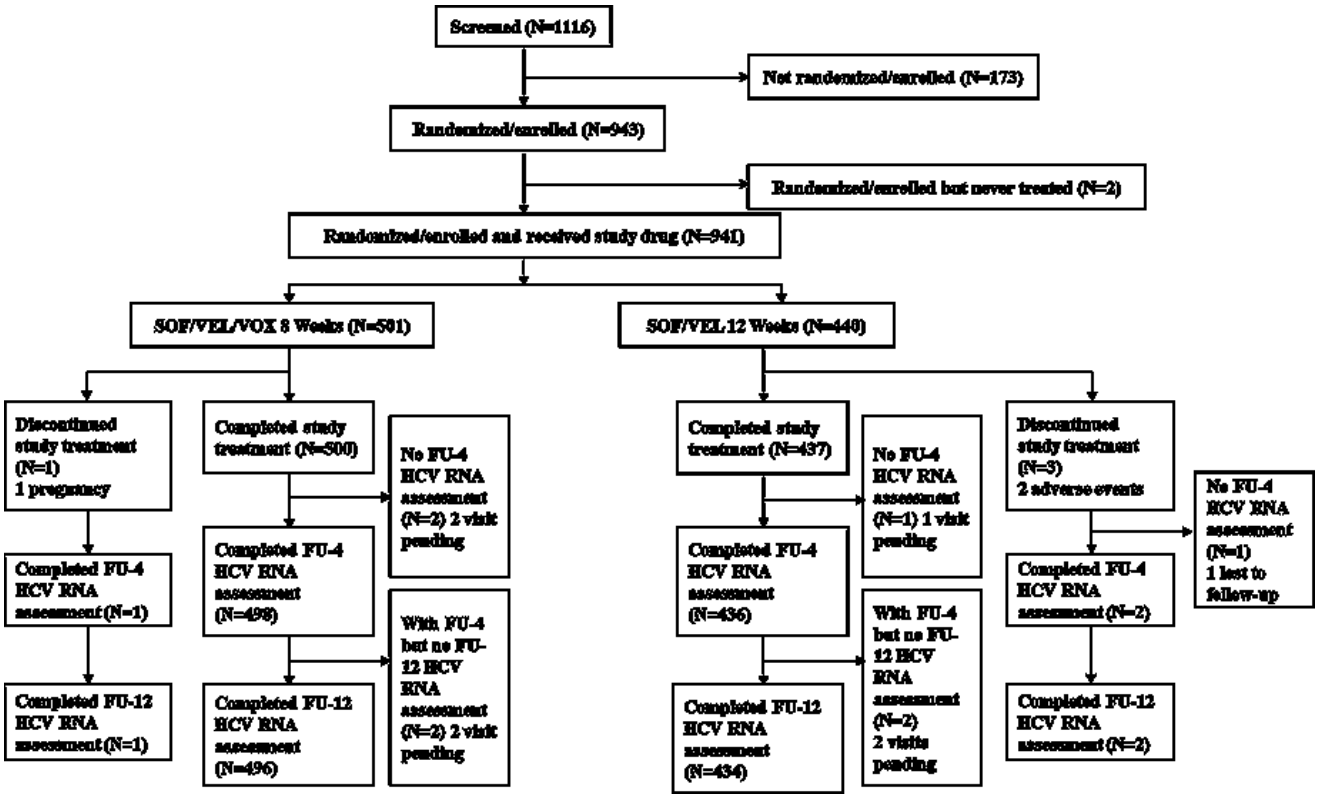
In the POLARIS-2 study (Figure 3):

- SOF/VEL/VOX treatment arm:12 weeks treatment + 12 weeks follow-up
- SOLF/VEL treatment arm: 12 weeks treatment + 12 weeks follow-up

Figure 3: Patient disposition in POLARIS-2



FU-x = follow-up visit at x weeks after discontinuing treatment; HCV, hepatitis C virus; RNA, ribonucleic acid; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

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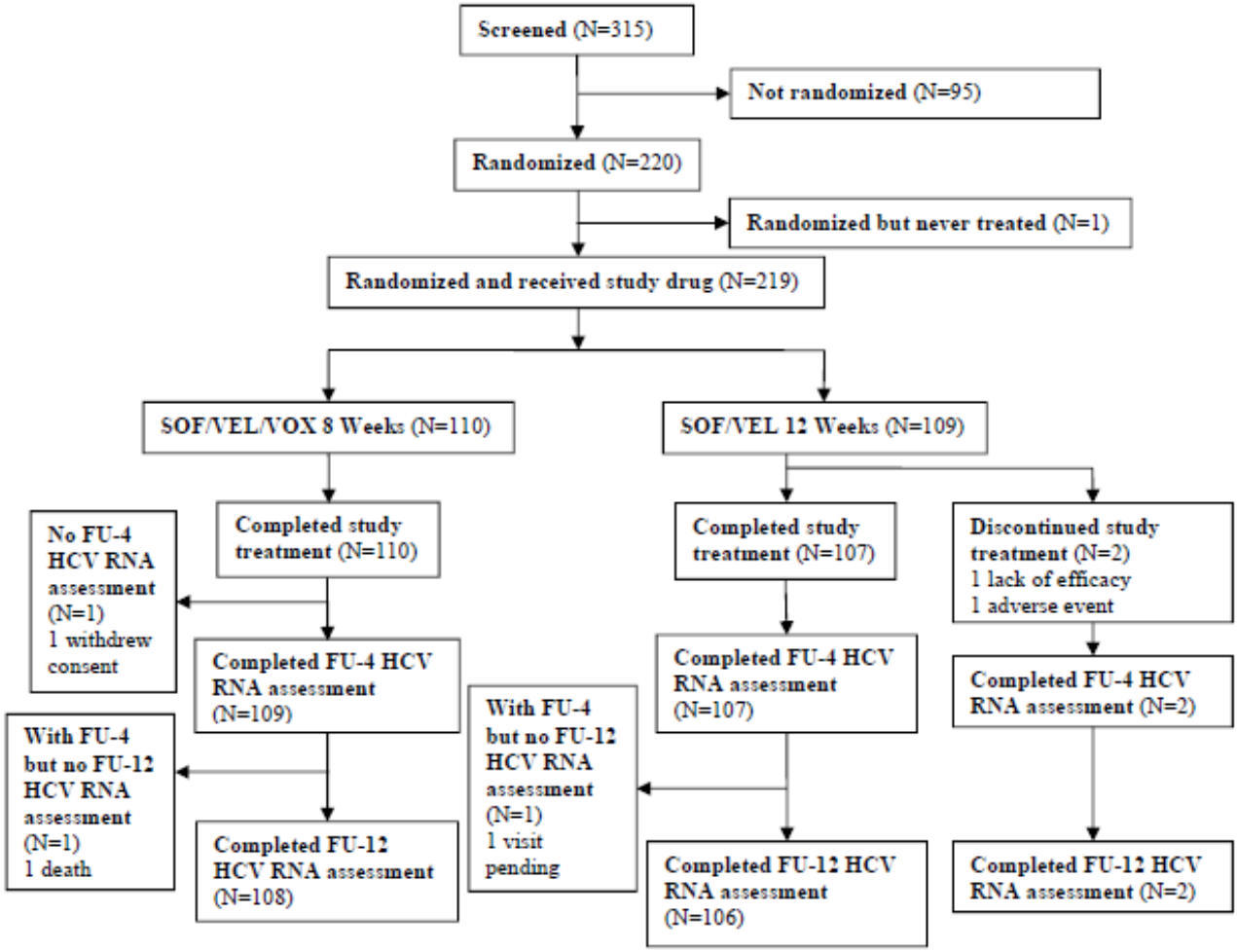
In the POLARIS-3 study (Figure 4):

- SOF/VEL/VOX treatment arm: 8 weeks treatment + 12 weeks follow-up
- SOLF/VEL treatment arm: 12 weeks treatment + 12 weeks follow-up

Figure 4: Patient disposition in POLARIS-3



FU-x = follow-up visit at x weeks after discontinuing treatment; HCV, hepatitis C virus; RNA, ribonucleic acid; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

A5. Section B.2.3.1 Table 9. The published paper (6) states that patients were stratified by three factors: genotype, cirrhosis status, and treatment history. However, in addition to the three factors listed in the published paper, the CS (Table 9) also includes 'Treatment-naïve' and 'Treatment-experienced with an IFN-based regimen'.

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Please clarify if these strata were within 'treatment history' or if an additional aspect of treatment history was used to stratify patients?

'Treatment-naïve' and 'Treatment-experienced with an IFN-based regimen' were within the strata of 'treatment history' (page 45, POLARIS-2 CSR (2) and page 44, POLARIS-3 CSR (3)). The definition of DAA-naïve (taken from the EASL 2016 guidelines (5) includes treatment-naïve patients as well as those who have previously received (and failed) on an IFN-containing regimen. DAA-naïve patients therefore include both 'Treatment naïve' and 'Treatment-experienced with an IFN-based regimen'. See question A3 for further detail on the categorisation of treatment history.

A6. Section B.2.3.4 Table13. The following discrepancies in the baseline characteristics were identified between the CS and the published paper.(6) For each of these, please clarify which is the correct value.

a) The mean age (range) of patients in the SOF/VEL arm of the POLARIS 2 study is given as 52 (19-82) whereas in the published paper (6) it is given as 55 (19-82).

For all data presented in the SOF/VEL/VOX ID1055 submission, data were sourced from the available CSRs, rather than any subsequent publications, see beginning of responses for further detail.

In this case, the paper appears to be reporting the median age (with range), and not the mean age (with range). Based on the CSR, the mean age was [redacted], and the median was [redacted]. The ranges reported for the median age in the CSR matches the range reported as "mean age" in the publication.

b) The number (proportion) of males in the SOF/VEL arm of the POLARIS 3 study is given as 83 (76.1) whereas in the published paper (6) it is given as 100 (92).

In the CSR for POLARIS-3 (page 58 (3)) the number of Males (%) was [redacted]; it is not clear why the number in the publication is different. As stated in previous responses, for this submission (ID1055) data from the primary source of clinical data (i.e. the CSRs) have been used to inform the evidence submission.

c) The value (range) for BMI in the SOF/VEL arm of the POLARIS 3 study is given as 27.8 (17.8-50.4) whereas in the published paper (6) it is given as 27.3 (17.8-45.5).

The BMI value (range) for SOF/VEL in the submission was incorrect (this was the overall baseline BMI [range]), and should be [redacted] (range: [redacted]), as reported in the paper and the POLARIS-3 CSR (page 59 (3)).

A7. Section B.2.3.4 Table 13. There appears to be an error in Table 13, Polaris 3: Number of patients receiving at least one concomitant medication shows SOF/VEL/VOX as n=153 and SOF/VEL as n=132, however the number of

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participants per trial arm is reported as SOF/VEL/VOX n=110 and SOF/VEL n=109. Please confirm the correct number of participants receiving at least one concomitant medication in each trial arm.

This is a typographical error, the corrected numbers are detailed below (Table 15.11.7.4, POLARIS-3 CSR (3)):

- Number of Subjects Receiving at Least One Concomitant Medication in POLARIS-3:
  - SOF/VEL/VOX treatment arm: [redacted]
  - SOF/VEL treatment arm: [redacted]

A8. Section B.2.6.1.2 Table 21. States SVR24 data not available until 2018. Published paper (7) says "Of the 253 patients with a sustained virologic response at week 12 after treatment, 249 returned for the post-treatment week 24 visit. All 249 patients had a sustained virologic response at that time." Please would the company indicate whether this post-treatment week 24 visit data provides the SVR24 (albeit with missing data for four patients)?

Data from the CSRs was used to inform the submission, and at time of submission this SVR24 data was unavailable in the POLARIS-1 CSR. At the time of publication of the paper, we confirm that SVR24 was 249/249 on patients who had attended the post-treatment week 24 visit – with data missing for four patients. This missing data will be reconciled in the final CSR due in 2018.

A9. Section B2.6.1.2 Development of resistance. Please clarify the following:

a) The number and proportion of patients with baseline NS3 and/or NS5A resistance-associated variants. The CS reports 78.8% but the published paper(7) reports only those with viral sequence data available as 205/248 (83%).

The number of patients with baseline NS3 and/or NS5A was [redacted], the proportion of patients was [redacted] (page 82, Table 9-11, POLARIS-1 CSR (1)). For the purposes of virologic resistance analysis presented in this section of the submission, the Resistance Analysis Population was defined as all subjects in the Safety Analysis Set with a confirmed virologic outcome. The Resistance Analysis Population included [redacted] randomized/enrolled into SOF/VEL/VOX 12 week group.

b) What did the results of NS3, NS5A and NS5B gene sequencing show for the 6 patients for whom baseline and post-virologic failure sequencing were available? Supplementary material to the published paper (Bourliere 2017, Table S5) suggests no new NS3 resistance-associated substitutions were acquired and one patient acquired a new NS5A resistance associated substitution (Y93H).

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The results of NS3, NS5A and NS5B gene sequencing are shown in the table below (taken from page 85, Table 9-17, POLARIS-1 CSR (1)).

Table 3: GS-US-367-1171: Baseline and Post-treatment RAVs in Subjects with Virologic Relapse in the SOF/VEL/VOX 12 Week group (15% cut-off)

Subject ID	GT	Prior DAA	Baseline	Relapse	Baseline	Relapse	Baseline	Relapse
[redacted]								

GT = genotype; DAA = direct-acting antivirals.

[a] Results from NS5B short fragment sequencing amino acid positions 227-338.

A10. Section B.2.6.2.2 Table 28. Please clarify the discrepancy between the published paper (7) and the CS Table 28 in respect of the data indicated in the table below.

	From CS Table 28 SOF/VEL, 12 weeks, N=151	Bourliere et al. 2017
Completed study treatment	[redacted]	14 (9%)
Discontinued study treatment	[redacted]	
On-treatment virologic failure	[redacted]	1 (1%)

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There were [redacted] patients in POLARIS-4 on the SOF/VEL arm who relapsed after completing treatment; i.e. HCVRNA <LLOQ at last on treatment visit, then confirmed HCV-RNA >/= LLOQ in the post treatment period. [redacted] had completed study treatment. [redacted] discontinued SOF/VEL as described in the safety section of the manuscript on page 2142:

"[redacted]."

A11. **Priority question:** Section B.2.6.3.2 Table 31. Please clarify the discrepancy between the SVR24 values for POLARIS 2 reported in table 31 (SOF/VEL/VOX [redacted]; SOF/VEL [redacted]) and the data reported in the published paper (6) which states that "In the sofosbuvir-velpatasvir-voxilaprevir group, [redacted] with SVR at post-treatment week 12 returned for the post-treatment week 24 visit, and [redacted] had SVR at that visit." and "In the sofosbuvir-velpatasvir group, [redacted] with SVR at post-treatment week 12 returned for the post-treatment week 24 visit, and [redacted] had SVR at that visit." Also clarify the discrepancy for POLARIS 3 SVR24 between the data reported in Table 36 and the published paper (6)

The discrepancy is explained by the pre-specified plan for handling missing values as reported in the CSR under Table 15.9.2.2.

"SVRx is sustained virologic response (HCV RNA < LLOQ) x weeks after stopping study treatment.

A missing SVR value is imputed as a success if it is bracketed by values that are termed successes (i.e., '< LLOQ TND' or '< LLOQ detected'); otherwise, the missing SVR value is imputed as a failure. TND = target not detected.

Missing SVR24 will be imputed as success if SVR12 is achieved with no follow-up values or by bracketed success."

Clinical data for the POLARIS trials in the submission were obtained from the CSRs, for further detail see beginning of responses.

A12. **Priority question:** Section B.2.6.2.3 Table 33. Please explain what the denominators are for the 'Relapse' row and two of the rows within this section "Completed study treatment" and "Discontinued study treatment".

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In Table 33 in Section B.2.6.3.2, virologic failure was descriptively summarised as "on-treatment virologic failure" or "relapse" (which was summarised by completed study treatment/ discontinued study treatment). Patients who did not achieve SVR12 and did not meet criteria for virologic failure were categorised as "Other." The denominator for relapse was the number of patients who had HCV RNA < LLOQ at their last observed on-treatment HCV RNA measurement; otherwise, the denominator was the number of subjects in the FAS. The data have been sourced from the POLARIS-2 CSR (Table 15.9.2.1.1, page 222) – the denominator for "completed study treatment" for the SOF/VEL/VOX arm has been incorrectly reported, and should be [redacted].

A13. Section B.2.11.1. Please explain the difference between "treatment-emergent" and treatment-related" adverse events. In particular, please clarify the difference between data reported in the CS B.2.11.1 Table 40, row "Grade 3 or above treatment related AE" and that in the POLARIS 1&4 trial publication (7) Supplementary material Table S11 Highest Grade, Grade 3 (Severe) which shows a greater number of events.

"Treatment-emergent" adverse events were defined as events that met at least 1 of the following criteria:

- Any AEs with onset dates on or after the study drug start date and no later than 30 days after the permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug

"Treatment-related" adverse events is a subset of "treatment emergent", to which the investigator has assessed a possible or probable causal relationship of the event to the study drug or procedures.

A14. Section B.2.11.2. Table 41 does not contain entries for dizziness or arthralgia but these appear in the published paper (7) Table 3 as having occurred in at least 5% of participants. Please clarify this difference.

The information provided in the submission document is taken from the POLARIS-4 CSR rather than the published paper (7). In Table 41 only adverse events occurring in ≥5% of patients are reported. In the POLARIS-4 CSR the adverse events for both dizziness ([redacted]) and arthralgia ([redacted]) are not included as they are below 5% reporting threshold (Table 15.11.2.1.2 (4)).

A15. Section B.2.11.4 Table 43. [redacted] of the 110 in the SOF/VEL/VOX group experienced an adverse event. This would be [redacted] as reported in the published paper and not [redacted] as reported in Table 43. Please confirm if this is the case?

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This is a typographical error, in Section B.2.11.4 Table 43 the number of patients experiencing any adverse event in the SOF/VEL/VOX group should read [redacted].

A16. Section B.2.11.2. Table 43 does not contain an entries for asthenia but this appears in the published paper (7) Table 3 as having occurred in at least 5% of participants. Please clarify this difference.

The information provided in the submission document is taken from the POLARIS-3 CSR rather than the published paper (3). In Table 43 only adverse events occurring in ≥5% of patients are reported. In the POLARIS-3 CSR the adverse event for asthenia for the SOF/VEL/VOX group is [redacted] and for the SOF/VEL group [redacted]. In the publication both figures have been included as the percentages have been rounded up and are reported as [redacted].

A17. **Literature searching**: Appendix D.1.1.5 Table 1 what is the rationale for the exclusion of the drug terms listed in line 21 [(amantadine or thymosin or albuferon or daclatasvir or vitamin d or balapiravir or tegobuvir or filibuvir or danoprevir or pioglitazone or viramidine or albinterferon or albuferon or interferon beta 1a or vitamin B).mp.]. In particular, it is noted that this list includes daclatasvir which appears in line 4 of the same search strategy [Daclatasvir/ or (daclatasvir or daklinza$).mp.]

The treatments were excluded predominately based on licensed indication (either treatment was never licensed or was discontinued). The treatments excluded and reason for exclusion are presented below in Table 4.

Daclatasvir was inadvertently excluded from the literature search, however it was still included as a comparator within the analysis. The ALLY-3 and ALLY-3+ trials were used to inform modelling inputs for daclatasvir, which is consistent with the SOF/VEL submission. A pragmatic retrospective search did not identify any additional new studies published since the SOF/VEL submission that would provide evidence for daclatasvir. The analysis of daclatasvir would therefore have continued to have been based upon ALLY-3 and ALLY-3 and the base case results would remain unchanged.

Table 4. Treatments excluded from the clinical literature search

Treatment	Reason for exclusion
Amantadine	Discontinued in 2014
Thymosin	Not licensed for HCV
Albuferon	Ceased development in 2010

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Vitamin d	Found to be not effective https://www.ncbi.nlm.nih.gov/pubmed/23396730
Balapiravir	Not licensed for HCV
Tegobuvir	Discontinued
Filibuvir	Not licensed for HCV
Danoprevir	Not licensed for HCV
Pioglitazone	Not licensed for HCV
Viramidine	Not licensed for HCV
Albinterferon	Not licensed for HCV
Albuferon	Not licensed for HCV
Interferon beta 1a	Not licensed for HCV
Vitamin B	Not licensed for HCV
Amantadine	Discontinued 2014
Thymosin	Not licensed for HCV
Albuferon	Ceased development in 2010

A18. **Priority question:** Appendix D.1.1.6 Table 2. What were the eligibility criteria for Study Design? The text here is a duplicate of the text from the row above providing details on the eligible outcomes.

This is a typographical error. The eligibility criteria in Table 2 in Appendix D.1.1.6 should state the following:

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

A19. Appendix D.1.1.6 Table 2. Were studies of patients with decompensated cirrhosis excluded from the systematic review?

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The license for SOF/VEL/VOX does not include patients with decompensated cirrhosis, therefore studies including patients with decompensated cirrhosis were excluded from the systematic literature review.

A20. Appendix D.1.1.6 Table 2. Were combinations of the individual interventions/comparators listed in the table included in the systematic review?

Combination therapies were included in the systematic review. The individual interventions were searched, returning both monotherapy and combination therapy articles. During the screening phase of the review, the articles with combination therapies including an intervention not on the list were excluded.

A21. **Priority question:** Appendix D.1.1.10 Table 3. Please add lists of the studies with reference numbers to cells of this table where indicated. A reference list of included studies is provided (D.1.1.11) but this does not indicate which references apply to which patient groups in the table. Also it is noted that the number of studies represented in Appendix D Table 3 is 92, whereas the number of studies included in the qualitative synthesis is given as 108. Please explain the reason(s) for this difference.

The table (included below as Table 5) has been updated to include reference citations for each of the publications.

The 92 incidences in Table 5 are not necessarily unique, as publications may have reported data for multiple GTs and multiple outcomes. In addition, some publications reported GT grouped together and therefore are not reported in the original table.

Table 5. Overview on number of studies identified by HCV GT and previous treatment experience

Number of studies	DAA-naïve		DAA-experienced	
	SVR12	SVR24	SVR12	SVR24
GT1	36 (Afdhal 2014 (8) Kowdley 2014 (9) Stickel 2013 (10) Bronowicki 2013 (11) Lagging 2008 (12) Lawitz 2013 (13) Dore 2016 (14) Feld 2014 (15) Buti 2014 (16)	8 (Bronowicki 2013 (11) Buti 2014 (16) Lawitz 2013 (13) Dore G.J. et al (14) Poordad F. et al (40) Feld J.J, et al (41)	5 (Lawitz 2014 (23) Lawitz 2014 (23) Bouliere 2015 (44) Pianko 2015 (45) Afdhal 2014 (8))	9 (Zeuzem 2014 (46) Dalgard 2008 (47) Pol 2013 (48) Diango 2007 (49) Flamm 2013 (50) Zeuzem 2011 (51)

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	Ferenci 2014 (17) Isakov 2016 (18) Sulkowski 2010 (19) Lawitz 2017 (20) Flisiak 2016 (21) Kwo 2016 (22) Lawitz 2014 (23) Gane 2014 (24) Lawitz 2014 (23) Poordad 2014 (25) Rustgi 2015 (26) Jacobson 2015 (27) Pearlman 2015 (28) Forns 2014 (29) Charlton 2015 Pearlman 2015 (28) Lawitz 2015 (30) Reddy 2015 (31) Kwo 2017 (32) Sherman 2011 (33) Poordad 2010 (34) McHutchison 2009 (35) McHutchison 2009 (36) Kwo 2017 (32) Jacobson 2014 (37) Zeuzem 2011 (38) Lawitz 2016 (39))	Kowdley 2014 (42) Davitkov 2016 (43))		Pianko 2015 (45) Kowdley 2014 (42) Davitkov 2016 (43))
GT2	0	4 (Dalgard 2008 (47) Dalgard 2010 (52) Diango 2010 (49) Heidrich 2015 (53))	0	1 (Heidrich 2015 (53))
GT3	11 (Heidrich 2015 (53) Foster 2015 (54)	5 (Shoeb 2014 (59)	0	1 (Heidrich 2015 (53))

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	Foster 2015 (55) Pianko 2015 (45) Reau 2016 (56) Foster 2015 (57) Foster 2015 (54) Foster 2015 (55) Gane 2015 (58) Lawitz 2017 (20) Isakov 2016 (18))	De Meyer 2013 (60) Diango 2010 (49) Dalgard 2010 (52) Dalgard 2008 (47))		
GT4	6 (Kwo 2017 (32) Hezode 2015 (61) Waked 2016 (62) Gentile 2014 (24) Hezode 2015 (61) Zeuzem 2015 (63))	3 (El Khayat 2012 (64) Ferenci 2008 (65) Poordad F. et al (40))	0	0
GT6	3 (Kwo 2017 (32) Gentile 2014 (66) Zeuzem 2015 (63))	0	0	0

Section B: Clarification on cost-effectiveness data

B1. **Priority question.** In addition to the lists of studies (with reference identifiers) requested for Table 3 in Appendix D.1.1.10 please also provide the SVR rates for the studies identified in the company searches for genotype 3 (i.e. SVR12 for the 11 studies GT3 DAA-naive, SVR24 for the 5 studies GT3 DAA-naive, and SVR24 for the single study GT3 DAA-experienced. In addition please check that no studies reporting SVR rates for GT3 were missed from the table; the total number of studies included in the table is 92, not 108 as identified in your systematic review.

Please see response to A21 regarding the 92 versus 108 studies.

SVR data by study is detailed in Table 6 (SVR12 in GT3 DAA-naïve patients),

Table 7 (SVR24 in GT3 DAA-naïve patients) and

Table 8 (SVR24 in GT3 DAA-experienced patients).

Table 6. SVR12 rates in GT3 DAA-naive HCV patients

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Publication	**Trial**	**Arms/Interventions**	**Overall**	**Non-cirrhotic**	**Cirrhotic**
Isakov 2016 (18)	NR	Sof16 400mg/d + R16 1000 or 1200mg/d (N=30)	87%	83%	88%
		Sof24 400mg/d + R24 1000 or 1200mg/d (N=31)	90%	60%	96%
Lawitz 2017 (20)	C-SWIFT	Elbas8 50mg + Grazo8 100mg + Sof8 400mg in non-cirrhotic (N=15)	93%	93%	NR
		Elbas12 50mg + Grazo12 100mg + Sof12 400mg in non-cirrhotic (N=14)	100%	100%	NR
		Elbas12 50mg + Grazo12 100mg + Sof12 400mg in cirrhotic (N=12)	83.3%	NR	83.3%
Gane 2015 (58)	NR	Ledi 90mg/d + Sof 400mg/d (N=25)	64%	NR	NR
		Ledi 90mg/d + Sof 400mg/d + R 1000mg/d or 1200mg/d (N=26)	100%	NR	NR
Foster 2015 (55)	ASTRAL-2 and ASTRAL-3	Sof12 400mg/d + Vel12 100mg/d (N=206)	97%	NR	NR
		Sof12/24 400mg/d + R12/24 (N=204)	86%	NR	NR
Foster 2015 (54)	NR	Sof16 400mg/d + R16 (N=91)	77%	NR	NR
		Sof24 400mg/d+ R24 1000mg/d (<75kg) or 1200mg/d (>=75kg) (N=94)	88%	NR	NR
		Sof12 400mg/d+ R12 1000mg/d (<75kg) or 1200mg/d (>=75kg) + Pega2a 180mg/w (N=94)	95%	NR	NR
Foster 2015 (57)	BOSON	Sof16 400mg/d + R16 1000-1200mg/d (N=91)	77%	83%	57%
		Sof24 400mg/d + R24 1000-1200mg/d (N=94)	88%	90%	82%

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			SVR12 results		
Publication	**Trial**	**Arms/Interventions**	**Overall**	**Non-cirrhotic**	**Cirrhotic**
		Sof12 400mg/d + R12 1000-1200mg/d + Pega2a 180mg/w (N=94)	95%	96%	91%
Reau 2016	ASTRAL-3	Sof12 400mg/d+ Vel12 100mg/d (N=206)	97%	98%	93%
		Sof24 400mg/d+ Vel24 100mg/d (N=201)	87%	90%	73%
Pianko 2015 (45)	NR	Sof12 400mg/d + Vel12 25mg/d (N=52)	71%	85%	58%
		Sof12 400mg/d + Vel12 25mg/d + R12 (N=53)	91%	96%	84%
		Sof12 400mg/d + Vel12 100mg/d (N=53)	94%	100%	88%
		Sof12 400mg/d + Vel12 100mg/d + R12 (N=52)	98%	100%	96%
Foster 2015 (55)	ASTRAL-2 and ASTRAL-3	Sof12 400mg/d + Vel12 100mg/d (N=71)	90%	NR	NR
		Sof12/24 400mg/d + R12/24 (N=71)	63%	NR	NR
Foster 2015 (54)	NR	Sof16 400mg/d + R16 (N=90)	64%	NR	NR
		Sof24 400mg/d+ R24 1000mg/d (<75kg) or 1200mg/d (>=75kg) (N=88)	80%	NR	NR
		Sof12 400mg/d+ R12 1000mg/d (<75kg) or 1200mg/d (>=75kg) + Pega2a 180mg/w (N=87)	91%	NR	NR
Heidrich 2015 (53)	OPTEX	1.5µg/kg Pa2b24 (N=41)	66%	NR	NR
		1.5µg/kg Pa2b24 + R24 800-1400mg (N=42)	55%	NR	NR

d: day; Mg: milligram; n: sample size; NR: not reported; SVR: Sustained Virologic Response.

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Table 7. SVR24 rates in GT3 DAA-naive HCV patients

			SVR24 results		
Publication	**Trial**	**Arms/Interventions**	**Overall**	**Non-cirrhotic**	**Cirrhotic**
Shoeb 2014 (59)	STEPS	Arm 1: Pa2a24 180µg/w + R24 800mg (N=69)	48%	NR	NR
		Arm 2: Pa2a48 180µg/w + R48 800mg (N=67)	42%	NR	NR
De Meyer 2013 (60)	NR	Arm 1: T26 750mg/8h (N=8)	50%	NR	NR
		Arm 2: T24 750mg/8h + Pa2a2 180µg/w + R24 400mg/td (N=9)	66.7%	NR	NR
		Arm 3: T24 750mg/8h + Pa2a24 180µg/w + R24 400mg/td (N=9)	44.4%	NR	NR
Diango 2010 (49)	ACCEL ERATE	Arm 1: Pa2a16 180µg/w + R16 800mg/d (N=458)	84%	NR	NR
		Arm 2: Pa2a24 180µg/w + R24 800mg/d (N=405)	90%	NR	NR
Dalgard 2010 (52)	NR	Arm 1: Pega2b14 1.5µg/kg/w + R14 800mg/d (<65kg) 1000mg/d (65-85kg) 1200mg/d (86-105kg) 1400mg/d (>105kg) (N=199)	89.7%	NR	NR
		Arm 2: Peg2b24 1.5µg/kg/w + R24 800mg/d (<65kg) 1000mg/d (65-85kg) 1200mg/d (86-105kg) 1400mg/d (>105kg)	93.5%	NR	NR

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			SVR24 results		
Publication	**Trial**	**Arms/Interventions**	**Overall**	**Non-cirrhotic**	**Cirrhotic**
		(N=98)			
Dalgard 2008 (47)	NR	Arm 1: Pega2b14 1.5µg/kg/w + R14 800mg/d (<65kg) 1000mg/d (65-85kg) 1200mg/d (86-105kg) 1400mg/d (>105kg) in patients with RVR, defined as HCV RNA levels of <50 IU/mL after 4 weeks of treatment (N=148)	84%	NR	NR
		Arm 2: Pega2b24 1.5µg/kg/w + R24 800mg/d (<65kg) 1000mg/d (65-85kg) 1200mg/d (86-105kg) 1400mg/d (>105kg) in patients with RVR, defined as HCV RNA levels of <50 IU/mL after 4 weeks of treatment (N=150)	92%	NR	NR
		Arm 3: Pega2b24 1.5µg/kg/w + R24 800mg/d (<65kg) 1000mg/d (65-85kg) 1200mg/d (86-105kg) 1400mg/d (>105kg) in patients without RVR, defined as HCV RNA levels of <50 IU/mL after 4 weeks of treatment (N=130)	54.8%	NR	NR

d: day; Mg: milligram; n: sample size; NR: not reported; SVR: Sustained Virologic Response.

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Table 8. SVR24 rates in GT3 DAA-experienced HCV patients

			SVR24 results		
Publication	**Trial**	**Arms/Interventions**	**Overall**	**Non-cirrhotic**	**Cirrhotic**
Heidrich 2015 (53)	OPTEX	Arm 1: 1.5µg/kg Pa2b24 (N=41)	66%	NR	NR
		Arm 2: 1.5µg/kg Pa2b24 + R24 800-1400mg (N=42)	55%	NR	NR

d: day; Mg: milligram; n: sample size; NR: not reported; SVR: Sustained Virologic Response.

B2. **Priority question.** Please add references for the trials used in Table 60 for SVR rates and provide a rationale for the choice of study used in the economic model.

References and rationale for study choice for Table 60 are outlined below in Table 9.

Table 9. SVR rates for DAA-experienced (all GTs) and DAA-naïve patients with GT3 infection (with or without cirrhosis)

Treatment experience	**GT**	**CC/ NC**	**Intervention / Comparator**	**Base-case SVR**	**Data source**	**Rationale**
DAA-experienced	All	All	SOF/VEL/VOX	96.2 %	POLARIS 1 (1) (DAA-experienced population) POLARIS 4 (4) (DAA-experienced population) (to be run as sensitivity analysis: 97.8%)	Head-to-head trial of SOF/VEL/VOX vs current standard of care (no treatment). No other suitable data sources identified for comparison.
			No treatment	0%	POLARIS 1 (1) (placebo arm) (DAA-experienced population)	
DAA-naïve	3	CC	SOF/VEL/VOX	96.4 %	POLARIS 3 (3) (DAA-naïve population)	Active controlled head-to-head trial of SOF/VEL/VOX

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Treatment experience	GT	CC/ NC	Intervention / Comparator	Base-case SVR	Data source	Rationale
			SOF/VEL	96.3 %	POLARIS 3 (3) (DAA-naïve population) ASTRAL 3 (67) (to be run as sensitivity analysis)	vs commonly used existing comparator (SOF/VEL)
			SOF+DCV+ RBV	83.3 %	ALLY 3+ (68) (DAA-naïve population)	Consistent with previous submissions including SOF/VEL. No more appropriate data identified since previous submission.
			SOF+RBV	66.3 %	ASTRAL 3 (67) (DAA-naïve population)	
			Peg-IFN2a+RBV	29.7 %	Sovaldi SmPC [FISSION] (69) (TN population)	
			SOF+Peg-IFN2a+RBV	91.3 %	BOSON (70) (TN population)	
			No treatment	0%	POLARIS 1 (1) (placebo arm) (treatment-naive population)	
		NC	SOF/VEL/VOX	98.9 %	POLARIS 2 (2) (DAA-naïve population)	Active controlled head-to-head trial of SOF/VEL/VOX vs commonly used existing comparator (SOF/VEL)
			Peg-IFN2a+RBV	71.2 %	Sovaldi SmPC [FISSION] (69) (TN population)	Consistent with previous submissions including SOF/VEL. No more appropriate data identified since previous submission.
			SOF+Peg-IFN2a+RBV	95.8 %	BOSON (70) (TN population)	

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Treatment experience	GT	CC/ NC	Intervention / Comparator	Base-case SVR	Data source	Rationale
			SOF/VEL	96.6 %	POLARIS 2 (2) (DAA-naïve population) ASTRAL 3 (67) (TN population) (to be run as sensitivity analysis)	Active controlled head-to-head trial of SOF/VEL/VOX vs commonly used existing comparator (SOF/VEL)
			SOF+DCV	97.3 %[a]	ALLY-3 (71), DCV SmPC (72); TA364 limits this to F3 only (73)	Consistent with previous submissions including SOF/VEL. No more appropriate data identified since previous submission.
			No treatment	0%	POLARIS 1 (1) (placebo arm) (treatment-naïve population)	
DAA-experienced	All	All	SOF/VEL/VOX	96.2 %	POLARIS 1 (1) (DAA-experienced population) POLARIS 4 (4) (DAA-experienced population) (to be run as sensitivity analysis: 97.8%)	Head-to-head trial of SOF/VEL/VOX vs current standard of care (no treatment). No other suitable data sources identified for comparison.
			No treatment	0%	POLARIS 1 (1) (placebo arm) (DAA-experienced population)	
DAA-naïve	3	CC	SOF/VEL/VOX	96.4 %	POLARIS 3 (3) (DAA-naïve population)	Active controlled head-to-head trial of SOF/VEL/VOX

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Treatment experience	GT	CC/ NC	Intervention / Comparator	Base-case SVR	Data source	Rationale
			SOF/VEL	96.3 %	POLARIS 3 (3) (DAA-naïve population) ASTRAL 3 (67) (to be run as sensitivity analysis)	vs commonly used existing comparator (SOF/VEL)
			SOF+DCV+ RBV	83.3 %	ALLY 3+ (68) (DAA-naïve population)	Consistent with previous submissions including SOF/VEL. No more appropriate data identified since previous submission.
			SOF+RBV	66.3 %	ASTRAL 3 (67) (DAA-naïve population)	
			Peg-IFN2a+RBV	29.7 %	Sovaldi SmPC [FISSION] (69) (TN population)	
			SOF+Peg-IFN2a+RBV	91.3 %	BOSON (70) (TN population)	
			No treatment	0%	POLARIS 1 (1) (placebo arm) (treatment-naive population)	
		NC	SOF/VEL/VOX	98.9 %	POLARIS 2 (2) (DAA-naïve population)	Active controlled head-to-head trial of SOF/VEL/VOX vs commonly used existing comparator (SOF/VEL)
			Peg-IFN2a+RBV	71.2 %	Sovaldi SmPC [FISSION] (69) (TN population)	Consistent with previous submissions including SOF/VEL. No more appropriate data identified since previous submission.
			SOF+Peg-IFN2a+RBV	95.8 %	BOSON (70) (TN population)	

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Treatment experience	GT	CC/ NC	Intervention / Comparator	Base-case SVR	Data source	Rationale
			SOF/VEL	96.6 %	POLARIS 2 (2) (DAA-naïve population) ASTRAL 3 (67) (TN population) (to be run as sensitivity analysis)	Active controlled head-to-head trial of SOF/VEL/VOX vs commonly used existing comparator (SOF/VEL)
			SOF+DCV	97.3 %[a]	ALLY-3 (71), DCV SmPC (52); TA364 limits this to F3 only (47)	Consistent with previous submissions including SOF/VEL. No more appropriate data identified since previous submission.
			No treatment	0%	POLARIS 1 (1) (placebo arm) (treatment-naïve population)	

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; TN, treatment-naïve; VEL, velpatasvir; VOX, voxilaprevir.
[a] See response to B5.

B3. **Priority question.** Please clarify how the SVR values for SOF + DCV + RBV for treatment naive patients with cirrhosis are derived as the ALLY 3 trial was for SOF + DCV, rather than SOF + DCV + RBV (CS Table 60).

The SVR values for SOF+DCV+RBV for treatment (DAA)-naive patients with cirrhosis are derived from the ALLY 3+ trial (68), rather than the ALLY-3 trial (which investigated treatment with SOF+DCV and was not used to inform efficacy inputs for the treatment (DAA)-naïve cirrhotic population).

In the ALLY 3+ trial, treatment-naïve and treatment-experienced (IFN-experienced) patients received 12 weeks treatment with SOF+DCV+RBV. In the treatment (DAA)-naïve cirrhotic cohort, SVR was recorded in 15/18 patients (83%). This was used as the efficacy input for this treatment option in the cost-effectiveness model.

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B4. Please confirm whether the values for SOF + RBV for treatment naive patients with cirrhosis should be 77.3%, rather than 66.3% as these appear to be the values in ASTRAL 3 (CS Table 60).

The efficacy input for SOF+RBV for treatment-naive patients with cirrhosis were derived from the ASTRAL-3 trial (67). This trial investigated treatments in treatment-naïve and treatment-experienced patients, however all of the treatment-experienced patients had received prior treatment with interferon-based regimens, hence are considered to be DAA-naïve.

SVR was recorded in 33/45 (73.3%) treatment-naïve patients and in 22/38 (57.9%) treatment-experienced (DAA-naïve) patients. The combined total for all DAA-naïve patients is therefore 55/83, hence the efficacy input for SOF + RBV in this population was 66.3%. This input has taken into account SVR data for all DAA-naïve patients involved in the ASTRAL-3 trial (i.e. all treatment-naïve patients as well as patients who have previously failed an IFN-treatment, but have not previously received a DAA therapy). For further detail on categorising patient treatment history see question A3.

B5. Please confirm whether the values for SOF + RBV for treatment naive patients without cirrhosis should be 97.3%, rather than 96.3% as reported in Table 60.

SOF+RBV is not included as a comparator in the treatment (DAA)-naïve non-cirrhotic population. The efficacy input for SOF+DCV reported in Table 60 of the submission should read [redacted] (rather than 96.3%) due to typographical error, however within the cost-effectiveness model the correct SVR rate of [redacted] was employed. This change therefore does not impact modelling results.

B6. Please explain why SOF / VEL has not been included as a comparator for DAA experienced patients, even though evidence for this group is available in Polaris 4?

SOF/VEL was not included as a relevant comparator as the analysis sought to characterise SOF/VEL/VOX versus current treatment practice. SOF/VEL is not licensed for the treatment of DAA-experienced patients and is not reimbursed in England. These patients currently lack a licensed and reimbursed treatment option, and therefore “no treatment” was included as the only comparator reflecting current practice.

B7. **Priority question**: The company’s decision problem for the DAA-naïve population focuses on the GT3 subgroup only, whereas other genotypes are included in the final scope from NICE. Please reconsider whether it is necessary to provide analyses for other genotypes within the DAA-naïve population or provide further justification for excluding them. In addition, please confirm that you are aware and accept that the committee will not be able to recommend the technology to the breadth of the

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marketing authorisation if these subgroups are excluded from the company's analyses.

As detailed in section B1.1. of the submission it is recognised that the submitted population in DAA-naïve patients (limited to GT3 patients) is narrower than the pan-genotypic marketing authorisation of SOF/VEL/VOX as well as the NICE scope.

The GT3 sub-population of DAA-naïve patients reflects where SOF/VEL/VOX can provide the most clinical benefit:

- GT3 infection is regarded as a difficult to treat population, with high unmet need. Approximately 44% of the total CHC population have GT3 infection (74), and are at the highest risk of progressing from non-cirrhotic to cirrhotic (75)
- For those with and without compensated cirrhosis the option of 8 weeks of treatment compared with 12-24 weeks is likely to offer benefits in terms of efficacy, adherence and tolerability due to shorter treatment duration

Gilead Sciences understands that the committee will not be able to recommend SOF/VEL/VOX for populations not included within the submission.

B8. **Priority question.** Please clarify why a treatment duration of 12 weeks has been used in the model for cirrhotic patients receiving SOF/PEG/RBV, whilst the recommended treatment duration is for 24 weeks according to NICE Technology Appraisal TA330.

The rationale for this comparator is alignment with prior NICE submissions and UK clinical practice. Note that SOF+PEG+RBV 12 weeks was used in SOF/VEL submission [TA430], and it is supported by clinical evidence published from the BOSON trial.

The SOF/VEL submission [TA430] is more recent than the SOF submission [TA330], and it may be the case that the SOF submission used a different source of information that guided the use of 24 weeks of treatment. The SOF/VEL/VOX submission has used the most recently available evidence to inform treatment duration for comparators.

In addition, 24 weeks of SOF+PEG+RBV is not used in current clinical practice. This is largely in relation to cost and efficacy of newer all oral DAA regimens.

B9. **Priority question.** The CS section B.3.6.5 Table 63, page 157 reports that treatment-specific QoL for patients with GT3 have been taken from Younossi et al. (2016) (ref 132). However, this reference does not appear to report these values.

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Please provide the correct reference(s) for these QoL and/or explain how they have been derived, and update the table if appropriate.

HRQoL data collected in the ASTRAL-3 trial indicated that no on-treatment decrements in utility were observed in patients receiving 12 weeks treatment with SOF/VEL (67). It was assumed that other SOF-containing regimens without interferon or ribavirin constituents would also experience no utility decrement. The following treatments in the cost-effectiveness model were associated with a zero utility decrement:

- SOF/VEL/VOX (12 weeks)
- SOF/VEL/VOX (8 weeks)
- SOF/VEL (12 weeks)
- SOF+DCV (12 weeks)

The data relating to other treatment-specific QoL is derived from "An In-Depth Analysis of Patient-Reported Outcomes in Patients With Chronic Hepatitis C Treated With Different Anti-Viral Regimens" by Younossi et al. (2016) (76). This paper is the correct reference 132. In this study, patients achieving SVR12 with a range of treatments responded to the SF-6D survey and their results were recorded. Patients treated with an interferon- and ribavirin-containing regimen were associated with a 4.7% utility decrement and those treated with an interferon-free, ribavirin-containing regimen were associated with a 2.5% decrement (Table 3 in the publication). Both utility decrements were significant. Hence the following regimens in the cost-effectiveness model were associated with a 4.7% utility decrement:

- Peg-IFN2a+RBV (24 weeks)
- SOF+Peg-IFN2a+RBV (12 weeks)

The following regimens were associated with a 2.5% utility decrement:

- SOF+DCV+RBV (12 weeks)
- SOF+RBV (24 weeks)

This approach to treatment-specific QoL is consistent with the submission of SOF/VEL.

B10. **Priority question.** Please explain why the transition probabilities used from Cardoso et al (2010) differ from those reported in Table 2 of that study (CS Table 51).

From	To	TP (annual probabilities)	Source
Compensated cirrhosis	Decompensated cirrhosis	0.0438	Cardoso *et al.* 2010 (77)
	HCC	0.0631	Cardoso *et al.* 2010 (77)
Compensated cirrhosis SVR	Decompensated cirrhosis	0.0064	Cardoso *et al.* 2010 (77)

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	HCC	0.0128	Cardoso *et al.* 2010 (77)
Decompensated cirrhosis	HCC	0.0631	Cardoso *et al.* 2010 (77)

The transition probabilities reported were calculated using the values reported in Cardoso et al. 2010 (77) as opposed to directly utilising the reported rates. The calculation was initially undertaken in response to appraisal committee comments during the submission of Harvoni® (LDV/SOF; TA363 (78)) and the same values were utilised for the appraisal of SOF/VEL.

The calculation process followed a stepwise approach. An example using the transition probability for compensated cirrhosis (without SVR) to HCC is detailed below, the same methodology is used to compute the other transition probabilities.

- Calculate the probability of an event (Cardoso Table 2, Table 1)

$$Total\ events / total\ patients = 40/204 = 0.1961$$

- Calculate the average follow-up (in years) per patient within the individual group (Cardoso Table 2, Table 1)

$$Total\ cohort\ follow-up\ years / total\ patients = 683.5/204 = 3.35$$

- Convert the probability to a rate and adjust by the calculated follow-up duration to calculated rate per year

$$-LN(1 - probabilty\ of\ event) / follow-up\ per\ patient = -LN(1-0.1961)/3.35 = 0.0651$$

- Convert this rate back to a probability over one year

$$1 - EXP(-adjusted\ rate\ of\ events \times 1) = 1 - EXP(-0.0651 \times 1) = 0.0631$$

B11. Please explain the discrepancies in the following AE costs as reported in CS and the model.

i. In CS Table 58, the weekly AE cost of anaemia (epo) is reported as £13.27 but the model uses a value of £2.21

The weekly cost of treating anaemia involves treating 1% of patients with 40,000 units of Binocrit® (epoetin alfa), at the cost of £0.01 per unit (rounded). This is a weekly cost of £2.21. The value used in the model is correct, however there is a typographical error in Table 58 of the submission, this value should read £2.21.

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ii. In CS Table 59, the total AE cost of anaemia treatment (epo) in outpatient setting is reported as £240.00 whereas the model uses a value of £2.40. Similarly, the cost of specialist is reported as £129.97 in the CS versus £1.30 used in the model.

The unit cost of anaemia (epo) treatment in the outpatient setting is £40 and patients receive the treatment 6 times. 1% of SOF/VEL/VOX patients require treatment for this adverse event and 100% of those patients receive it in the outpatient setting. Hence the total cost for each patient who receive the treatment is £240, and the total cost incurred by the SOF/VEL/VOX cohort is £2.40 (the value employed in the cost-effectiveness model). Hence, the relevant row in Table 59 of the submission should read as follows:

Adverse event	Items	% of patients	Units	Cost	Total cost	Source
Anaemia (Epo)	Outpatient	1%x100% (1% of patients require treatment, and 100% of them receive it in the outpatient setting)	6	£40.00	£2.40	KOL Opinion; PSSRU unit costs 2016 - Hospital, day ward; Each visit is assumed to take 1 hour (79)

Similarly, in the specialist setting the unit cost of anaemia (epo) treatment is £259.94 and patients receive the treatment once. 1% of SOF/VEL/VOX patients require treatment for this adverse event and 50% of those patients receive it in the specialist setting. Hence the total cost for each patient who receives the treatment is £129.97, and the total cost incurred by the SOF/VEL/VOX cohort is £1.30 (the value employed in the cost-effectiveness model). Hence, the relevant row in Table 59 of the submission should read as follows:

Adverse event	Items	% of patients	Units	Cost	Total cost	Source
Anaemia (Epo)	Specialist	1%x50% (1% of patients require treatment, and 50% of them receive it in the	1	£259.94	£1.30	KOL Opinion; PSSRU unit costs 2016 - Hospital, day ward; Each visit is

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Adverse event	Items	% of patients	Units	Cost	Total cost	Source
		specialist setting)				assumed to take 1 hour (79)

iii. In CS Table 59, the total cost of anaemia treatment (blood transfusion) is reported as £129.97 but the model uses the value of £0.91.

The unit cost of anaemia (blood transfusion) treatment in the specialist setting is £259.94 and patients receive the treatment once. 0.7% of SOF/VEL/VOX patients require treatment for this adverse event and 50% of those patients receive it in the specialist setting. Hence the total cost for each patient who receives the treatment is £129.97, and the total cost incurred by the SOF/VEL/VOX cohort is £0.91 (the value employed in the cost-effectiveness model). Hence, the relevant row in Table 59 of the submission should read as follows:

Adverse event	Items	% of patients	Units	Cost	Total cost	Source
Anaemia (blood transfusion)	Specialist	0.7%x50% (0.7% of patients require treatment, and 50% of them receive it in the specialist setting)	1	£259.94	£0.91	KOL Opinion; PSSRU unit costs 2016 - Hospital, day ward; Each visit is assumed to take 1 hour (79)

B12. **Priority question:** Tables 64, 69, 76, 77, 78 and 79 show results for a population including all genotypes but it is not clear how these have been calculated as the model provides results for specific genotype populations. For instance, Table 64 titled "Base-case results: DAA-experienced (pan-GT and all non-cirrhotic/compensated cirrhosis) (list price)" in the CS with an ICER of £8,153 per QALY gained is the model's result for a genotype 3 sub-population and not all genotypes as stated in the CS.

a. Please clarify whether the results reported in these tables are only for a specific genotype or for all genotypes.

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For analyses involving DAA-experienced patients, a blended SVR rate (incorporating efficacy data across all genotypes) is used in the analysis. However, due to model functionality this data is stored within genotype 3 cells within the model.

The results for the DAA-experienced population should therefore be interpreted as representative of all genotypes rather than GT3. The DAA-experienced analysis cannot be undertaken for individual genotypes. DAA-experienced inputs across multiple sheets are located in GT3TE cells but refer to all genotypes as described above. This functionality is considered a limitation of the current model.

b. If the results are for DAA-experienced all-genotypes combined or for DAA-experienced GT3 subgroup only, please provide the GT-specific results.

The results for the DAA-experienced population are representative of all genotypes; there are no genotype-specific results to display. Please see response to a. for further details.

B13. **Literature searching:** In Appendix H Table 24 (HRQL search strings) the search is shown as identifying 726 references, whereas in Appendix H.1.8 Figure 7 the number of records identified through database searching is given as 932. Please clarify the discrepancy. For the clinical evidence (Appendix D table 1 and Figure 1) and the cost-effectiveness studies (Appendix G Table 21 and Figure 6) the values in the table and corresponding figure match.

An updated PRISMA is presented below. The discrepancy was due to a typographical error in accounting for the number of sources identified during the grey literature search.

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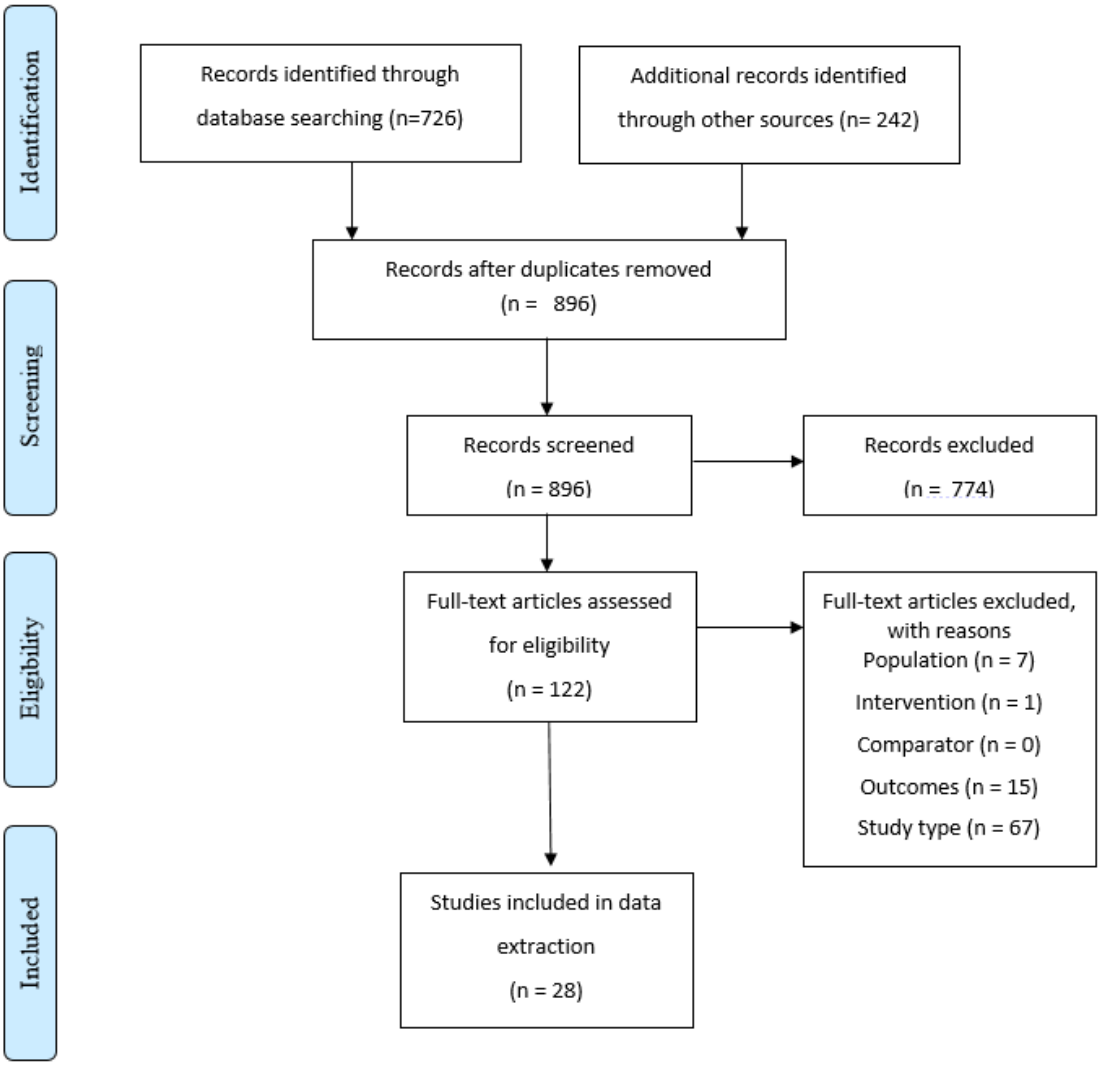
Figure 5. PRISMA diagram for HRQL systematic literature review



Section C: Textual clarifications and additional points

C1. Section B.2.4 Table18. There appears to be duplication of text in the column "Data management and withdrawals" (second bullet point) as shown with underlining in this reproduction of the text: "For categorical HCV RNA data, if a data point was missing, and was preceded and followed by values that were a success (<LLOQ TND and/or <LLOQ detected) then the missing data point was termed a bracketed success; otherwise the data point was termed a bracketed failure (≥LLOQ detected), otherwise, the data point was termed a bracketed failure (i.e. ≥LLOQ detected) ", can you please provide the correct text.

The correct text should read "otherwise, the data point was termed a bracketed failure (i.e. ≥LLOQ detected)" – see page 46, POLARIS 1 (1).

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Patient organisation submission

Sofosbuvir-velpatasvir-voxilaprevir for treating chronic hepatitis C [ID1055]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	The Haemophilia Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Haemophilia Society is the only UK wide charity for people with genetic bleeding disorders, we provide information and support for our community including those affected by the contaminated blood tragedy.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We speak to our member regularly, run services for people with Hepatitis C and clinical advisors. These help us understand the impact of Hepatitis C and it's treatment for our community.
Living with the condition	
6. What is it like to live with the condition? What do carers	Many of our members tell us their lives are severely impacted by their Hepatitis C infection, they have chronic fatigue, memory problems, get muddled and depressed. Others tell us they are particularly

experience when caring for someone with the condition?	susceptible to the cold and need to have their heating on much more than normal. At the later stages of disease people are often in pain, nauseous, and very itchy. Many are very distressed by these symptoms. Many of our members have had to give up work prematurely, or have never been able to work due to the impact of their hepatitis. Carers tell us the personality of their loved one can change where they become much more frustrated and angry and their tiredness has a significant impact on family life and the responsibilities of the rest of the family. It is both upsetting and distressing to see the impact of Hepatitis C on a family member.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Many of our members have had multiple treatment for their Hepatitis and found interferon treatment exceptionally distressing, so are keen for any future treatment not to require interferon. The prioritisation process implemented by NHS England has caused concern for many of our members who have been infected for 30+years due to their NHS treatment for a bleeding disorder. Many are concerned of progression to cirrhosis and so any delay is of huge concern. However, they are very positive about the benefits of the new generation treatments and the positive outcomes.
8. Is there an unmet need for patients with this condition?	For people infected via treatment for a bleeding disorder, we know many were infected with multiple genotypes, there is a need for a choice of treatments that do not require interferon but that can treat all genotypes.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	We have heard from members who have received new generation treatment that they are very positive about the treatment and its outcomes.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	We haven't discussed this with our members.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	As people with genetic bleeding disorders were infected with concentrated blood products and so received factor infected with multiple genotypes this technology is particularly beneficial. To be able to have a treatment hat will cover all possible genotypes (that may not all have been identified) is a huge benefit. We have heard from some members who have been successfully treated with another new generation product that is targeted at a specific genotype, but their hepatitis has recurred some time later. They have been informed that this may be due to multiple genotype infection.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Due to the nature of the infection route for people with bleeding disorders (via NHS treatment) with potentially multiple genotypes, we believe people with a bleeding disorder should be seen as priority for this treatment.

Other issues	
13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- This treatment is of particular benefit to people with a bleeding disorder who were often infected with multiple genotypes via their NHS treatment
- The fact this treatment does not require interferon or ribavirin is a significant benefit to people who have received these previously
- People with a bleeding disorder should be given priority for this treatment as they were usually exposed to multiple genotypes
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Patient organisation submission

Sofosbuvir-velpatasvir-voxilaprevir for treating chronic hepatitis C [ID1055]

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You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	The Hepatitis C Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The national patient charity for people living with or affected by hepatitis C funded by grant-making trusts, individual donations, some government grants and grants from industry. We have over 3,000 members of our patient association.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Through our national helpline which takes about 150 calls a week and our work on the ground through our peer community and prison projects and our outreach service
Living with the condition	
6. What is it like to live with the condition? What do carers	This varies. Some people experience few if any symptoms, while others can be so debilitated that they cannot work and find much of their social/emotional/sexual life significantly impaired (by for example

experience when caring for someone with the condition?	chronic fatigue, mood swings and sexual dysfunction). Equally some people encounter stigma (because of the association with drug use usually) and even discrimination, including loss of job. People who were infected through the NHS often feel extremely angry and bitter because they feel the government has never accepted responsibility or adequately compensated them. In some parts of the country people living with hepatitis C are currently experiencing significant uncertainty about when they will have access to interferon-free therapy and hence a cure because NHS England has introduced a cap on the number to be treated in 2017/18. The experience for carers varies in the same way, depending how symptomatic the patient is. For carers one of the most difficult issues is when treatment does not work or the patient is diagnosed too late and develops liver cancer. Good treatments for liver cancer do not exist and unless it is caught early enough for resection or transplantation, it is generally fatal within months.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	They are generally happy that interferon-free treatment is available for everyone except those with genotype 2. They are not happy that the only treatment available is whatever is cheapest that month, rather than the best for them. They are not happy they cannot be retreated if treatment does not work, especially if they were not allowed the best option initially. Those having to wait for treatment want to know why people with hepatitis C are singled out for rationing and believe it is only because of the stigma of hepatitis C. They are not happy that NICE has allowed this to happen.
8. Is there an unmet need for patients with this condition?	Yes. The biggest unmet need is retreatment, which is currently not available. This is a huge problem as those for whom treatment is least likely to work are those most in need (e.g. people with cirrhosis). There may also be some sub-types that are very resistant to treatment, such as genotype 1l, which may be prevalent in west Africa and hence in some immigrant populations and which may therefore need the most potent combination available (i.e. this one) In the current environment where price is the over-riding consideration and where NICE's determinations are largely irrelevant (not least because the price NICE uses has not had any relationship with the actual

	price) instead of not wanting 'me-too' drugs, now we do want them because they provide competition and rive the price down. In other words the unmet need is drugs that are cheap enough to persuade NHS England to give them to everyone
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	That it has very high cure rates That it works very well for people who have been unsuccessfully treated before
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	None of significance, although protease inhibitors tend to have slightly more side-effects
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so,	No

please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No
Other issues	
13. Are there any other issues that you would like the committee to consider?	No

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • This provides very high cure rates and would be the treatment of choice but it will be too expensive • This provides an excellent retreatment option, where none currently exists • This may be useful in certain subtypes which, although rare in the UK, may be resistant to current regimens • Eventually this may help drive down prices •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Professional organisation submission

Sofosbuvir-velpatasvir-voxilaprevir for treating chronic hepatitis C

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Society of Gastroenterology : liver section**
3. Job title or position	[redacted]

4. Are you (please tick all that apply):	✓ ☐ an employee or representative of a healthcare professional organisation that represents clinicians? ✓ ☐ a specialist in the treatment of people with this condition? ✓ ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Society of Gastroenterology is an organisation focused on the promotion of gastroenterology within the United Kingdom. It has over three thousand members drawn from the ranks of physicians, surgeons, pathologists, radiologists, scientists, nurses, dietitians, and others interested in the field. Founded in 1937 it has grown from a club to be a major force in British medicine, with representation within the British Royal Colleges and consequently the Department of Health and Government. Internationally it is represented at World and European level. The BSG is a registered charity. It is funded by subscription from members.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The goal of therapy is to cure hepatitis C virus (HCV) infection to prevent progressive hepatic fibrosis and eventual cirrhosis with subsequent symptomatic (decompensation) cirrhosis, hepatoma development , severe extrahepatic manifestations and death .

7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The endpoint of therapy is undetectable HCV RNA in blood (lower limit of detection ≤15 IU/ml) at 12 weeks known as sustained virological response (SVR 12). In patients with advanced fibrosis and cirrhosis, HCV eradication reduces the rate of decompensation and will reduce, the risk of hepatocellular cancer.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Urgent need: • Effective re-treatment options for all HCV genotypes treatment failures with previous DAA (particularly NS5A inhibitor) exposure. Those individuals exposed to NS5A inhibitors represent the majority of recent treatment failures and may have long lasting resistance associated substitutions (RAS) in HCV viral population. Although treatment failure is rare, numerically in England, due to the large existing disease burden, these patients will represent a substantial population. • Shorter treatment regimens - particularly for special groups eg.Prison population • Pangenotypic therapy with equal efficacy in cirrhotic & non cirrhotic patients • Ribavirin (RBV) free treatment regimes to minimise side effects of treatment
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Patients are treated via regional HCV operational delivery networks (ODNs). Individual cases are discussed at local HCV multi-disciplinary meetings (MDM) with a decision to treat HCV on criteria of disease severity (to prioritise cases) and other clinical and social considerations. Complex cases are discussed directly with the regional ODN MDM. The numbers of patients that can be treated each month are limited by the NHSE “run rate”. The regimens used to treat HCV are dictated by NHSE, with the cheapest effective NICE approved regime being recommended, With the exception of HCV genotype 2, all first line regimens are now Peg interferon (IFN) free known as direct acting antiviral (DAA) therapy, although RBV is still used in selected cases with SVR rates of > 95% irrespective of genotype, fibrosis stage or co-infection with HIV. Comparators for new

	HCV treatments should be with NHSE approved HCV first line regimens, with treatment populations stratified according to genotype, treatment experience (DAA exposure), presence of cirrhosis, co-infection with HIV.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The American Association for the study of Liver disease (AASLD) and European Association for Study of the Liver (EASL) publish annual updated evidence based guidelines.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Care pathways are well defined. In general there is little difference of opinion from professionals regarding treat regimens usually based on AASLD[1] or EASL guidelines[2]
• What impact would the technology have on the current pathway of care?	Provide additional treatment options for HCV therapy with regard to: 1) Re-treatment of all HCV Genotypes patients exposed to DAA therapy[3] 2) Pangenotypic treatment of HCV patients [3,4] 3) Shorter 8 week DAA regimens for most patients with HCV[4] 4) RBV free treatment [3,4]
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between	None

the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Primary & secondary care equally applicable although decision to treat should come from secondary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional expenditure as infrastructure as outlined in section 9 in place.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	For the re-treatment of all HCV genotype previous treatment failures previous DAA (particularly NS5A inhibitor) exposure
• Do you expect the technology to increase	Only in the above groups

health-related quality of life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Greater efficacy in HCV Patients with all HCV patients that require re-treatment as outlined above. Contra- indicated in patients with decompensated cirrhosis (Child Pugh B &C) as increased mortality risk
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No
14. Will any rules (informal or formal) be used to start or stop	No

treatment with the technology? Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Reduction in side effects from treatment as therapy will be free from ribavirin (RBV) use. Also shorter treatment duration of 8 weeks in the majority of HCV patients will minimise exposure to side effects. Increase in numbers of patients treated in difficult to access patient groups (eg. prison population or people who inject drugs with poor engagement with hospital services). These treatment naïve patients can be easily treated in the community with no need to pre genotype or stage disease.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-wise change' in the management of the condition?	No
• Does the use of the technology address any	Yes

particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Serious adverse events have been rare in trials (2%) and similar to placebo . Discontinued treatment because of adverse events is low (range, 0%-1%) Limitations of prescription are well recognised with drug- drug interactions resulting in either a change in concomitant medication or the technology being contraindicated. Patients with decompensated cirrhosis are not suitable for this HCV regimen due to the risk of further hepatic decompensation and death.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Sustained virological response @ 12 weeks (SVR 12) – measured in trials
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	SVR is associated with improved long-term outcome in HCV patients [5]

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Unknown as yet
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 'Sofosbuvir–velpatasvir for treating chronic hepatitis C' [TA430]?	Yes : Glecaprevir/Pibrentasvir

21. How do data on real-world experience compare with the trial data?	Unknown as yet as not funded by NHSE or NICE approved thus not in use outside of trials.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	Not applicable

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Pangenotypic treatment with response rates similar in cirrhotic & non cirrhotic patients-thus avoid need to genotype or stage pre HCV treatment in treatment naïve patients with associated total cost reduction & thus ease of use in community practice in patient groups not keen to engage with hospital based services or prison populations
- Shorter 8 week DAA treatment for most patients with HCV (treatment naïve/ non genotype1a)
- RBV free pangenotypic HCV therapy
- Re-treatment of all HCV treatment failures with previous DAA (particularly NS5A inhibitor) exposure

References

1) http://www.hcvguidelines.org/
2) http://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/easl-recommendations-on-treatment-of-hepatitis-c-2016
3) Bourlière, M, Gordon, SC, M.D., Flamm, SL et al. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. N Engl J Med 2017; 376:2134-2146 DOI: 10.1056/NEJMoa1613512
4) Jacobson IM, Lawitz E, Gane EJ, et al . Efficacy of 8 Weeks of Sofosbuvir, Velpatasvir, and Voxilaprevir in Patients With Chronic HCV Infection: 2 Phase 3 Randomized Trials. Gastroenterology. 2017 Jul;153(1):113-122. doi: 10.1053/j.gastro.2017.03.047. Epub 2017 Apr 5.
5) Simmons B, Saleem J, Heath K et al. Long-Term Treatment Outcomes of Patients Infected With Hepatitis C Virus: A Systematic Review and Meta-analysis of the Survival Benefit of Achieving a Sustained Virological Response Clin Infect Dis. 2015 Sep 1; 61(5): 730–740. Published online 2015 May 17. doi: 10.1093/cid/civ39

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Sofosbuvir-velpatasvir-voxilaprevir for treating chronic hepatitis C

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Pathologists**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**Royal College of Pathologists**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	Virological cure, with reduction in the risk of long-term disease progression

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The sustained virological clearance at 12 weeks post end of therapy (SVR12) is generally considered to be the gold standard assessment of treatment response. Measures of reduction in risk of disease progression would include numbers of patients developing, and time to development of cirrhosis, decompensated complications of cirrhosis, hepatocellular carcinoma or requiring liver transplantation
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Existing NICE approved therapies have very high SVR12 rates, but there are still subpopulations of patients who would benefit from even better drug regimens e.g. those with genotype 3 infection, particularly if cirrhotic, and those who have failed interferon-based or direct acting antiviral agent-based therapy.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Through a variety of regimens of directly acting antiviral agents, the precise regimen being dependent on genotype, cirrhosis status, previous treatment experience, and cost. In practice, NICE guidelines are very much secondary to dictats by NHS England which stipulate precisely which regimen is to be used for each patient if the hospital managing that patient wishes to be reimbursed for the cost of the drugs.
• Are any clinical guidelines used in the treatment of the	NHS England issue a rate card at roughly 6 monthly intervals which specifies precisely which drugs many be used for which patients. I hesitate to call this a clinical guideline. There are guidelines available from

condition, and if so, which?	learned societies such as the European Society for the Study of the Liver and the American Association for the Study of Liver Disease
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	NHS England have set up an operational delivery network through which patients can access DAA therapy. Differences of opinion amongst professionals are irrelevant in this context as NHS England clearly stipulates which drug regimens may be used on patients.
• What impact would the technology have on the current pathway of care?	This would be entirely dependent on whether or not NHS England were prepared to allow prescription of these drugs once they are licensed, irrespective of what NICE says. It is highly likely that these drugs would be of benefit to many patients with chronic HCV infection, especially those who have previously failed DAA therapy, but NHS England does not currently permit use of DAAs for this purpose.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	See answers to above questions
• How does healthcare resource use differ between the technology and current care?	It wouldn't. Current care already involves the use of similar DAA drugs.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Currently, treatment of HCV infection has to be administered through the Operational Delivery Network set up by NHS England. This, however, is not ideal for many of the patient sub-groups who suffer from chronic HCV infection e.g. prisoners and people who inject drugs. Delivery of healthcare in the community would be a much better model and we should be moving towards this.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None, other than permission from NHS England to prescribe the drugs.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	I would expect SVR12 rates for genotype 3 patients with cirrhosis to be improved, and likewise for certain subgroups of patients who have failed previous DAA-based therapy e.g. Gt1 patients who have failed previous NS5a containing regimens.
• Do you expect the technology to increase length of life more than current care?	For those patients who have failed previous DAA containing regimens, these more potent drugs offer a better chance of HCV cure
• Do you expect the technology to increase health-related quality of life more than current care?	No. An SVR12 is an SVR12, no matter which drugs induced it.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Certain subgroups of patients who have failed DAA-containing regimens. Genotype 3 cirrhotic patients
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No difference

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes – see above comments on limitation of use of all DAA drugs by NHS England
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	The trial data that I have seen suggests these are more potent agents with a more pan-genotypic profile and with possibly a higher barrier to resistance than some of the current DAA drugs.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No. Introduction of DAA therapy was a step-change. Introduction of second generation DAA drugs will improve SVR12 rates from very high to extremely high.
• Does the use of the technology address any particular unmet need of the patient population?	Yes for those patients who have failed DAA containing regimens
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Not aware of any significant side effect profile. Would be surprised if there was one.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Inasmuch as we would like to treat our HCV patients with all oral interferon and ribavirin free highly potent pangenotypic regimens with no side effects.

• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	SVR12 rates. Yes
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	SVR12 is itself a surrogate outcome. Trials to assess change in long-term outcomes are very difficult to conduct in a disease which has a natural history measured in decades, but yes, long-term morbidity and mortality data would undoubtedly be helpful.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator	Abbvie are generating data using Gle-Pib; Merck have a new combo coming through clinical trials

treatment(s) since the publication of NICE technology appraisal guidance [TA430]?	
21. How do data on real-world experience compare with the trial data?	Real world usage of DAAs results in very comparable SVR12 rates to those generated in clinical trials (I have been involved in the data collection process to prove that through HCV Research UK).
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Access to more potent, more pangenotypic DAA drugs will increase virological cure rates
- Usage of these drugs within the NHS will be entirely dependent on permission granted by NHS England
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Sof/Vel/Vox for treating chronic hepatitis C

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you	
1. Your name	**Malcolm Qualie/Graham Foster**
2. Name of organisation	**On behalf of NHS England**

3. Job title or position	**Pharmacy Lead and National Hepatitis C ODN Clinical Lead, NHS England**
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? ☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☒ an expert in treating the condition for which NICE is considering this technology? ☒ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England is the responsible commissioner for all hepatitis C treatments. Graham Foster is clinical lead for the HCV Operational Delivery Networks and a consultant hepatologist at Barts Health
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	Malcolm Qualie - none Graham Foster - my department has received funding from Gilead for participation in clinical trials and I have received personal fees for speaking and attending advisory boards.
Current treatment of the condition in the NHS	
6. Are any clinical guidelines used in the treatment of the	There are national guidelines for managing chronic HCV infection developed by the clinical community and a well established prioritisation process managed through regional operational delivery networks with

condition, and if so, which?	oversight from NHS England.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is very well defined and equity of access is monitored by NHS England. Resources to deliver the pathway are provided through CQUIN funding
8. What impact would the technology have on the current pathway of care?	The technology provides an alternative to current technologies. All of the available technologies have excellent response rates (as evidenced by high rates of viral clearance) but for many regimens the duration of therapy varies for different genotypes. This technology establishes a fixed duration therapy for all genotypes with durations modified by the degree of liver fibrosis. The availability of a short duration therapy (8 weeks) for all patients with mild disease provides an opportunity for 'immediate access' to therapy without the need for viral genotyping and this may facilitate access to care for patients who have problems engaging in traditional care pathways. However, given that patients with HCV are treated by experienced teams working in multi-disciplinary networks, the benefits of this approach are marginal. At present there is no licensed therapy for the very few patients who have failed to respond to currently available treatments. This new technology provides a treatment option for such patients and an analysis of the cost-effectiveness of this approach would be very valuable.
The use of the technology	
9. To what extent and in which population(s) is the technology	It is currently unlicensed and so there is no access outside any commercially run clinical trials.

being used in your local health economy?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – NHS England anticipates that this new technology will be administered to patients according to local priorities
• How does healthcare resource use differ between the technology and current care?	Current care requires viral genotyping, disease staging and treatment in line with current NICE guidance. The new technology provides the opportunity for shorter treatment durations which may be advantageous in selected patient groups. Importantly this technology provides a therapeutic option for the small number of patients who have failed current treatments
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology should be delivered by Operational Delivery Networks who oversee and guide on drug selection and supervise therapy in the most appropriate clinical setting.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	NHS England fund hepatitis C treatments via a managed access programme which will fund a target of 12,500 patients in 2017/2018 – it is not envisaged that extra resource will be required for this technology appraisal.
• If there are any rules (informal or formal) for	Current rules recommend stopping therapy if there is evidence of virological failure and we would recommend that these rules be applied to the new technology

starting and stopping treatment with the technology, does this include any additional testing?	
11. What is the outcome of any evaluations or audits of the use of the technology?	None yet available
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	None noted
12b. Consider whether these issues are different from issues with current care and why.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Addendum to NICE response (applies to all DAA treatment HTAs)
As requested, NHS England is providing an addendum to our organisation submission for ID1085 "Glecaprevir with Pibretasvir for treating chronic hepatitis C" and subsequent DAA HTAs. You have requested additional information focusing on the continuing added value to the NHS of paragraph 1.2 being included in the wording of this Technical Appraisal, consistent wi.th NICE statements governing the other treatment options for patients for this disease

> "*It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need*"

It has been indicated that the committee could be minded to conclude that continued inclusion of the statement would not add value to the guidance, informed by a number of considerations:

1. How NHS England's lack of detailed commentary reaffirming support for this aspect of NICE's current guidance was interpreted by the committee.

2. The suggestion that the use of 'multidisciplinary teams to prioritise treatment for people with the highest unmet clinical need' is no longer considered the efficient way of handling treatment decisions, and is now a straightforward tick-box exercise

3. That ODNs are an accepted route to commissioning

4. Views expressed that the capacity issues prevalent at the time of first introduction of these new drugs are no longer an issue

5. That prioritising people with highest unmet clinical needs is no longer necessary

Firstly, we set out further information that the committee will need to conclude its deliberations on the issue of ODN MDT prioritisation and treatment decisions. In our view, this information demonstrates the considerable value of the existing NICE recommendations for ODN MDTs to prioritise treatment for people with the highest unmet clinical need and thus the need for its continuation.
Secondly we set out major challenges that a fundamental change in approach caused by this proposed change at this time would create. The conditions may be right to consider such a change at some point within the coming years, but they are not appropriate today. To make revisions at a later point would avoid the disruption that will result from a change now, and avoid setting back the strategy for combating the disease to the detriment of the interests of patients and taxpayers.
As an annex to this addendum we lay out a response to each of the five considerations you have outlined to assist the committee in reconsidering this issue.

The continuing important role of ODN Multidisciplinary Teams in prioritising treatment for people with highest unmet need

The selection, commissioning, development and funding of ODNs has been a major undertaking. The value they add is to ensure that historical inequities in treatment are addressed. This planned system of care is organised to ensure the right patient gets the right treatment at the right time. Initially, ODNs have been focused on ensuring their available capacity has been used for treating those with the highest unmet clinical need – often the most severe disease. This strategy is having an impact on HCV related mortality, morbidity and demand for HCV related transplantation. NHS England considers that the ODNs have and will continue to make an important contribution. It is hard to see how the important progress made on outcomes as well as use of NHS resources - including moving from [redacted] to nearly [redacted] patients getting the lowest acquisition cost treatment option that is clinically appropriate to their treatment history, genotype, and condition - would have occurred without their important role. It is also hard to see how this would be sustained if ODNs role in prioritisation and treatment selection does not continue.
It is the clinically driven treatment choice alongside the prioritisation of patients by MDTs that has enabled the NHS to ramp up treatment choices cost-effectively. This is a clear example of the 'value-

add' from the existing guidance and the value that would be destroyed by disrupting these arrangements through removing the guidance.

The disruption of a change to the current approach at this time would set back the strategy for combatting the disease by undermining its foundation

[redacted] investment has been made by the NHS to establish and develop ODNs whose expertise and effectiveness in driving change with network partners is growing. [redacted] The ODNs are formally contracted until March 2019, [redacted] and a fundamental operational redesign of the co-ordination and organisation of treatment decisions which would deflect focus from the important role of ramping up treatment volumes and capturing vital intelligence in the new national registry and treatment outcome database.

We recognise the valuable role NICE has played in ensuring that all new DAAs are available. The guidance has underpinned NHS England's commercial activity which has used competition in the market and the principle of lowest acquisition cost for these range of effective treatments to secure an even better deal for the taxpayer. [redacted] the commercial strategy which has shown proven effectiveness based on the current guidance and has allowed reinvestment into expansion in treatment numbers to meet the projected growth forecast by NICE in previous TAs for DAAs. Removal of this element of the guidance and the commercial environment it has created would seriously affect the timing and effect of a strategic procurement we have been working on with industry involvement for over 12 months. That procurement, [redacted], aims to make elimination a reality (and possibly sooner than 2030) [redacted]

When the committee previously considered issues relating to NHS England's responsibilities it noted:

> *The responsibility for securing care for the NHS in England rests with NHS England. NICE should be cautious and sure of its judgement before requiring NHS England to provide services that it does not consider that it can provide, or provide safely and efficiently. In effect, NICE would have to conclude that NHS England was mistaken….. Its position, in setting out what it believes it needs to do to put the necessary arrangements in place, has credibility. NICE needs to be wary of substituting its judgement for NHS England's in this respect.* [1]

We would hope the committee will recognise that NHS England's responsibilities in securing care efficiently extend to applying specialist commercial expertise for bringing down prices to levels being achieved in other developed health systems, which despite some good progress to date is still yet to be achieved until our commercial strategy is fully implemented during 2018.

The National Clinical Advisory Group for Hepatitis C, who provide independent expert clinical advice NHS England have also written to NICE and to NHS England to set out their assessment of the balance of benefit and risk in making changes to this guidance. NICE has advised that for procedural reasons the committee cannot recognise that expert group as a separate stakeholder, but we feel they make an important contribution so have included their letter as annex 2 below. Their assessment aligns with our own, that continued inclusion of para 1.2 is important at the present time.

[1] TA330 Paragraph 5.8

Annex 1

1. Did NHS England's lack of detailed commentary about this aspect of NICE's current guidance suggest its declining importance?

NHS England did not include specific commentary on this point in its original submission because prioritisation of highest unmet clinical need is a fundamental principle underpinning all the NICE guidance on DAAs and in turn NHS England's sustainable roll out strategy, having been reflected in all previous TAs for DAAs. NHS England has adopted NICE's guidance on this matter and is committed to making it work.

NHS England assumed that this would continue to apply to new treatments, as has been the case in other DAA TAs. Had NHS England's position changed in relation to the importance or effectiveness of this aspect of guidance, or had there been evidence the capacity constraints giving rise to the original guidance were no longer significant, our submission would have made this point. On the contrary, it is precisely because the current arrangements **are** enabling effective ramp up in treatment levels **and** highly effective impacts on health outcomes, that NHS England believes no changes are needed to current arrangements including prioritisation at this time.

2. Is MDT decision making efficient and important or simply a tick-box exercise?

MDTs are a central feature of models of care which aim to balance access to expert advice and increasing access to treatment for patient benefit. HCV ODNs are an excellent example of this. ODN MDTs ensure through support in patient selection, treatment selection, patient support and management of complications that even local non specialist services can offer treatment to patients.
The national clinical lead for Hepatitis C and vice chair of the clinical hepatitis advisory group, Professor Graham Foster comments:

> *"Despite recent advances, treatment for hepatitis C remains complex with many patients (e.g. those with HIV infection, those with mental health problems requiring anti-psychotic agents) taking medication that can interact with the antiviral drugs. Such patients require specialist pharmacy input and support. Resistance motifs (e.g. the NS5A Y93 polymorphism in Genotype 1a that modifies response to Grazoprevir) and viral hybrids (e.g. the 'St Petersburg' 1a/2k hybrid) as well as exotic strains with novel resistance profiles (e.g. G1l) require specialist virological expertise to allow the most appropriate treatment choice. Given the cost and complexity of managing patients who have failed to respond to first line treatment it is essential that the most effective drugs are selected for initial therapy. The increasing diversity of patients with HCV who are being treated necessitates a collective approach to management – deciding when a chaotic, homeless hepatitis C infected active drug user should be considered for therapy and what support needs to be provided is not trivial and without a multidisciplinary approach such people are unlikely to be provided with the care that they need – inexperienced providers often decline to treat patients with complex co-morbidities and the MDT environment ensures equal access for all patients as well as providing education for those who are unfamiliar with these challenging individuals. ODN MDTs ensure through support in patient selection, treatment selection, patient support and management of complications that even local non specialist services can offer treatment to patients. For example in East London addiction nurse specialists now manage chaotic drug users in the community without the need for direct medical supervision – support through the MDT with shared decision making and robust assessment of the risk-benefits for each patient ensures the safety governance of this approach and provides appropriate clinical governance allowing treatment of some of the most disadvantage members of society. ODNs have ensured that the work of all local partners meet local needs for example Bart's Health ODN is working across the partner organisations to identify and prioritise treatment of patients from immigrant populations which are a high need local population whereas Brighton has chosen to focus on the needs of the homeless."*

This is far from a 'tick box exercise', as was suggested to the committee. Furthermore, far from declining, the utility of this MDT approach will be increased in the coming years as ODNs turn their attention to prioritising treatment of patients such as PWIDs which will require greater involvement of non NHS local services and models of care which effectively support adherence. In the absence of an MDT it is difficult to see how equitable access to the most effective therapies can be maintained.

3. Do capacity issues remain a relevant factor in treating Hepatitis C in 2017?

The guidance that ODN MDTs prioritise patients with the highest unmet clinical need was issued to the NHS in November 2015 and implemented in February 2016. The record of the committee deliberations state:

> *The Committee understood that NHS England considered these new oral treatments to be excellent options, but was concerned about the increase in investment and capacity needed for their implementation.*
> *The Committee heard from the patient expert that people with chronic hepatitis C appreciated the capacity constraints placed on the NHS in delivering treatment for every eligible person.*
> *The Committee recalled that treatment decisions are influenced by clinical characteristics including HCV genotype, level of liver damage, comorbidities and treatment history (see section 4.2).With these factors in mind, people with chronic hepatitis C may accept treatment being prioritised for those with highest unmet clinical need (including some people without cirrhosis), potentially determined by multidisciplinary teams.*

The backdrop to these considerations is that the NHS was on course to treat around 6,000 patients by March 2016, but Public Health England estimated there were 160,000 estimated patients with hepatitis in 2015 with around 50% thought to be diagnosed and around 4,000 new chronic diagnoses per year adding to the numbers to be treated.

It is encouraging that the NICE committee has recognised the substantial investment and attention given to developing the NHS services in the 19 months since the original guidance was implemented. The NHS is now on track to treat around 12,500 in the year to March 2018, but there remain an estimated 140,000 HCV infected patients still to treat, together with retreatment of those who fail DAAs, and new infections.

The opinion the committee heard suggesting capacity is not an issue is not borne out by the current data held by NHS England, including working hard with services in formerly underserved areas who are finding the rate of expansion NHS England is driving to be challenging.

This is not to say, the capacity picture is entirely uniformly distributed, and where clinics are struggling to achieve expansion goals, NHS England has called for clinics in other areas with localised spare clinic capacity to take on additional patient volumes, ensuring the national expansion can be achieved without sacrificing the important health equity commitment of expanding underserved areas. It is important to note there were fewer networks able to take on additional patient volumes than networks struggling with their numbers in our most recent assessment two months ago.

As increased case-finding and testing is undertaken and as treatment includes those being retreated, capacity constraints will remain and in order that ODNs can focus their attention of those with the greatest unmet need, prioritisation will continue to be required.

Our experience in working with all 22 ODNs across the country, together with the national data informs our evidence to the committee that the imbalance between demand and capacity remains substantial; hence the need for NHS England to exercise our statutory responsibility to plan capacity of the NHS to treat HCV remains. There is no consensus in the NHS that capacity issues previously considered by the committee are behind us.

4. **Is the established nature of ODNs grounds for removing recommendations about their role in prioritising and guiding treatment?**

The role, scope and authority of ODNs is inextricably linked to the existing NICE guidance, NHS England has invested in their role, not only in respect of prioritisation and prescribing decisions It is precisely because the guidance enables their role that removing the guidance would have an adverse impact on their authority to ensure treatment remains appropriate. It might be argued that the guidance still retain the requirement for ODN oversight but without prioritisation. However, the potential loss of authority of ODNs that would result from removal of their role in prioritising and guiding treatment choices is in our judgment fundamental. Furthermore, it would also adversely impact the important structures of consistent monitoring and data collection which remain vital to tracking of patients and eliminating the disease in the face of major uncertainty in expert estimates about the number of undiagnosed patients. Prioritising treatment allows oversight not only of treatment but adherence to the data quality and completeness that is critical.

5. Is it still necessary to prioritise people according to unmet clinical need?

Nationally recognised expert clinical opinion on the value of MDT consideration of treatment decisions set out above makes a strong case for the value added by MDTs in their current oversight and prioritisation role in its own right. That prioritisation is integral to this role is the inescapable conclusion of two factors: First, that demand is substantially in excess of the capacity of the NHS to treat all diagnosed patients. Second, that treating those whose health consequences are most likely to escalate ahead of those for whom such escalation is less imminent, will achieve greater health benefit if the NHS does not have the capacity to treat all patients in a short time period.

ODNs have developed approaches to prioritisation to meet the needs of their local populations. Even now, to identify just one of the risk factors for escalation that NICE previously considered, around 20% of patients being treated have cirrhosis. With the estimated 140,000 HCV infected patients still to treat, together with retreatment of those who fail DAAs and this means that there remains a real and significant potential for services to be overwhelmed by demand, and unless all patients can be treated in a short time period a sequential treatment of patients would mean more patients suffer adverse health consequences than a clinically prioritised treatment approach.

This need for prioritisation is underlined by the apparent positive progress being made on case finding. [redacted] If this serves as a proxy for diagnosis and case finding, at a rate just above the expanded rates of treatment being delivered, it supports the view that the nature of the imbalance between diagnosed patients known to services and capacity will not diminish in the near future.

To summarise our evidence in relation to the five considerations set out:

- The lack of detailed commentary previously was a sign that we believe the current guidance needs no change
- MDT decision making adds great clinical value including playing an important role in health inequalities for vulnerable individuals and is far from a tick box exercise
- Capacity issues remain a relevant factor for HCV treatment in 2017: The imbalance between demand and NHS capacity is evidenced by the national data to remain substantial
- The established nature of ODNs does not in any way remove the need to remain explicit about their role in prioritising and guiding treatment
- The greater health outcomes gain for patients from prioritised rather than sequential treatment remains as true today as it was when committee considered it 19 months ago

Having seen, as a result of the prioritisation that NICE recommended, a 10% fall in HCV mortality, and from our commissioner data an over 50% fall in HCV related transplant requirements we are keen to continue to make health gains from this approach and in the face of strong clinical evidence of benefit from the current clinical treatment strategy, a change to this approach should not be made by changing the guidance.

Annex 2

Dear Mr Boysen

I am writing on behalf of the clinical members of the NHS England Hepatitis C Advisory Group. The Advisory Group works to maximise equitable access to new HCV treatments.

At our meeting on 7th November, we received feedback on the discussion that took place at the committee meeting with regard to ID1085 "Glecaprevir with Pibrentasvir for treating chronic hepatitis C". It was noted that following discussion at the meeting NICE indicated they were minded not to include in the guidance the role of ODN MDTs, and to retrospectively remove this requirement from all published guidance. NHS England also confirmed that they had been invited to submit an addendum to their original evidence submission on this point.

We are aware that the guidance relating to the MDT and prioritisation has caused debate. Although the patient representative on the Advisory Group, Charles Gore from the Hepatitis C Trust, expressed his opposition to the principle of prioritisation, the clinical members of group are clear that the guidance, and the ODNs that implement it, play an important role with regard to the principles of:

- Securing equitable access for all patients
- Working towards the WHO goal of elimination of HCV as a public health threat by 2030

The network/MDT model of delivery was a key element of the Service Specification written by the Advisory Group in 2014, and it remains fundamental to the maintenance of universal high standards in the management of HCV.

The clinical members of the Hep C Advisory Group therefore concluded:

1. NICE appraisal of new HCV medicines is an important principle which underpins equitable access to clinically- and cost-effective medicines.

2. The guidance requirement 1.2 which states: "the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need" serves as an important cornerstone of England's strategy for sustainable roll out of HCV treatment.

3. The strategy for treatment has already resulted in significant improvements in uptake and outcomes, and the trajectory for this to continue is already set.

4. Any change in this guidance could in our opinion serve to undermine equitable access and hamper and delay efforts to eliminate the disease. We cannot see how this change would benefit patients.
The clinical members would advise that no change to guidance paragraph 1.2 is made at this time.

Yours sincerely

Peter Moss, Consultant in Infectious Diseases
Chair, NHS England Hepatitis C Advisory Group

on behalf of
Professor G R Foster
Dr K Agarwa
Professor D Mutimer

NICE National Institute for Health and Care Excellence

Clinical expert statement

Sofosbuvir-velpatasvir-voxilaprevir for treating chronic hepatitis C [ID1055]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Andrew USTIANOWSKI**
2. Name of organisation	**Regional Infectious Diseases Unit, North Manchester General, Pennine Acute Trust**

3. Job title or position	**Consultant in Infectious Diseases & Research Lead**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To cure individuals with chronic hepatitits C infection
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A negative plasma viral load 12 weeks after treatment completion – an SVR12.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The main unmet need remains those that have failed other direct-acting antiviral (DAA) regimens, but also the possibilities of expanding available pan-genotypic, ribavirin-free regimens.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Currently with all-oral direct-acting antivirals – the leading agents used are: Sofosbuvir/Ledipasvir, Sofosbuvir/Velpatasvir, Grazoprevir/Elbasvir, Ombitasvir/Paritaprevir/ritonavir +/- Dasabuvir, Glecaprevir/Pibrentasvir – the above with or without Ribavirin
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are NHS England directives on preferred agents that are based on cost and efficacy; international guidelines (EASL and AASLD); and also clinician consensus guidelines derived from an annual meeting of HCV-treating physicians in England
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	My experience is within England. There are differences in preferred agents utilised as a result of differing re-imbursement decisions from commissioners within the nations of the UK. There is more consensus within the treating community as to which would be preferred agents if there were no commissioning restrictions. The care pathways otherwise are fairly standardised
• What impact would the technology have on the current pathway of care?	It would provide options for treating individuals that have failed on previous DAA-based regimens
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	There will be no differences in care pathways with the exception of which patients are put forward for treatment with this technology (likely to be predominately those that have failed previous DAA-based regimens, though there is good efficacy in those naïve patients treated for 12 weeks)

• How does healthcare resource use differ between the technology and current care?	There are no/limited options for re-treating those that have failed previous DAA-based regimens (Glecaprevir/Pibrentasvir also has promise)
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Under the directions of specialists via operational delivery networks in England, and under the direction of HCV specialists (hepatology or infectious diseases) in other regions.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil specific
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes - for those with previous failure on DAA-based regimens
• Do you expect the technology to increase length of life more than current care?	Yes - for those with previous failure on DAA-based regimens

• Do you expect the technology to increase health-related quality of life more than current care?	Yes - for those with previous failure on DAA-based regimens
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes – more effective in those with previous failure on DAA-based regimens. No less effective in other groups than current standard of care
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	No difference to current standard of care

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Nil specific – planned regimen lengths (principally 12 weeks) with standard dosing. No specific rules and care as per current standard of care regimens
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The advantage of this technology is efficacy in those that have failed previous DAA-based therapy – but I would assume this is captured within the company-provided QALY estimates
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	There are currently no/limited options for treating and curing those individuals that have failed DAA-based regimens. This technology would provide a significant impact and benefits in this scenario

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Only for those that have failed previous DAA-based regimens. In this scenario then I consider it a 'step-change', but not in other populations
• Does the use of the technology address any particular unmet need of the patient population?	As above – for those that have failed previous DAA-based regimens where there are currently no/limited options
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are no significant adverse events noted with this technology or comparators that would be expected to affect average patients receiving these agents. All are exceptionally well tolerated.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	SVR12 (including in those subgroups with prior treatment and resistance), tolerability, discontinuation due to AEs – all measured in the trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Nil
20. Are you aware of any relevant evidence that might	Nil

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA430.	On-going NICE appraisal of Glecaprevir/Pibrentasvir is of relevance
22. How do data on real-world experience compare with the trial data?	Very similar/effectively identical for comparators. No significant real-world experience of this technology to date though there is no reason to assume any difference.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Nil specific – however this technology would not be recommended for those with severe renal impairment (eGFR<30) (as it contains Sofosubvir which is contra-indicated in such patients) or those with decompensated liver disease (as it contains an NS3/4 protease inhibitor which as a class are contra-indicated in such patients even though there is no specific data for Voxilaprevir in this scenario)

23b. Consider whether these issues are different from issues with current care and why.	Not significantly different

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- There is a need for agents for re-treatment of those that have previously failed DAA-based regimens, and significant efficacy has been demonstrated in this population with this technology
- It is well tolerated
- It does not require Ribavirin as a co-medication
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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

Sofosbuvir–velpatasvir–voxilaprevir for treating chronic hepatitis C

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Declared competing interests of the authors

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Rider on responsibility for report

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

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Contributions of authors

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

the clinical effectiveness systematic review and drafted the report; Dr. Keith Cooper, critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Mr. Olu Onyimadu, critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Dr. Joanna Picot, critically appraised the clinical effectiveness systematic review, drafted the report, project managed the review and is the project guarantor.

Word count: 42,133

[redacted]

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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.

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.

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)

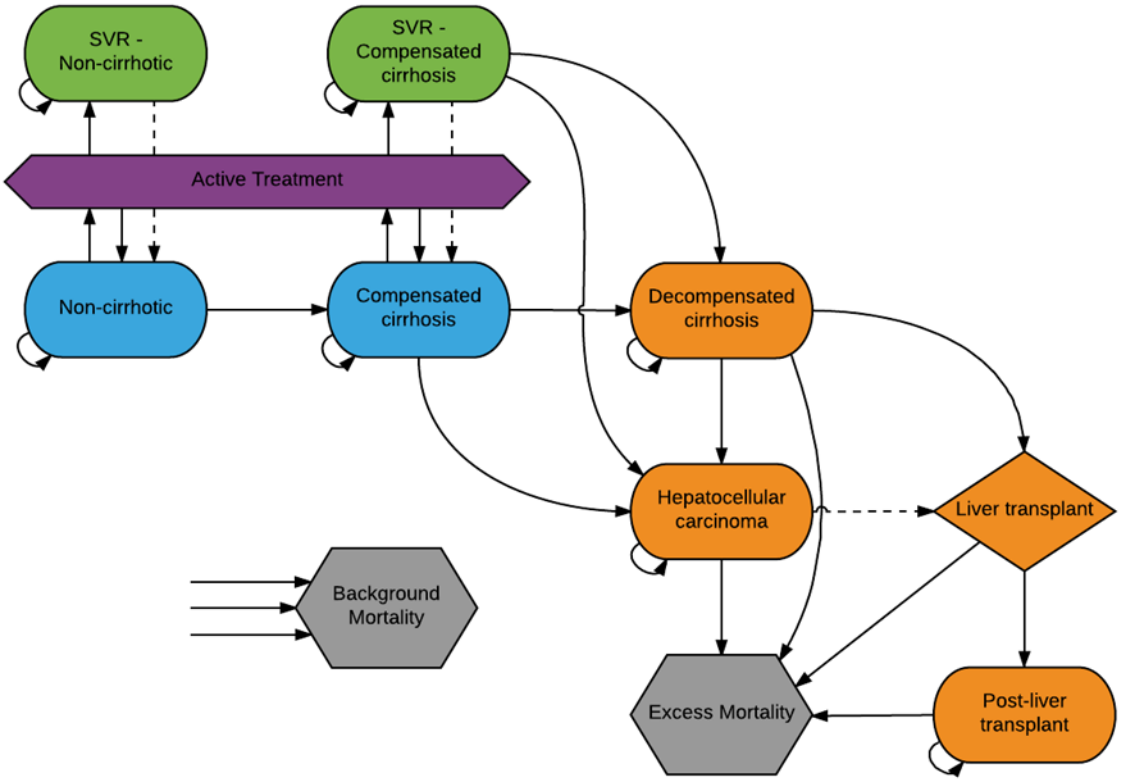


Figure 1: Model structure (CS Figure 3)

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.

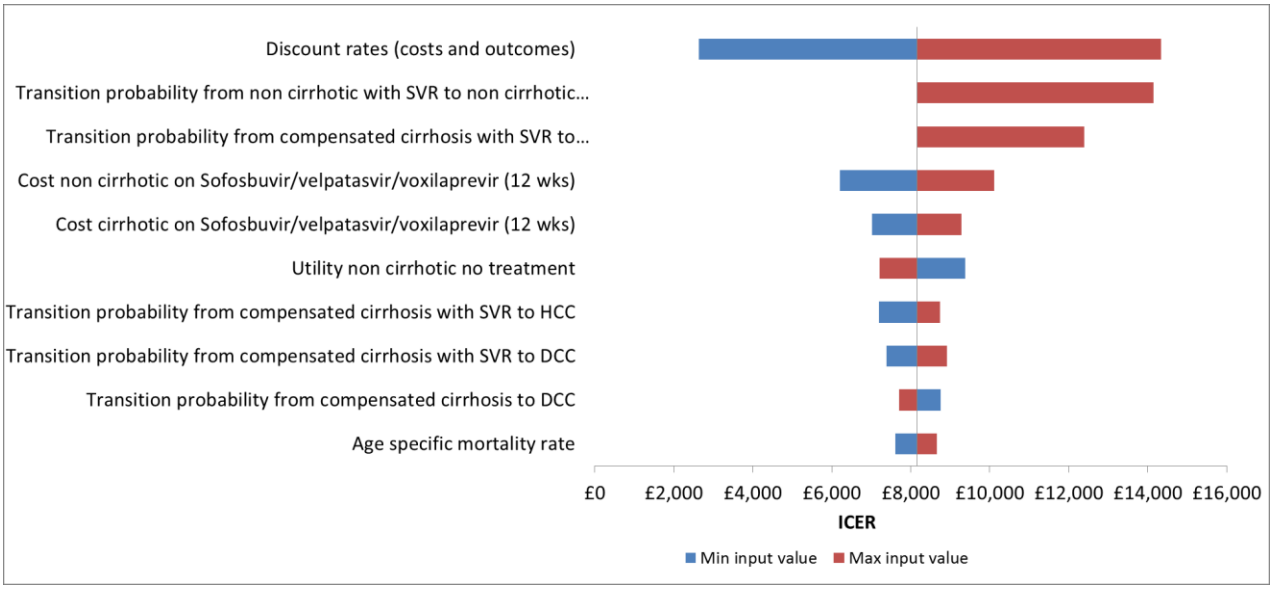


Figure 2: Tornado diagram: DAA-experienced (pan-GT and all non-cirrhotic/compensated cirrhosis): SOF/VEL/VOX 12 weeks vs no treatment (list price)

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

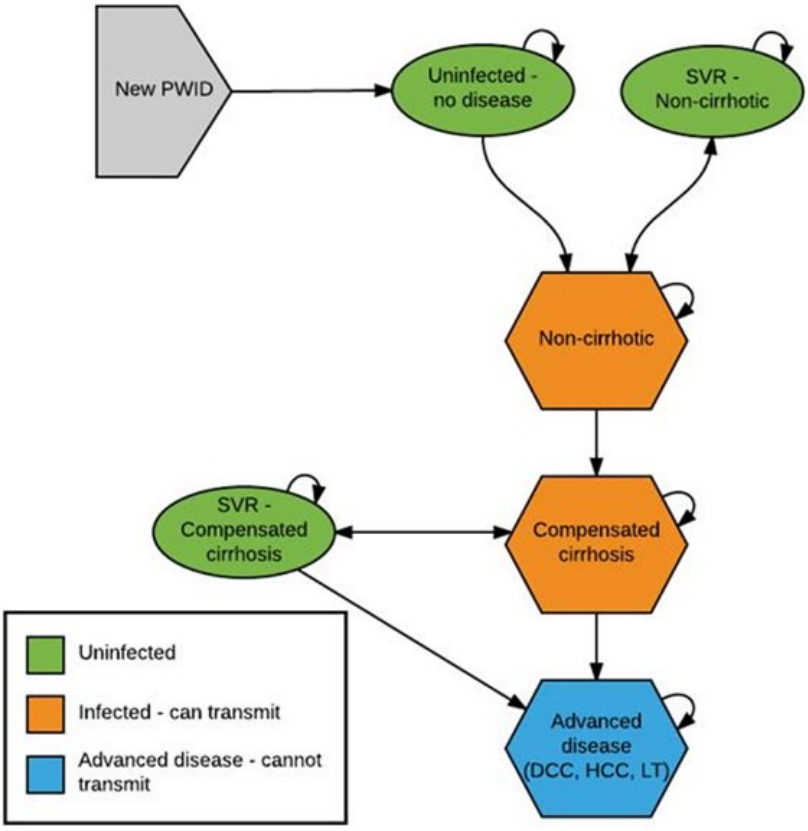
The company's dynamic transmission scenario explored the impact of Hepatitis C re-infection and onwards transmission in GT3 DAA-naïve patients. The CS stated that a similar analysis was not conducted on DAA-experienced patients as the impact of onward transmission and re-infection is expected to be minimal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

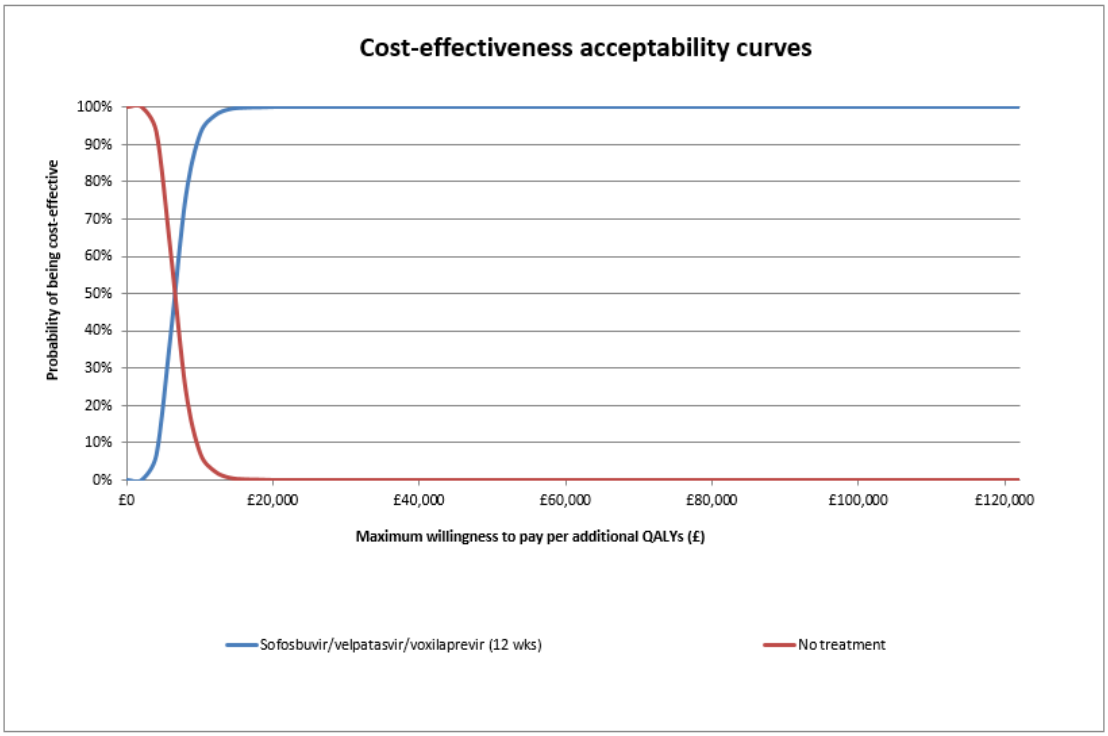


Figure 4: Cost-effectiveness acceptability curves for DAA-experienced patients (PAN genotypic and non-cirrhotic/cirrhotic)

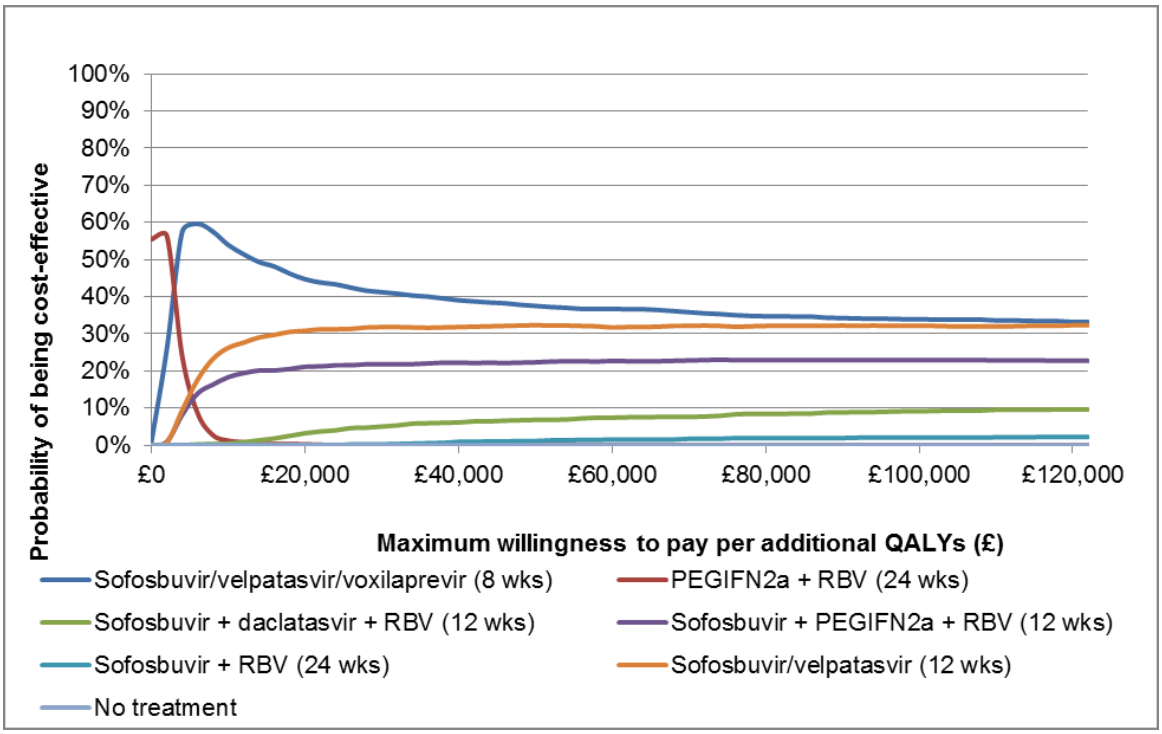


Figure 5: Cost-effectiveness acceptability curves for all treatments (genotype 3 treatment naïve cirrhotic, SOF/VEL/VOX 8 weeks)

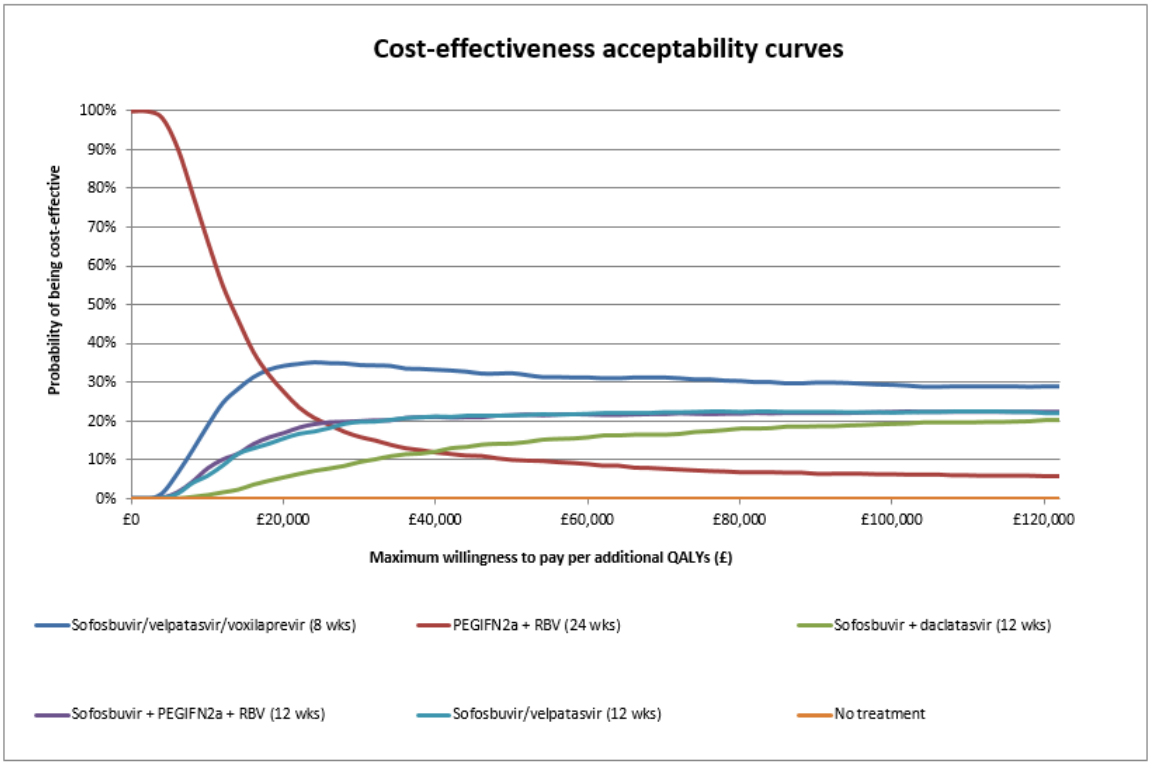


Figure 6: Cost-effectiveness acceptability curves for all treatments (genotype 3 treatment naïve non-cirrhotic, SOF/VEL/VOX 8 weeks)

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

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Sofosbuvir-velpatasvir-voxilaprevir for treating chronic hepatitis C [ID1055]

You are asked to check the ERG report from Southampton Health Technology Assessment Centre to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 7 November 2017** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Cirrhotic status definition

Description of problem	Description of proposed amendment (in red)	Justification for amendment	ERG response
Cirrhotic status definition not clear. Page 9 of the ERG report	(i) those who have had previous treatment with direct-acting antiviral (DAA) agents for chronic hepatitis C (CHC) (DAA-experienced) regardless of cirrhosis status, and (ii) those who have had no previous treatment with DAA agents for CHC (DAA-naïve) who have	Edits to ensure clarity on cirrhotic status within the two populations included in the company submission.	Not a factual error. This text exactly corresponds to the two groups of patients addressed in the company decision problem as stated in Table 1 of the CS.

	hepatitis C virus (HCV) of genotype 3 (GT3), with or without cirrhosis.		

Issue 2 Redaction of RAV information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Redaction of RAV information. Page 14 ERG report.	Removal of redaction for RAV information.	This information was not redacted in the company submission.	The ERG believed (incorrectly) that trial CSRs were supplied CIC and hence this information (which is not present in the main company submission document) was marked CIC in error. The redaction has now been removed.

Issue 3 Trial mislabelling for RAV information

Description of problem	Description of proposed amendment (in red)	Justification for amendment	ERG response
POLARIS-4 sited in RAV information section for DAA-naïve. Page 14 ERG report.	Should read "RAVs in the HCV NS3 or NS5A genes were present at baseline in both the POLARIS-2 and POLARIS-3 trial participants".	Factual error.	The ERG has corrected this typographical error.

Issue 4 Redaction of Adverse Event information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Redaction of all AE data from POLARIS 1-4. Page 16, 75-80 ERG report.	Redaction of all AE data from POLARIS 1-4 (i.e. all study arms). See **Appendix 1** to this pro-forma.	The company would prefer to redact all AE data for the POLARIS trials (i.e. both study arms).	Not a factual error. The ERG has matched the marking presented in the CS. The ERG also notes that much of the AE

			data is already in the public domain in the published papers or the supplementary information available with the published papers and therefore some of the AE data should not have been marked AIC in the CS.

Issue 5 Comparator omission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
SOF+DCV was omitted from the comparator list. Page 17 ERG report.	SOF+DCV to be added to the list of comparators in the paragraph.	SOF+DCV was one of the comparators reported in the manufacturer submission for this DAA-naïve, GT3 patients with CC.	SOF+DCV has not been omitted from the comparator list. However, on checking this item the ERG discovered that SOF+RBV had been omitted and this has now been corrected.

Issue 6 Time horizon and cycle length

Description of problem	Description of proposed amendment (in red)	Justification for amendment	ERG response
The time horizon of the model and the cycle length information was not correctly reported. Page 17 ERG report.	The model had a lifetime horizon of ~~30 years~~ allowing the user to follow a patient until the ages of 60, 80 or 100 years. With discounting at 3.5% per annum for costs and benefits, a cycle length of two weeks for the first ~~18 months~~72 weeks, followed by a 24-week ~~6-month~~ long cycle,	Information in the ERG report does not match the company submission.	We agree. The text has been changed as follows: 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,

Issue 7 SOF/VEL/VOX list price

Description of problem	Description of proposed amendment (in red)	Justification for amendment	ERG response
List price for the total pack of 8 weeks of SOF/VEL/VOX was incorrect. Page 18 ERG report.	Price to be change from £29,884.68 to £29,884.66.	Information in the ERG report do not match the company submission.	We agree. The price has been changed to £29,884.66.

Issue 8 Incremental costs and QALYs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 3, 4, 38 and 39 do not represent the information reported in Table 65 and 66 of the company submission.	See **Appendix 2** to this pro-forma, suggesting the amendment. NB: the suggested edit is to reflect the manufacturer submission. ERG may wish to include the incremental QALYs and Costs in addition in the ERG final report.	Tables 65 and 66 in the company submission report incremental costs and QALYs vs no treatment, and ICERs vs 1) no treatment and 2) incrementally. The tables in the ERG report include incremental Costs and QALYs, which are not included in the main company submission (incremental ICER is reported and all information is available from the model).	Although there are no errors in the ERG tables, the ERG concedes that the table headings for Table 3 and Table 38 could lead the reader to believe that they are direct copies of the CS tables. In fact the ERG tables are based on the CS tables but are not direct copies. The table headings for Table 3 and Table 38 have been altered to reflect this. Table 4 and Table 39 headings already indicate the tables are based on CS Table 66 but the

			wording has been altered to make it clearer that the ERG tables are a shortened and edited version of the CS table.

Issue 9 Study selection exclusion criteria omission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Exclusion criteria listed omitted animal and in vitro studies. Page 32 ERG report.	Animal and *in vitro* studies to be added to the list of exclusion criteria.	Omission of two exclusion criteria; amendment is to provide full exclusion criteria used for the systematic literature search.	Not a factual error. The ERG has indicated where the company reports inclusion and exclusion criteria and then the ERG has chosen to highlight only the criteria that exclude specific subgroups of participants.

Issue 10 Omission of POLARIS information

Description of problem	Description of proposed amendment (in red)	Justification for amendment	ERG response
Information from POLARIS 4 was omitted. Page 35 ERG report.	(POLARIS-1, -2, ~~and -~~ 3 and 4; n=1, 2, ~~and~~ 1 and 0, respectively).	Information was not reported in the ERG report.	POLARIS-4 was omitted because there were no patients did not get the study drug in this trial. The ERG accepts that this should have been made clear and the text has been amended to show this.

Issue 11 Redaction of information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Some information were highlighted as CIC instead of AIC. Page 66 ERG report.	Please Change: **Page 66:** 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]. **Page 66:** 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].	No need for the information to be highlighted as CIC.	The status of this information has been changed from CIC to AIC.

Issue 12 Total AE costs (per episode)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Total AE costs (per episode) reported in Table 35 of the ERG report only take into account Table 58 of the company submission.	The manufacturer would suggest that drug unit costs (Table 57 of the manufacturer submission) should also be included in a total cost per episode calculation.	Better representation of the total AE costs per episode.	Not a factual error. These AE total costs (per episode) are extracted from the economic model and it is clearly stated in the text above the table that these costs were estimated as the sum of total AE drug costs, inpatient costs, outpatient costs, GP costs and specialist costs.

Issue 13 Missing label

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Missing label in Table 42 page 119 of the ERG report.	"DAA-naïve patients, GT3 infection, non-cirrhotic" should be added in the first column of the final row of Table 42.	Missing label.	We agree. We have added 'DAA-naïve patients, GT3 infection, non- cirrhotic'

Issue 14 Grammar and spelling

Description of problem	Description of proposed amendment (in red)	Justification for amendment	ERG response
Some grammatical and spelling errors have been identified in the ERG report	**Page 20:** 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.	Grammar.	Error corrected

	Page 86: 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~~ via: AASLD, DDW and EASL in annual conferences held from 1st January 2014 to 17 March 2017 **Page 133**: The company presented the base case results in terms of total costs, life years gained and total QALYs. The ICER results are presented incrementally and also for treatment versus no treatment (see CS tables 64, 65 and 66)	Consistency and spelling error. Clarity of sentence.	Consistency addressed. There is no spelling error, viz is an abbreviation (of the latin videlicet) but the ERG accepts that this term may not be widely known so has changed this to 'namely'. No change required. The sentence states that results are presented incrementally.

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.

.

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 **Error! Reference source not found.**.

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 **Error! Reference source not found.**). 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